A Critical Appraisal of Ward-based Interventions in the Care of the Acutely Unwell Patient

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Thesis submitted to Imperial College, London for the Degree of Doctor of Medicine (Research)
Abstract

Medical Emergency Teams and Critical Care Outreach services are used to try to improve the care of patients in the ward environment. The limited treatment options include oxygen therapy, non-invasive ventilation, intravenous fluid therapy and in some institutions, inotropic support. The efficacy of such interventions is unclear.

Four studies used both lung models and clinical observation to assess oxygen therapy. The model demonstrated a deterioration in oxygen delivery for the variable flow systems (Hudson mask, Hudson non-rebreather mask and nasal cannulae) as minute ventilation increased. Performance was relatively preserved for a venturi system and a high flow nasal cannula system (Vapotherm®).

Peak inspiratory flow rates (PIFR) were assessed in patients with respiratory distress and matched controls. This demonstrated a higher median PIFR of 76.5 l.min$^{-1}$ (IQR 51.25 l.min$^{-1}$) in patients when compared with controls, median of 30.00 (IQR 6.00 l.min$^{-1}$) (p<0.0001).

The model was used to assess continuous positive airway pressure (CPAP) and showed no deterioration in oxygen delivery with respiratory rate, with or without a CPAP valve. When applied clinically in patients with acute respiratory distress, a significant increase in mean arterial oxygenation was observed on moving from a venturi mask (FiO$_2$ 0.6) to CPAP even without the valve, with a mean increase of PaO$_2$ of 10.69 kPa (SD 5.14 kPa) p<0.0001 (n=53). The application of pressure with the CPAP valve did not increase this value over the 2 hours studied.
The use of intravenous fluid resuscitation (IFR) in the ward was audited. Delay in fluid administration, a wide range of volume delivered and a lack of monitoring were demonstrated. This audit produced the hypothesis that better monitoring of fluid therapy in the wards may reduce the volume delivered and incidence of complications. The final study thus compared a simple-to-use cardiac output monitor (Vigileo Flotrac®) to a dye-dilution system (LiDCO®). The two systems were found to have good agreement both in terms of cardiac output (bias positive in favour of the LiDCO 0.58 l.min⁻¹). The upper 95% limit is +1.40 l.min⁻¹ and the lower 95% limit, -0.28 l.min⁻¹. And stroke volume variation (Bias of 0 with 95% limits of +/- 3.3%).

In conclusion this thesis demonstrates the impact of abnormal ventilation on oxygen delivered by some mask systems. It shows the efficacy of a tight fitting CPAP mask and high flow generator, but incidentally demonstrates that, at least initially it is the mask system rather than the pressure that has a pronounced effect on oxygenation.

Fluid management in the ward patient appears poorly controlled and often excessive so may benefit from improved monitoring. To this end a cardiac output monitor that may be suitable for ward use has been shown to be comparable with a more established technique.
Declaration

The research leading to this thesis was carried out on the general wards, accident and emergency department and intensive care unit at Chelsea and Westminster Hospital, London between August 2005 and August 2007. All the work contained herein is my own. None of the data forms part of any other thesis.

All clinical studies were approved by Riverside Ethics Committee with written consent obtained from all participants prior to their involvement where appropriate.

The research was funded by the Dunhill Trust - a charitable organisation.

Additional donations were made from the Westminster Medical School Research Fund. No conflict of interest exists.

Adrian Wagstaff
Acknowledgements

I would like to thank and acknowledge the assistance of the following:

All patients who so kindly took part in my research. Their generosity and help is deeply appreciated.

The Chelsea and Westminster Critical Care Outreach Team and the Intensive Care Unit. A group of more talented, hard working, caring and kind people you could not hope to meet.

Kevin Haire, Jeremy Thompson and Denise Lillee for allowing me to join their team on Wednesdays.

Maureen Fortier, for keeping me solvent during my research post.

Professor Masao Takata, whose helpfulness and concern to see this thesis completed was consistent to the end.

Charlie Greenhill, for all his guidance of College protocol.

Clare Glover, for her excellent statistical support.


Sian Jaggar, for her unfailing support during the writing of this thesis, above and beyond the call of duty. Without her care and concern and thoughtful insights I would have struggled to continue.

I would like to especially thank my supervisor, Neil Soni. He has been always generous and kind when I needed guidance, loyal and supportive whenever I needed help, and cheerful and bright during difficult times. His continued encouragement during bleak days has sustained me sufficiently to produce this work.

But most of all I would like to thank my darling wife Naomi without whose unwavering support, organisational qualities and childcare, this thesis would never have been written. Thanks for standing with me.
Publications and Presentations

The following work has been published in peer-reviewed journals or presented at learned societies:

**Publications:**

**Presentations:**
2005: ‘Performance of Oxygen Delivery Devices Across a Range of Respiratory Rates’ Doctors Updates, 8th Anaesthesia Forum, Doctors Updates, Da Balaia, Portugal

2006: ‘CPAP: Physics or physiology?’ 17th Anaesthesia Update, Doctors Updates, Belle Plagne, France


‘CPAP: an update’. 9th Anaesthesia Forum, Doctors Updates, Da Balaia, Portugal

Arterial oxygenation in respiratory failure: the importance of the CPAP valve. 8th Current Controversies in Anaesthesia and Perioperative Medicine, Dingle, Eire. Awarded joint first prize.
For Naomi, Bethany and Abigail

The ladies in my life
# Table of Contents

**Abstract** ................................................................................................. 2

**Declaration** ............................................................................................. 4

**Acknowledgements** ................................................................................. 5

**Publications and Presentations** ................................................................. 6

**Publications:** ............................................................................................ 6

**Presentations:** .......................................................................................... 6

**Table of Contents** ..................................................................................... 8

**Table of Figures** ....................................................................................... 20

**Table of Tables** ....................................................................................... 23

**Chapter 1** ................................................................................................ 26

**Introduction** ............................................................................................. 26

1.1 **Introduction** ........................................................................................ 26

1.1.1 **Recognition** .................................................................................. 26

1.1.2 **Intervention** .................................................................................. 26

1.2 **Sub-optimal Care Leads to Increased Mortality** ................................. 28

1.2.1 **Evidence** ....................................................................................... 28

1.3 **Early Warning Scores** ........................................................................ 29

1.3.1 **Physiological variables and Outcome** ........................................... 30

1.3.2 **History of Early Warning Scores** .................................................. 32
1.3.3 Validation

1.4 EARLY INTERVENTION IMPROVES OUTCOME

1.4.1 Early Goal Directed Therapy

1.4.2 Impact of Critical Care Skills

1.4.3 The Surviving Sepsis Campaign Guidelines

1.5 MEDICAL EMERGENCY AND CRITICAL CARE OUTREACH TEAMS

1.5.1 History of Critical Care Outreach

1.5.2 Evolution of Healthcare Practice

1.5.3 The UK Critical Care Outreach Model

1.5.4 Outreach Interventions

1.6 EVIDENCE FOR CRITICAL CARE OUTREACH

1.6.1 Reduction in Cardiac Arrest Rate

1.6.2 Reduction in Readmission Rate

1.6.3 Cost-effectiveness

1.6.4 In-hospital Mortality

1.6.5 The MERIT Study

1.6.6 Further Evidence

1.6.7 Summary of the Evidence

1.6.8 CCOT Interventions

1.7 THESIS AIMS

1.7.1 Oxygen Delivery
CHAPTER 2

MATERIALS AND METHODS

2.1 INTRODUCTION

2.2 OXYGEN DELIVERY

2.2.1 Assessment of Common Oxygen Delivery Systems via a Model

2.2.2 Peak Inspiratory Flow Rates in Respiratory Distress

2.2.3 Continuous Positive Airway Pressure

2.2.4 Assessment of CPAP via a Model

2.2.5 Clinical Audit of the Application of CPAP to Patients

2.2.6 Summary

2.3 FLUID RESUSCITATION

2.3.1 An Audit of Ward-based Intravenous Fluid Resuscitation

2.3.2 Cardiac Output Monitoring

2.4 REFERENCES
CHAPTER 3 ................................................................. 80

THE PERFORMANCE OF OXYGEN DELIVERY DEVICES AT VARYING RESPIRATORY RATES 80

3.1 BACKGROUND ........................................................................................................ 80

3.1.1 Oxygen delivery ................................................................................................... 81

3.1.2 Difficulties in Measuring \( \text{FiO}_2 \) ........................................................................... 82

3.1.3 Aims ....................................................................................................................... 83

3.2 METHODOLOGY ..................................................................................................... 83

3.2.1 Study Design ......................................................................................................... 83

3.2.2 The Model ............................................................................................................. 84

3.2.3 Calibration ............................................................................................................ 86

3.2.4 Devices .................................................................................................................. 87

3.2.5 Assessment .......................................................................................................... 89

3.2.6 Statistical Analysis ............................................................................................... 91

3.3 RESULTS .................................................................................................................. 91

3.3.1 Inter-device variability ......................................................................................... 91

3.3.2 Variable Performance Systems ............................................................................ 91

3.3.3 Fixed Performance System ................................................................................. 102

3.3.4 High Flow, High Concentration Systems ............................................................ 105

3.4 DISCUSSION ........................................................................................................... 108

3.4.1 Clinical Implications ............................................................................................ 110

3.4.2 Mechanism of Failure .......................................................................................... 112
3.4.3 The Model as a Reflection of Real Life

3.4.4 Conclusions

3.5 REFERENCES

CHAPTER 4

PEAK INSPIRATORY FLOW RATES IN RESPIRATORY DISTRESS

4.1 BACKGROUND

4.1.1 The Relationship between Inspiratory Flow and Oxygen Delivery

4.1.2 Literature Review

4.1.3 Hypothesis

4.1.4 Aims

4.2 METHODOLOGY

4.2.1 Study Design

4.2.2 Study 1: Normal subjects

4.2.3 Study Equipment

4.2.4 Testing of normal subjects

4.2.5 Study 2: Patients

4.2.6 Controls

4.2.7 Testing of patients and controls

4.2.8 Data Collection

4.2.9 Statistical Analysis
4.2.10 Sample Size ........................................................................................................ 126

4.3 RESULTS .................................................................................................................... 127

4.3.1 Study 1: Normal subjects ..................................................................................... 127

4.3.2 Study 2: Patients .................................................................................................. 129

4.4 DISCUSSION ............................................................................................................. 132

4.4.1 Clinical Implications ......................................................................................... 133

4.4.2 Conclusions ....................................................................................................... 135

4.5 REFERENCES .......................................................................................................... 137

CHAPTER 5 ...................................................................................................................... 138

CONTINUOUS POSITIVE AIRWAY PRESSURE ............................................................ 138

5.1 BACKGROUND ....................................................................................................... 138

5.1.1 History ............................................................................................................... 139

5.1.2 Mechanism of Action ....................................................................................... 140

5.1.3 Clinical Uses of CPAP ...................................................................................... 140

5.1.4 Complications of CPAP .................................................................................... 144

5.1.5 Aims ................................................................................................................... 147

5.2 METHODOLOGY .................................................................................................... 147

5.2.1 Statistical Analysis ............................................................................................ 149

5.3 RESULTS ............................................................................................................... 150

5.4 DISCUSSION .......................................................................................................... 156
5.4.1 Clinical Implications

5.4.2 Problems with the Model

5.4.3 Conclusions

5.5 REFERENCES

CHAPTER 6

THE EFFECT OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON OXYGENATION IN ACUTE RESPIRATORY FAILURE

6.1 INTRODUCTION

6.1.1 Physiological Effects of CPAP

6.1.2 Aims

6.2 METHODOLOGY

6.2.1 Inclusion criteria:

6.2.2 Relative exclusion criteria were those for applying CPAP in the ward:

6.2.3 Data collection

6.2.4 Statistical analysis

6.2.5 Sample Size

6.3 RESULTS

6.4 DISCUSSION

6.4.1 Critique of the Audit

6.4.2 Clinical Implications
6.4.3 Conclusions ........................................................................................................... 187

6.5 REFERENCES ............................................................................................................. 188

CHAPTER 7 ....................................................................................................................... 191

AN AUDIT OF FLUID RESUSCITATION OF WARD patients ......................................... 191

7.1 BACKGROUND ........................................................................................................ 191

7.1.1 Hypotension and Early Circulatory Failure ......................................................... 192

7.1.2 Intravenous Fluid Resuscitation ......................................................................... 194

7.2 METHODOLOGY ..................................................................................................... 197

7.2.1 Inclusions ............................................................................................................. 197

7.2.2 Exclusions ........................................................................................................... 197

7.2.3 Definitions .......................................................................................................... 198

7.2.4 Practical Application of the Method .................................................................... 199

7.2.5 Statistical analysis ............................................................................................. 204

7.3 RESULTS .................................................................................................................. 204

7.3.1 General observations ......................................................................................... 204

7.3.2 First involvement of the CCOT .......................................................................... 207

7.3.3 Ward patients compared to those in the Rivers EGDT study.............................. 208

7.3.4 Resolution of the Target Indication for Intervention ........................................ 210

7.3.5 Poor Patient Outcomes ...................................................................................... 211

7.3.6 Complications associated with fluid administration ........................................... 212
7.3.7 Volumes and Rate of Fluid Delivery .......................................................... 214

7.4 DISCUSSION ................................................................................................. 214

7.4.1 Summary ................................................................................................... 214

7.4.2 Comparison with the EGDT Protocol of Rivers et al ................................. 215

7.4.3 Response Time ......................................................................................... 217

7.4.4 The Efficacy of the Intervention ............................................................... 218

7.4.5 Fluid management ...................................................................................... 219

7.4.6 Complications of Fluid Management ....................................................... 220

7.4.7 Limitations of the Audit ............................................................................ 221

7.4.8 Conclusions ............................................................................................... 222

7.5 REFERENCES ............................................................................................... 224

CHAPTER 8 ........................................................................................................... 227

THE COMPARISON OF AN UNCALIBRATED CARDIAC OUTPUT MONITOR WITH A DYE DILUTION PULSE CONTOUR METHOD .......................................................... 227

8.1 BACKGROUND ............................................................................................. 227

8.1.1 Oxygen Delivery ....................................................................................... 227

8.1.2 Interventions to Improve $DO_2$ ............................................................... 229

8.1.3 Cardiac Output Monitoring ...................................................................... 230

8.1.4 Stroke Volume Variation ........................................................................... 233

8.1.5 Cardiac Output Monitoring of Ward Patients .......................................... 234
Pulse Contour Wave Analysis ............................................................................. 235
Aims .................................................................................................................. 237

Methodology ..................................................................................................... 237
Study Design ...................................................................................................... 237
Statistical Analysis ............................................................................................. 239
Sample Size Calculation .................................................................................... 240

RESULTS .......................................................................................................... 240

DISCUSSION ..................................................................................................... 247
Cardiac Output ................................................................................................... 247
Stroke Volume Variation .................................................................................... 250
Conclusions ........................................................................................................ 252

REFERENCES ................................................................................................. 254

CHAPTER 9 ........................................................................................................ 258
THESIS CONCLUSIONS ..................................................................................... 258

Review of Thesis ............................................................................................... 258
Performance of Oxygen Masks ......................................................................... 258
Peak inspiratory flow rates in respiratory distress ........................................... 260
Continuous Positive Airway Pressure ............................................................... 261
The Efficacy of CCOT in Delivering Fluid Resuscitation on the Wards .......... 263
The Comparison of a Novel Cardiac Output Monitor with a Standard .......... 266
9.2 LIMITATIONS OF THE THESIS ........................................................................267
9.3 RECOMMENDATIONS FOR CLINICAL PRACTICE ........................................268
  9.3.1 Oxygen Therapy ..................................................................................268
  9.3.2 Critical Care Outreach ........................................................................269
  9.3.3 Cardiac Output Monitors ......................................................................270
9.4 RECOMMENDATIONS FOR FUTURE RESEARCH ..........................................271
9.5 FINAL CONCLUSIONS ...............................................................................272
9.6 REFERENCES ..............................................................................................274

APPENDIX 1 ........................................................................................................276

MATHEMATICAL DERIVATION OF THE POSSIBLE CONTRIBUTION OF DEAD SPACE GASES TO
THE EOIC ........................................................................................................276

A.1 INTRODUCTION ..........................................................................................276
  A.1.1 Carbon Dioxide ....................................................................................277
  A.1.2 Water Vapour .......................................................................................278
  A.1.3 Dead Space ............................................................................................278
A.2 EXAMPLES ....................................................................................................279
  A.2.1 Example 1: Hudson Mask 500 ml. Effect of Varying Proportion of Vt that is
  \( V_d \) ..............................................................................................................280
  A.2.2 Example 2: Hudson Mask Vt 500 ml. Effect of varying the value of EtO\(_2\) ....283
A.3 REFERENCES ................................................................................................287
Table of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIGURE 1.1</td>
<td>The Early Goal Directed Therapy Protocol (reproduced with permission)</td>
<td>38</td>
</tr>
<tr>
<td>FIGURE 3.1</td>
<td>The experimental rig</td>
<td>85</td>
</tr>
<tr>
<td>FIGURE 3.2</td>
<td>Hudson mask at 300 ml tidal volume</td>
<td>93</td>
</tr>
<tr>
<td>FIGURE 3.3</td>
<td>Hudson mask at 500 ml tidal volume</td>
<td>94</td>
</tr>
<tr>
<td>FIGURE 3.4</td>
<td>Hudson non-rebreather mask, at 300 ml tidal volume</td>
<td>95</td>
</tr>
<tr>
<td>FIGURE 3.5</td>
<td>Hudson non-rebreather mask, at 500 ml tidal volume</td>
<td>96</td>
</tr>
<tr>
<td>FIGURE 3.6</td>
<td>Nasal cannulae at 300 ml tidal volume</td>
<td>98</td>
</tr>
<tr>
<td>FIGURE 3.7</td>
<td>Nasal cannulae at 500 ml tidal volume</td>
<td>99</td>
</tr>
<tr>
<td>FIGURE 3.8</td>
<td>Thermovent T2 HME at 300 ml tidal volume</td>
<td>100</td>
</tr>
<tr>
<td>FIGURE 3.9</td>
<td>Thermovent T2 HME at 500 ml tidal volume</td>
<td>101</td>
</tr>
<tr>
<td>FIGURE 3.10</td>
<td>Venturi mask at 300 ml tidal volume</td>
<td>103</td>
</tr>
<tr>
<td>FIGURE 3.11</td>
<td>Venturi mask at 500 ml tidal volume</td>
<td>104</td>
</tr>
<tr>
<td>FIGURE 3.12</td>
<td>Vapotherm at 300 ml tidal volume</td>
<td>106</td>
</tr>
<tr>
<td>FIGURE 3.13</td>
<td>Vapotherm at 500 ml tidal volume</td>
<td>107</td>
</tr>
<tr>
<td>FIGURE 4.1</td>
<td>The change in peak inspiratory flow rate in 10 normal subjects on climbing 6 flights of stairs</td>
<td>128</td>
</tr>
<tr>
<td>FIGURE 4.2</td>
<td>A box and whisker plot demonstrating the difference in peak inspiratory flow rates between the patients and controls</td>
<td>132</td>
</tr>
<tr>
<td>FIGURE 5.1</td>
<td>CPAP System at 300 ml tidal volume (FiO&lt;sub&gt;2&lt;/sub&gt; 0.6)</td>
<td>151</td>
</tr>
<tr>
<td>FIGURE 5.2</td>
<td>CPAP System at 500 ml tidal volume (FiO&lt;sub&gt;2&lt;/sub&gt; 0.6)</td>
<td>152</td>
</tr>
<tr>
<td>FIGURE 5.3</td>
<td>CPAP System at 300 ml tidal volume (FiO&lt;sub&gt;2&lt;/sub&gt; 1.0)</td>
<td>153</td>
</tr>
<tr>
<td>FIGURE 5.4</td>
<td>CPAP System at 300 ml tidal volume (FiO&lt;sub&gt;2&lt;/sub&gt; 1.0)</td>
<td>154</td>
</tr>
</tbody>
</table>
FIGURE 5.5 MEAN PRESSURES WITHIN THE INSPIRATORY AND EXPIRATORY LIMBS OF THE CPAP SYSTEM. .......................................................................................................................... 155

FIGURE 5.6 THE EFFECT ON EIOC ON CHANGING FROM A VENTURI SYSTEM TO A CPAP SYSTEM WITH NO VALVE AT 2 TIDAL VOLUMES. FiO₂ 0.6, RESPIRATORY RATE 30 BREATHS.min⁻¹ ...... 159

FIGURE 6.1 SEQUENTIAL CHANGE IN OXYGEN DELIVERY DEVICE DELIVERED TO THE PARTICIPATING SUBJECTS (AS PER HOSPITAL PROTOCOL/GUIDELINE) ................. 172

FIGURE 6.2 MEAN PAO₂ IN PATIENTS WITH RESPIRATORY FAILURE ........................................ 177

FIGURE 6.3 MEAN PACO₂ IN PATIENTS WITH RESPIRATORY FAILURE ........................................ 178

FIGURE 6.4 MEAN RESPIRATORY RATES IN PATIENTS WITH RESPIRATORY FAILURE ............ 179

FIGURE 6.5 A BOX AND WHISKER PLOT OF THE COMFORT SCORE EXPRESSED BY PATIENTS WITH RESPIRATORY FAILURE ........................................................................ 180

FIGURE 7.1 THE EARLY GOAL DIRECTED THERAPY PROTOCOL (REPRODUCED WITH PERMISSION) 8 ......................................................................................................................... 200

FIGURE 7.2 THE INDICATIONS FOR THE INSTITUTION OF IVR – THE TARGET ......................... 205

FIGURE 7.3 LENGTH OF STAY FOR THE PATIENTS PRIOR TO THE INSTITUTION OF IVR .......... 206

FIGURE 7.4 CAUSATIVE PATHOPHYSIOLOGY UNDERLYING THE CONDITIONS OF THE PATIENTS IN THE AUDIT ........................................................................................................... 206

FIGURE 7.5. RESPONSE TIMES FROM FIRST APPEARANCE OF TARGET ABNORMALITY. ....... 208

FIGURE 8.1 BLAND-ALTMAN PLOT OF THE DIFFERENCE BETWEEN FLOTRAC AND LiDCO DERIVED CARDIAC OUTPUTS .................................................................................. 244

FIGURE 8.2 BLAND-ALTMAN PLOT FOR ΔSVV AFTER A FLUID CHALLENGE ......................... 245

FIGURE A.1 THE EFFECT OF VARYING THE VD:VA RATIO ON THE EIOCcorr FOR A HUDSON MASK DELIVERING OXYGEN AT 4 L.min⁻¹ TO A VT OF 500 ML WITH AN ASSUMED EtO₂ OF 30%. ........................................................................................................ 282
FIGURE A.2 THE EFFECT OF VARYING THE EtO2 ON THE EIOCcorr FOR A HUDSON MASK
DELIVERING OXYGEN AT 4 L.min⁻¹ TO A VT OF 500 ML WITH AN FIXED VD:VA RATIO OF 30:70.
Table of Tables

TABLE 1.1 EARLY WARNING SCORE (EWS) AFTER MORGAN ET AL.13 ...........................................33
TABLE 1.2 ACCP/SCCM CONSensus Conference Definition of the Systemic Inflammatory Response Syndrome.21 ........................................................................................................37
TABLE 1.3 'COMPREHENSIVE CRITICAL CARE' CLASSIFICATION OF CRITICAL CARE PATIENTS ACCORDING TO CLINICAL NEED33 ..................................................................................................................45
TABLE 1.4 INTERVENTIONS PERFORMED OR RECOMMENDED BY CRITICAL CARE OUTREACH STAFF (AFTER MCDONNELL ET AL.)35 ......................................................................................................................51
TABLE 1.5 WARD INTERVENTIONS USED BY THE CCOT AT CHELSEA AND WESTMINSTER HOSPITAL.................................................................................................................................61
TABLE 3.1 FACTORS THAT INFLUENCE THE FiO2 DELIVERED TO A PATIENT BY OXYGEN DELIVERY DEVICES5 .................................................................................................................................82
TABLE 3.2 DEVICES SELECTED FOR STUDY (MANUFACTURER)...........................................................................88
TABLE 3.3 MANUFACTURERS RECOMMENDATIONS FOR OXYGEN FLOW RATES AND RESULTANT OXYGEN CONCENTRATIONS FOR THE VARIABLE PERFORMANCE DEVICE23 (SEE APPENDIX 2)..109
TABLE 4.1 DEMOGRAPHICS OF THE NORMAL SUBJECTS ..........................................................127
TABLE 4.2 THE MEAN PEAK INSPIRATORY FLOW RATES IN NORMAL SUBJECTS AT REST AND AT PEAK EXERCISE. ...........................................................................................................................128
TABLE 4.3 CHARACTERISTICS OF PATIENTS WITH RESPIRATORY FAILURE AND CONTROLS. ....130
TABLE 4.4 MEAN PEAK INSPIRATORY FLOW RATES AND RESPIRATORY RATES FOR PATIENTS AND CONTROLS.................................................................................................................................131
TABLE 5.1 RECOGNISED COMPLICATIONS OF CPAP................................................................................145
TABLE 6.1 BENEFICIAL PHYSIOLOGICAL EFFECTS OF CPAP .....................................................................167
TABLE 6.2 SUMMARY OF THE CHELSEA AND WESTMINSTER WRITTEN PROTOCOL / GUIDELINE FOR THE INTRODUCTION OF CONTINUOUS POSITIVE AIRWAY PRESSURE ........................................ 171
TABLE 6.3 BASELINE CHARACTERISTICS OF THE PATIENTS ............................................. 176
TABLE 6.4 CLINICAL DIAGNOSES OF AETIOLOGY OF ACUTE RESPIRATORY FAILURE IN AUDIT SUBJECTS ........................................................................................................... 176
TABLE 6.5 MEAN PAO₂ IN PATIENTS WITH RESPIRATORY FAILURE ................................ 177
TABLE 6.6 MEAN PACO₂ IN PATIENTS WITH RESPIRATORY FAILURE ............................... 178
TABLE 6.7 MEDIAN RESPIRATORY RATE IN PATIENTS WITH RESPIRATORY FAILURE ......... 179
TABLE 6.8 MEDIAN COMFORT SCORES FOR PATIENTS WITH RESPIRATORY FAILURE ....... 180
TABLE 7.1 PHYSIOLOGICAL CLASSIFICATION OF CIRCULATORY SHOCK^{10} ......................... 193
TABLE 7.2 DEFINITIONS OF TARGETS FOR IVR .................................................................. 201
TABLE 7.3 DATA RECORDED DURING AUDIT AT BASELINE AND REVIEWS AT 6, 24, 48 AND 72 HOURS ...................................................................................................................... 202
TABLE 7.4 BASELINE CHARACTERISTICS OF THE PATIENTS ........................................ 207
TABLE 7.5 RESOLUTION OF TARGET ABNORMALITY ......................................................... 211
TABLE 7.6 COMPLICATION RATES AND THE TIME OF THEIR APPEARANCE ..................... 213
TABLE 7.7 RESULTS FOR FLUID VOLUMES AND RATES ADMINISTERED OVER THE 4 TIME INTERVALS .................................................................................................................. 213
TABLE 8.1 CURRENT METHODS OF MEASURING CARDIAC OUTPUT IN PATIENTS ............... 231
TABLE 8.2 BASELINE CHARACTERISTICS OF THE PATIENTS AT RECRUITMENT .............. 241
TABLE 8.3 CLINICAL DIAGNOSIS OF PARTICIPATING SUBJECTS ...................................... 242
TABLE 8.4 CARDIAC OUTPUT MEASURES FOR LiDCO AND VIGILEO AT 4 TIME POINTS (L.MIN⁻¹) ......................................................................................................................... 243
TABLE 8.5 ΔSVV AFTER A FLUID BOLUS FOR THE LiDCO AND VIGILEO SYSTEMS ............ 246
TABLE A.1 EFFECTIVE INSPIRED OXYGEN CONCENTRATION (EIOC) VALUES FOR A HUDSON MASK AT A TIDAL VOLUME OF 500 ML. .................................................................280

TABLE A.2 EIOCcorr FOR A HUDSON MASK AT 500 ML ASSUMING AN EtO2 OF 0.3 AND A VD:VA RATIO OF 30:70..................................................................................281

TABLE A.3 THE HUDSON MASK WITH OXYGEN FLOW RATE OF 4 L.min⁻¹ AND A Vt OF 500 ML. THE EFFECT ON EIOCcorr OF ALTERING THE VD:VA RATIO ASSUMING A CONSTANT EtO2 OF 30%. ..................................................................................................................283

TABLE A.4 HUDSON MASK AT 500 ML DELIVERING 4 L.min⁻¹ OXYGEN FLOW RATE. EFFECT OF VARYING THE EtO2 ON THE EIOCcorr IF THE VD:VA RATIO IS CONSTANT AT 30:70 ..........284
Chapter 1

Introduction

1.1 Introduction

Since the turn of the millennium there has been an increasing focus in the delivery of intensive care-type management to ward patients. Evidence that sub-optimal care prior to death or ICU admission have led to the evolution of practices which demand a greater awareness of critical illness, its recognition and treatment. It is believed that these developments will lead to better outcomes for acutely ill patients on the hospital wards.

The current strategies in use fall into broadly two types. Firstly, the recognition of critical illness or its impending appearance and secondly interventions to attempt to treat or avert a deterioration which may prove life threatening.

1.1.1 Recognition

Recognition is important as it is believed that early intervention will lead to a reduction in morbidity and mortality. This belief has lead to the evolution of a variety of scoring systems to rapidly detect the acutely unwell patient on the ward.

1.1.2 Intervention

Acute interventions in this group of patients remain relatively limited. The techniques used are intended to stabilise physiology whilst further diagnostic and curative
strategies are employed. Essentially they remain oxygen delivery, non-invasive ventilatory support, fluid resuscitation, medical investigation e.g. arterial blood gas analysis, invasive monitoring and, in some centres, vasoactive circulatory support. One less obvious ‘intervention’ is the recognition that significant deterioration in condition is part of a non-salvageable situation. This leads to discussion and completion of a ‘do not actively resuscitate’ (DNAR) order.

Overseeing the greater part of these practices are the novel Critical Care Outreach Teams (CCOTs), Medical Emergency Teams (METs) or Patient-At-Risk teams (PARTs). They are the interface between the ICU and the wards and are increasingly employed by National Health Service (NHS) hospitals to perform or supervise the above.

The zeal with which the adoption of such strategies has been embraced has little strong evidence. The use of these teams has been studied but only in a relatively small number of studies. Less attention, almost none has been focused on the interventions employed. Most commonly the evidence cited is literature gleaned from sources dissimilar to the scenarios commonly seen in ward patients. This produces several questions: Are acute interventions used on the wards employed appropriately? Does critical illness change their effectiveness? Should such interventions be adjusted in this heterogenous patient group? Are there further developments which can be employed to improve their delivery?

The introduction to this thesis will discuss early recognition and means of intervention by teams to set the scene for studying what those teams do in practice once alerted to a problem. This thesis aims to address the interventions actually used in greater or lesser part. To do the subject justice there needs to be context
and so firstly the current evidence for initial care of the acutely ill ward patient and how this has evolved in recent years will be reviewed. The development of scoring systems and then of intervention teams will be discussed. This will lead to the questions asked by this thesis which are how the specific interventions then employed actually work.

The null hypothesis is that: "Some of the interventions employed by outreach teams in the wards do not work as they are intended". To achieve this end a series of in vitro and in vivo studies examining methods of oxygen delivery and fluid resuscitation; how they are delivered; whether the current modes of delivery are effective and whether their delivery conveys morbidity that could be improved upon.

This chapter now summarises the current evidence for assessment and intervention in the acutely unwell ward patient.

1.2 Sub-optimal care leads to increased mortality

1.2.1 Evidence

It is believed that on admission to ICU, patients referred from the general wards have often received sub-optimal care. To look more closely, McQuillan et al. Studied 100 patients admitted to two intensive care units (ICU) in UK district general hospitals.

The care received immediately prior to admission was assessed by two independent clinicians. Adequacy of the management of airway, breathing, circulation, oxygen therapy and monitoring were graded on a linear analogue score. The results demonstrated agreement between the two assessors that 20% were well managed and 54% of
patients received sub-optimal care prior to admission. More patients received sub-optimal care before admission to ICU in the intensive care non-survivors group (26/37, 70%), than in the survivors group (28/63, 44%) (p=0.04). 39% of patients had been admitted late in their clinical course. They concluded that sub-optimal care had definitely contributed to morbidity or mortality in 32.5%, probably in 21% and possibly in 32.5%. This important study was one of the first to critically appraise the influence of pre-admission care on ICU mortality. Other studies have shown similar results. Mcgloin et al. performed a similar study and found a highly significant increase in mortality in the group receiving sub-optimal care\(^2\). It would be fair to say that improvements in monitoring and clinical care of ward patients are important. It is also possible to hypothesise that such improvements should lead to a reduction in ICU admissions and mortality.

This need for better ward care has led to the establishment of two important innovations over the last decade:

1. Early warning scores to identify the patients at risk.
2. Critical Care Outreach Teams (also known as METs, PARTs etc.) to implement curative activity through a relatively limited panoply of interventions.

### 1.3 Early Warning Scores

Early warning scores (EWS) are designed to identify and monitor ward patients who are, or may become critically ill. They usually summarise objective physiological variables, but can allow for subjective assessments such as concern by nursing staff. Single scoring values can be weighted appropriately to define a patient as critically
unwell. The sum of multiple physiological values can be also be used as such a tool. Repeated measurement of a score provides a method of following improvement or deterioration in the patient’s physiology. The key aspect of these scoring systems is that they provide a trigger to a predefined response. This response is aimed at producing prompt and targeted intervention to prevent further deterioration and to effect clinical improvement.

1.3.1 Physiological variables and Outcome

Physiological abnormality is associated with poor outcomes. Critical care uses a variety of physiological models to predict outcome e.g. APACHE II\(^3\), Simplified Acute Physiology Score\(^4\) (SAPS II), Mortality Probability Models\(^5\) (MPM II). Highly abnormal physiological values when processed through these models predict poor outcome. Patients who suffer in-hospital cardiac arrest demonstrate abnormal physiological values in the hours prior to the event\(^6,7\). The same is true for those who die on the wards\(^8,9\). Goldhill \textit{et al.} described the physiological values in ward patients over the preceding 24 hours prior to ICU admission\(^10\). They demonstrated that simple physiological markers such as heart rate, respiratory rate, oxygen saturations (SpO\(_2\)) are commonly measured within this period and are often abnormal signifying significant critical illness. In subsequent work the same workers described how there is a direct relationship between the number of physiological abnormalities and mortality\(^11\). On a single day they recorded the following physiological markers for 433 inpatients:
- Age
- Respiratory rate
- Heart rate
- Systolic pressure
- Temperature
- Oxygen saturation
- Inspired oxygen.
- Level of consciousness
- Urine output for catheterised patients

They then followed them up for 30 days with death as the primary endpoint. 26 patients died during the 30 day follow-up period. Of those 26, mortality increased with the number of physiological abnormalities. (0.7%: no abnormalities, 4.4%: 1 abnormality, 9.2%: 2 abnormalities and 21.3%: 3 or more abnormalities, p<0.0001).

They also observed that those patients that die are older and have been in hospital longer than those that survive\(^{12}\). Hospital mortality rose from 47.1% to 67.2% for ICU patients admitted after more than 3 days hospital admission. This is intuitive as such patients are likely to have clinical reasons for remaining in hospital. Indeed it could be argued that these reasons not only puts a patient at greater risk of acute deterioration, but also that the potential for recovery is lower.

The clear relationship between abnormal physiological values and in-hospital mortality should permit early detection of incipient deterioration and lead to an option to intervene promptly in an attempt to arrest the process. It is rare for patients to die, require cardiopulmonary resuscitation or be admitted to ICU as an emergency.
without abnormal physiological values. Thus measuring these values, an early warning score or can be developed.

1.3.2 History of Early Warning Scores

Morgan et al first described a physiologically-based early warning score designed to identify critically ill ward patients (Table 1.1)\textsuperscript{13}. Variations of this or the Modified Early Warning Score (MEWS) are commonly used as scoring systems in the UK. As can be seen from Table 1.1, zero points are awarded for normal physiological values. More points are awarded to increasingly abnormal variables. The results are totalled to give the score. These total scores are then used as triggers to an appropriate response. The nature of that response shall be discussed later.

This early version of an early warning score has been updated and modified by various authors, each adjusting their scoring system to incorporate other physiological variables and/or varying the emphasis each variable has within an aggregate scoring system. Other writers choose a single parameter scoring system, where no summation is performed. Of the several stipulated variables, a trigger is made when one or more reaches a predetermined ‘extreme’. In a recent review by the Intensive Care Audit and Research Centre (ICNARC), of 35 papers pertaining to early warning scores, 25 different tools were described. 13 utilised a single parameter method, 11, aggregate scoring systems and one described a multiple parameter method similar to the single tool, but requiring at least two or more variables to be abnormal\textsuperscript{14}. It is clear that there are many early warning scores in circulation.
1.3.3 Validation

Assessment of these early warning scoring systems is important in order to validate their use. They must be sensitive enough to distinguish those that require a response, from those that do not. This is not only important from a resources point of view, i.e. avoiding inappropriate calls to a patient that has a low probability of deterioration or ICU admission, but also avoiding undue confusion or stress to the patient concerned. It is interesting that 25 systems have been described, implying therefore that not one system is applicable to all. Indeed the emphasis put on each of the physiological variables included may differ depending on the nature of the patient group or the environment in which they are cared for. However, a recent report by the Royal College of Physicians into acute medicine recommends the

Table 1.1 Early Warning Score (EWS) after Morgan et al.\textsuperscript{13}

<table>
<thead>
<tr>
<th>Score</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate: Beats per minute</td>
<td>≤40</td>
<td>41-50</td>
<td>51-100</td>
<td>101-110</td>
<td>111-130</td>
<td>≥130</td>
<td></td>
</tr>
<tr>
<td>Systolic Blood Pressure: mmHg</td>
<td>≤70</td>
<td>71-80</td>
<td>81-100</td>
<td>101-199</td>
<td>≥200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate: breaths per minute</td>
<td>≤8</td>
<td>9-14</td>
<td>15-20</td>
<td>21-29</td>
<td>≥30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature: °C</td>
<td>≤35</td>
<td>35.1-36.5</td>
<td>36.6-37.4</td>
<td>≥37.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system: AVPU</td>
<td>A</td>
<td>V</td>
<td>P</td>
<td>U</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
adoption of one early warning score across the National Health Service (NHS); the so-called NHS Early Warning or NEW score. Interestingly the National Institute for Health and Clinical Effectiveness (NICE), whilst endorsing the use of early warning scores were unable to recommend either the NEW score or another version for the NHS in general.

Validation of early warning scores has been undertaken by several authors. Hodgetts et al. examined physiological variables of 118 patients who suffered cardiac arrest compared to 132 controls and then formulated activation criteria for a MET. This system incorporated the eight variables that had been identified as significantly different between the two groups, namely: increased respiratory rate, new shortness of breath, low SpO₂, abnormal heart rate, chest pain, low systolic blood pressure, abnormal temperature and the subjective concern of a doctor or nurse. An expert panel weighted the scores depending on the odds ratio for cardiac arrest thus developing the cumulative scoring method to activate the MET. Applying this system to the patients in the study, they demonstrated that a score of 8 on their scale was associated with a sensitivity of 52% and a specificity of 99% for cardiac arrest. Lower scores of 5-7 demonstrated a sensitivity of 84% and specificity of 89%. However, they choose not to use this level as an MET activator. It is inferred that resource limitations prevented the MET team from attending all such patients, though they do not comment on the likely burden that such a commitment would have incurred. They chose cardiac arrest as the endpoint, but did not comment on ICU admission in both groups. This study was retrospective and of a small number, however it was the first attempt to derive a scoring system from clinical data, rather than others that have been subjectively derived from clinical experience. Problems with this approach are highlighted by the presence of three different aspects of blood
pressure change within the scoring system. All ‘necessarily’ included as each was demonstrated to be independently associated with cardiac arrest; but significantly adding to the complexity of scoring in any given patient. Simplicity of assessment, calculation and recording are important in the success of these systems in stimulating the appropriate response to clinical change. Burdensome complexity is likely to lead to poor documentation and reduce the scoring system’s effectiveness in defining those in need.

Subjective systems have also been assessed for their validity in identifying patients who suffer cardiac arrest, are admitted to ICU or die\textsuperscript{7, 11, 18, 19}. Though methodologically different, they all reiterate the importance of monitoring physiological variables to detect patients at risk of deterioration. The ICNARC systematic review of early warning scoring in 2007 looked at datasets obtained from 31 of 92 UK hospitals that collected data from their early warning scoring\textsuperscript{14, 15} systems were identified and the data was analysed based on the composite endpoints of death, admission to ICU, DNAR orders and cardiac arrest – the ‘presence of established critical illness’. These endpoints occurred between 5.7% and 64.7% of patients, depending on hospital. Median sensitivities were low 43% (inter-quartile range 25.4–69.2) with median positive predictive values of 36.7% (inter-quartile range 29.3 – 43.8%). Median specificity was 89.5% (inter-quartile range 64.2–95.7%) with a negative predictive value of 94.3% (inter-quartile range 89.5 – 97.0%). This implies that none of the early warning systems achieved the requirements of a level 1 clinical decision rule. Such a rule is defined as ‘that which has been validated for use in a wide variety of settings with confidence that it can change clinical behaviour and improve patient outcomes’\textsuperscript{20}. This appears disappointing, however the sample sizes were small and not all the possible outcomes comprising the composite
outcomes were recorded. There is no data on response to a trigger and/or any interventions. This would introduce significant bias.

Nevertheless, most clinicians would agree that early warning scores have value in identifying patients at risk. They increase the awareness of critical illness amongst clinical staff and permit a closer working relationship between those with appropriate skills in the care of such patients. They are thus an advance on what was previous practice. Early warning scores are valuable in themselves, but it is their synonym, ‘Track and Trigger Scores’ that crystallises their clinical use. The appropriate response to an abnormal score is their value and the nature of that response is now discussed.

1.4 Early intervention improves outcome

1.4.1 Early Goal Directed Therapy

Having identified those as critically ill, or at risk of developing critical illness, institution of clinical management is the next step. There is now strong evidence that early aggressive management of certain patients with abnormal physiological variables improves outcome. Almost no work has been published from the ward environment. However information can be extrapolated from other areas. The most well conducted trial to evaluate this has been conducted in the Emergency Room of an American tertiary referral centre. Published in 2001, Rivers et al. recruited 263 patients with septic shock and randomised them to receive standard care or ‘early goal-directed therapy’ (EGDT). Septic shock was defined as, two of four criteria of the systemic inflammatory response (Table 1.2) and either a blood pressure below 90mmHg after 20-30 ml.kg⁻¹ crystalloid resuscitation or a blood lactate concentration
of ≥4 mmol.l\(^{-1}\). Both groups received arterial and central venous cannulation.

Thereafter, the standard care group were managed at the clinician’s discretion, with or without critical care consultation and were admitted to the next available inpatient bed. The EGDT group had their central venous oxygenation (ScvO\(_2\)) measured by spectrophotometry and were treated for at least 6 hours in the emergency department prior to transfer to the intensive care unit under the care of the critical care physicians. Their haemodynamics were managed by a strict protocol based on measurements of central venous pressure (CVP), mean arterial pressure (MAP), Lactate and ScvO\(_2\) (Figure 1.1).

Table 1.2 ACCP/SCCM Consensus Conference Definition of the Systemic Inflammatory Response Syndrome.\(^{21}\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>≤ 36(^{\circ})C or ≥ 38(^{\circ})C</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>≥ 90 beats per minute</td>
</tr>
<tr>
<td>Respiratory</td>
<td>≥ 20 breaths per minute or PaCO(_2) ≤ 32 mmHg</td>
</tr>
<tr>
<td>White Blood Cell Count</td>
<td>≥ 12,000 cells.mm(^{-3}) or ≤ 4000 cells.mm(^{-3}) or &gt;10 % bands</td>
</tr>
</tbody>
</table>
The results showed well matched groups with a predominance of pneumonia and urosepsis. The EGDT group demonstrated a more rapid improvement of MAP, ScvO₂, pH, base deficit, and serum lactate. The appearance of multi-organ dysfunction syndrome was less at 72 hours, and most remarkably of all mortality was reduced from 61% in the standard care group to 40% in the EGDT group at 28 days (RR 0.58 95% CI 0.39-0.87: p=0.01). Mortality was also significantly different at 60
days, standard care 70%, EGDT 50% (RR0.67 95% CI 0.46-0.96: p=0.03). The patients in the EGDT group received significantly more fluid, red cell transfusions and inotropic support during the initial 6 hour period. However in the ensuing 7-72 hours the standard care group received significantly more fluid, red cell transfusion, vasopressor support and a greater incidence of mechanical ventilation. The total fluid requirements were similar for the 72 hour period of study from recruitment (p=0.73) as was the use of inotropic agents (p=0.15).

This study has had a large impact on the care of critically unwell patients with septic shock. This is interesting as previous studies had not been able to show significant benefits of goal-directed therapy in the ICU environment. Gattinoni et al were unable to demonstrate a difference in mortality between three groups of general adult intensive care patients. The first group had treatment aimed at a normal cardiac index, the second a 'supra-normal' cardiac index and the third to maintain the mixed venous oxygen saturations at >70% (or a difference of <20% with arterial oxygen saturation). Whilst this is not a direct comparison with Rivers et al. in methodology or patient groups, the mortality rate was similar for the normal cardiac index group. This was achieved in 94.3% of patients within 6 hours of randomisation, which was encouraged as soon as possible after meeting the inclusion criteria (Simplified Acute Physiology Score (SAPS) of >11). This study only adds to the evidence that monitoring and aggressive manipulation of the cardiovascular system in critical illness to optimise haemodynamic variables can lead to an improvement in survival, but the need to increase haemodynamics and oxygen delivery to above normal levels does not confer any benefit. A phenomenon also detected by Hayes et al. who found supra-normal physiology to be potentially detrimental.
Physiologically, goal-directed therapy is likely to improve outcome by the restoration of oxygen delivery to the tissues via control of hypovolaemia and the restoration of appropriate haemodynamics. Early delivery of care prevents the progression of the pathological processes involved in shock and aims to head off the associated cellular and thus organ dysfunction, whilst curative strategies such as surgery or antibiotics facilitate cure. Rivers et al. accentuates the need for a rapid response to the development of shock, which as an endpoint prior to cardiac arrest can be detected and potentially reversed improving survival. However, as shall be seen in section 1.4.3, there has been a desire amongst the acute medicine community to embrace the findings of Rivers et al. and then extrapolate its methodology to all those patients with deranged haemodynamics and resultant shock.

It is important to note that patients were recruited in the emergency department of a large tertiary referral hospital soon after hospital admission. The subjects also had a specific diagnosis (septic shock) to account for the deranged physiology. The interventions are therefore specific to this patient population in a relatively high-tech environment. It has not been proved that a similar approach could be extrapolated to the care of the ward patient, with a wide range of potential problems particularly if the deterioration may occur at any time over several days from admission. Early identification, a specific diagnosis, a high concentration of staff and technology are all less obvious in the ward. An early warning score may identify the a ward patient as suffering similar physiological embarrassment as a subject in the Rivers et al. paper, but should it receive the same response? This is not clear.
1.4.2 Impact of Critical Care Skills

In the Rivers et al. study, the patients in the EGDT group were cared for by intensive care physicians on an intensive care unit. Whilst it is likely that the benefits of EGDT are due to the interventions dictated by the protocol, some benefit may be derived from the skills and training of the medical staff. There is evidence that the environment in which septic shock is detected and initially treated affects outcome. Lundberg et al. published a small retrospective study of 41 patients with septic shock and related their outcome to their location when the shock first developed\textsuperscript{25}. 10/41 patients developed septic shock on the wards with a mortality of 70% at 28 days. 12/31 (39%) of the patients developing septic shock in the ICU died (OR 3.76 p=0.17). Interestingly the ICU patients had higher APACHE II scores and were older yet more survived. Though there were large differences in median time to first fluid bolus (15 mins ICU vs 27 mins ward), median time to vasoactive support (22.5 mins vs 310 mins) and a median delay of 67 minutes for admission to ICU from the ward, none of these factors proved to be significant predictors of mortality in univariate analysis. The study is clearly flawed by its small size, retrospective nature and also the patient groups examined did not reflect common patterns of infection (33% of ward patients had fungaemia). However it may suggest that the closer monitored, highly skilled ICU environment could confer an advantage in detection and treatment of septic shock above that of the ward environment. It is certainly a belief that underpins some ICU admissions, though not only those that are suffering septic shock: “They’ll be in a better environment if they go off”.

It is true that the ICU has physicians and nursing staff skilled in the care of the critically ill. There is more frequent monitoring of vital signs and other modes of assessment of haemodynamics. In contrast, general ward patients do not receive the
same level of such assessments and monitoring. This is likely to result in a
difference in the time to detection of shock onset. This is crucial as it is established
that prolonged periods of hypoperfusion of the major organs gives rise to multiple
organ dysfunction and/or failure with an associated higher rate of morbidity and
mortality\textsuperscript{26, 27}.

The common threads of early detection, early goal-directed therapy and appropriate
environment and monitoring, has bred a desire to develop protocols/guidelines to
care for all patients at risk or displaying signs of critical illness. They combine the
evidence for early warning scores and early intervention, most often Rivers \textit{et al.} as
a standard of care. Many of the patients for who the guidelines/protocols are
designed would not fit those described either by the literature surrounding early
warning scores, or Rivers \textit{et al.} However as an example I present the most widely
accepted example to date.

1.4.3 \textit{The Surviving Sepsis Campaign Guidelines}\textsuperscript{28, 29}

These guidelines were published by in 2004 and updated in 2008 following the
Barcelona Declaration of 2002\textsuperscript{27, 30}. This stated the world-wide aim to affect a 25%
relative reduction of mortality from sepsis in five years. Constructed using the Delphi
method of categorising scientific evidence and input from consensus conferences,
professional bodies and expert opinion, it delivers a set of evidence based guidelines
as ‘an international effort to increase awareness and improve outcomes in severe
sepsis.’ It recognises the significance of severe sepsis on mortality and morbidity;
that improvements can be made by ‘protocolisation’ of care; and though severe
sepsis is most commonly treated in the ICU, the paper makes the point that ‘… the
committee believes that currently, the greatest outcome improvement can be made
through education and process change for those caring for severe sepsis patients in
the non-ICU setting and across the spectrum of acute care...’. However further
discussion of what a non-ICU environment is, is sadly lacking. Would this just mean
other acute care settings such as the Accident and Emergency department,
operating theatres etc.? Or would it even apply to the longer term inpatient, General
Practice etc.?

The recommendations are extensive; however the initial resuscitation phase is
based entirely on the Rivers et al. data. Within 6 hours a patient needs to have been
resuscitated with intravenous fluid with or without inotropic support aiming for a
central venous pressure (CVP) of ≥ 8 mmHg, a MAP of ≥ 65 mmHg and an ScvO₂ of
≥70% and to use dobutamine if the above are not achieved. They also suggest
considering the use of vasopressors, corticosteroids and activated Protein C as part
of cardiovascular support. In the sections under diagnosis and antibiotic therapy the
guidelines recommend that suitable diagnostic cultures should be performed and a
first dose of antibiotics should be given within the first hour of diagnosis of severe
sepsis. This recommendation is based predominantly on a study by Kumar et al. in
which the data from 2731 patients with septic shock were retrospectively analysed.³¹
2154 patients received antimicrobial therapy and of those that were given a dose
within one hour of the onset of hypotension 78.9% survived to hospital discharge.
Each subsequent hour’s delay over the following 6 hours conferred a mean increase
in mortality of 7.5%. There are other recommendations within the surviving sepsis
campaign, but those highlighted here once again demonstrate the need for early
detection of severe (critical) illness and its early and appropriately monitored
treatment. However the paucity of good evidence in this field means that the
guidelines are limited to one or two trials and significant consensus opinion from
predominantly intensive care specialists. The guidelines may be valuable, but how
applicable to all patients across the spectrum of healthcare is questionable. Yet in many UK general hospitals they have been accepted as the standard of care for all patients ‘unwell’ with evidence of infection and frequently form the basis for the resuscitation of other patient groups. Once again this highlights the need to examine the specific interventions used in the far less clearly defined circumstances of the hospital general ward.

1.5 Medical Emergency and Critical Care Outreach Teams

If it is agreed that early detection and intervention is beneficial, a method is required to deliver this approach. Goldhill et al. demonstrated that the current ward environment cannot convey this intensity\(^\text{10}\). The large resource burden and potential hazards of ICUs prevent all patients being admitted to such high level environments. Thus novel techniques have evolved; in particular the MET/CCOT model.

In the UK and most developed nations the intensive care unit is usually centralised within a hospital, utilising a great deal of healthcare resource for a relatively small number of patients when compared to the total number within the institution. This ‘Ivory Tower’ concept, in which a salvage team attends from the ICU, removes a critical care patient (often \textit{in extremis}) from the ward, Accident and Emergency department etc. and returns to the unit from which they came, is easily recognisable. The patient is then cared for and, if they survive, returns to the ward area ‘fixed’ with little or no follow up or support for either medical or nursing staff.

A new ‘without walls’ model in which there is transfer of critical care knowledge, skills and technology to the general ward environment has evolved over the last two decades. This aims to improve the early recognition of critical ill patients and attempt
intervention to prevent clinical deterioration and ICU admission. If ICU admission is unavoidable then this model aims to ensure timely transfer. This ward-based support is in place to oversee the delivery of medical interventions which may be more usual in a level 2/3 environment (Table 1.3). What can be achieved on the wards in such a model is that which this thesis will attempt to examine more closely.

<table>
<thead>
<tr>
<th>Level of Care</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 0</td>
<td>Patients whose needs can be met through normal ward care in an acute hospital.</td>
</tr>
<tr>
<td>Level 1</td>
<td>Patients at risk of their condition deteriorating, or those recently relocated from higher levels of care whose needs can be met on an acute ward with additional advice and support from the critical care team.</td>
</tr>
<tr>
<td>Level 2</td>
<td>Patients requiring more detailed observation or intervention including support for a single failing organ system or postoperative care, and those stepping down from higher levels of care.</td>
</tr>
<tr>
<td>Level 3</td>
<td>Patients requiring advanced respiratory support alone or basic respiratory support together with support of at least two organ systems. This level includes all complex patients requiring support for multi-organ failure.</td>
</tr>
</tbody>
</table>
A second aspect of clinical care is post-ICU care to ensure safe discharges and in so doing reduce the risk of re-admission to the ICU. Readmission to ICU is associated increase in risk of mortality as demonstrated in a systematic review by Rosenberg et al. in 2000\textsuperscript{32}. This group demonstrated that the mean readmission rate in both Europe and the USA is approximately 7\% (range 4-14\%) and that mortality in these patients is between 2 and 10 times that of patients who survive ICU without readmission. This novel approach to critical care outside of the ‘Ivory Tower’ is commonly referred to as critical care outreach (CCO).

1.5.1 History of Critical Care Outreach

Historically CCO evolved from the METs developed in Liverpool, New South Wales, Australia by Hillman and colleagues from 1989 and more widely distributed through Australia in the 1990s\textsuperscript{34}. In this guise a team containing senior medical and nursing staff from critical care are available to be called by any member of the hospital staff when a trigger is reached, or if they were otherwise concerned. The team will then attend and intervene as appropriate. However akin to a cardiac arrest team, the team will disperse once the initial crisis has been managed and the ongoing responsibility will return to the attending physicians after a joint decision is made as to their ongoing care. On the other hand if the patient requires critical care then appropriate arrangements are made.

In the United Kingdom a similar system has evolved, namely the Critical Care Outreach Team (CCOT). Born out of the Audit Commission’s document ‘Critical to Success’ in 1999, development of CCOTs was recommended as high priority within acute hospitals\textsuperscript{35}. The report recognised that there were organisational and
economic imperatives for the development of CCOTs in addition to the clinical indications. What was not discussed was what these teams should do in the way of meaningful intervention.

1.5.2  *Evolution of Healthcare Practice*

Changes in working practices and levels of staffing, particularly amongst the medical staff, were recognised as contributory to the shortcomings of ward care\(^ {35}\). It was observed that a junior doctor in 1999 could be responsible for up to 100 ward patients and that the care they could expect to deliver would likely be reactive rather than proactive. Medical training has changed since that time. The introduction of firstly Calman, and subsequently ‘Modernising Medical Careers’ run-through training, both emphasising shorter training times and earlier specialisation, are believed to be compromising exposure of trainee doctors to the acutely unwell and their ability to recognise and treat\(^ {36-40}\). Furthermore the reduction in working hours required by the European Working Time Directive reduces education time, fragments the medical team and can lead to organisational difficulties particularly regarding medical handover. The potential problems for continuity of care are great and have been recognised by both the Royal College of Physicians and the National Institute for Health and Clinical Excellence\(^ {15, 16}\).

Hospitals are also evolving driven mainly by economic imperatives. The NHS organisation was once many local hospitals, but now there is increasing centralisation of acute hospital services within larger communities. Ambulatory care, primary care and care in other institutions now takes the greater part of chronic and some acute disease management\(^ {36, 41, 42}\). This leads to a greater concentration of


critically ill patients within the acute hospital requiring greater use of critical care services. However the cost of level 3 care is such that enormous expansion of such services is not feasible and so other ways of maintaining a level of care for the critically unwell needed to be developed.

1.5.3  The UK Critical Care Outreach Model

The principles of UK CCOTs were laid out in the Department of Health document Comprehensive Critical Care: A review of adult critical care services in 2000. CCO services had 3 key aims:

1. **To avert admissions** by identifying patients who are deteriorating and either helping to prevent admission or ensuring that admission to a critical care bed happens in a timely manner to ensure best outcome.

2. **To enable discharges** by supporting the continuing recovery of discharged patients on wards and post discharge from hospital, and their relatives and friends.

3. **To share critical care skills** with staff in ward and the community ensuring enhancement of training opportunities and skills practice and to use information gathered from the ward and community to improve critical care services for patients and relatives.

Since that time inclusion of research and audit as well as post-hospital discharge care/clinics have also fallen into the remit of CCOTs. In short by exporting ICU capability to the ward, the CCOTs aim is to reverse over-reliance on the ICU team to remove a critical care problem. In contrast they attempt to engender a ‘can do’
attitude to the general ward staff by supporting, educating and training, as well as delivering care for the critically ill patient using their own skills and attributes.

CCOT development was initially funded centrally, such was the political desire to see it introduced. With only the above principles espoused, it was left to individual trusts and critical care networks to develop their own services. Guidelines on the introduction of CCOTs were published by the Intensive Care Society (ICS) and in terms of membership of the CCOT, they recommended that:

- Medical input should comprise of sessions by critical care consultants and trainee medical cover for critical care with no other responsibilities to the ICU itself.
- Nursing input should consist of critical care nursing staff, with a possible lead role for a nurse consultant or clinical nurse specialist, supported by other appropriately trained nurses.
- Physiotherapy and other allied health professions such as Speech and Language therapists may also be included in the team.

The ICS also recommended that CCOTs should operate 24 hours a day as emergencies do not respect working hours, but they also recognised that recruitment, and funding may prove difficult in the initial stages.

In 2005, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) published the report ‘An acute problem?’ This examined the care of acute medical ICU admissions in the UK excepting Scotland. They identified 261 hospitals in the England, Wales and Northern Ireland with level 3 adult beds. 226 hospitals participated in a survey via posted questionnaires. They retrospectively looked at the pre-admission care received by all the adults admitted to general ICUs.
in June 2003. Three questionnaires were sent, one to the referring physician, one to the admitting ICU consultant and an organisational questionnaire to each hospital. It reaffirmed the appearance of abnormal physiological variables in the hours preceding deterioration and whilst 73% of trusts used early warning scores, instructions for parameters triggering patient review were rarely documented. Consultant involvement, both before and after admission to ICU was low, with 57% of ICU referrals being made without a consultant physician knowing. In terms of CCOTs, the report documented that 44% of the UK hospitals that responded did not provide outreach service and there was geographical inequality in its provision. The hospitals failed to show any improvements in early recognition and intervention in critically ill patients and there was no difference between hospitals with or without CCOTs in the appropriateness or timeliness of admission to ICU or ICU mortality. This report is subjective and retrospective, so it is difficult to draw any strong conclusions about the results. It did demonstrate that outreach provision had not been ubiquitously entertained by all despite its support from both government and professional bodies. In 2007, McDonnell et al. published another survey of implementation of outreach services in England performed in 2005. They received replies from 191/239 (79.9%) hospitals. CCOTs had been established in 72.8% of respondents, but interestingly, had been discontinued in 13.7% of the hospitals without CCO services. Lack of funding was the prime reason (6/7). The survey demonstrated that whilst 33.8% of hospitals with outreach services provided 24 hour telephone ‘hotline’ advice, only 14.5% provided direct bedside support on the same basis. 71.1% of CCOTs had no medical consultant input, generally being nurse-led with only 34.9% having a nurse consultant lead and 41% having no H or I grade
nurse involvement. Despite this, 62.2% of outreach teams reported independently delivering care. The nature of these interventions are summarised in Table 1.4.

Table 1.4 Interventions Performed or Recommended by Critical Care Outreach Staff (after McDonnell et al.)

<table>
<thead>
<tr>
<th>Critical care outreach activity</th>
<th>Perform Activity</th>
<th>Recommend activity</th>
<th>Perform and recommend activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations, e.g. venopuncture, CXR</td>
<td>39.1%</td>
<td>29%</td>
<td>31.9%</td>
</tr>
<tr>
<td>Change in patient position</td>
<td>56.9%</td>
<td>5.1%</td>
<td>38.0%</td>
</tr>
<tr>
<td>Changes in oxygen therapy</td>
<td>54.3%</td>
<td>5.8%</td>
<td>39.9%</td>
</tr>
<tr>
<td>Initiation of noninvasive ventilation</td>
<td>27.1%</td>
<td>48.1%</td>
<td>24.8%</td>
</tr>
<tr>
<td>Changes in fluid management</td>
<td>20.4%</td>
<td>49.6%</td>
<td>29.9%</td>
</tr>
<tr>
<td>Initiation of blood/colloid transfusion</td>
<td>19.0%</td>
<td>66.4%</td>
<td>14.6%</td>
</tr>
<tr>
<td>Initiation of vasoactive infusions</td>
<td>3.4%</td>
<td>86.2%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Adjustment to medication</td>
<td>3.8%</td>
<td>84.7%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Adjustment to feeding/nutrition</td>
<td>9.8%</td>
<td>78.0%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Adjustment to pain management</td>
<td>8.4%</td>
<td>75.6%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Initiation of DNAR decision</td>
<td>8.4%</td>
<td>80.2%</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

CXR, Chest X-Ray; DNAR, Do not actively resuscitate.

1.5.4 Outreach Interventions

It is clear from the table that outreach practitioners frequently perform simple adjuncts to clinical care such as improving patient position and applying oxygen therapy. 25% appear happy/free to institute non-invasive ventilation and 20% change fluid management or administer blood or colloid resuscitation. Advice is offered on what could be deemed the more ‘medical’ aspects of critical care such as vasoactive drugs and adjustments to medication, but no data is provided that
comments on the type of patient in whom such advice is offered, their immediate requirements for ongoing care and survival. There is also no reference to the types of CCOT that appear more 'free' to administer these more aggressive therapies. For example, does this group contain medical personnel within their ranks permitting direct institution of therapy without the need for referral to a doctor? These results demonstrate the general nature of most CCOTs in the UK in 2005. They are primarily nurse-led with little 24 hour or weekend cover. They perform simple clinical interventions independently, but only advise on significant escalation of patient therapy. They have a significant role in the care of the patient who is not regarded as likely to benefit from increased levels of care as evidence by their input into DNAR orders. Indeed the stratification of the ward patient in to those in whom an aggressive treatment strategy or a more palliative approach seems to be a major input from CCOTs.

1.6 Evidence for Critical Care Outreach
The enthusiasm for the establishment of CCOTs in UK hospitals, the relatively haphazard way in which they were introduced and the large variability in staffing, service and function, makes assessment of their utility difficult. It would be almost impossible and potentially unethical to begin a randomised controlled trial at the point of introduction, and as such most of the studies that have looked at outcomes of patients attended by a CCOT have been observational, retrospective with historical controls.
1.6.1 Reduction in Cardiac Arrest Rate

Buist et al. were the first to report the effect of the introduction of a MET to teaching hospital. The non-randomised study compared 22847 medical admissions to 19317 historical controls after the introduction of a MET. The end points were the incidence and mortality from unexpected cardiac arrest. They demonstrated that the introduction of a MET significantly reduced unexpected cardiac arrest from 3.77 per 100 admissions to 2.05 per 1000 admissions. Mortality was also reduced from 77% to 55%. This constituted an odds ratio for cardiac arrest of 0.50. (95% confidence interval (CI): 0.35-0.73). They concluded that in clinically unstable inpatients early intervention by a medical emergency team significantly reduces the incidence of and mortality from, unexpected cardiac arrest in hospital. However this reduction in unexpected cardiac arrest was largely due to the fact that the MET was able to anticipate futility and were able to place do not resuscitate orders. The study also showed an increase in unplanned admissions to the ICU after the introduction of the MET, although the statistical significance of this result was not stated. It is unclear what interventions apart from DNAR orders were key to these results.

1.6.2 Reduction in Readmission Rate

Ball et al. performed a similar study of patients versus historical controls in a UK teaching hospital after the introduction of a nurse-led CCOT. Available only 12 hours a day and operationally limited to the care of those patients discharged from the ICU, they demonstrated a borderline increase in survival to hospital discharge following introduction of the CCOT (risk ratio 1.08 (95% CI: 1.00 – 1.18)) and a significant reduction in ICU readmission rate (risk ratio 0.48 (95% CI: 0.26 – 0.87)).
However it is important to note that this reduction brought the readmission rate back to the national average of 8%.

Garcea et al. also published a retrospective, before and after, study for surgical wards\textsuperscript{48}. With a similar remit to the Ball group, they demonstrated a reduction in critical care mortality from 14.3\% to 9.8\% following the introduction of the CCOT as well as a reduction in readmission rates. In-hospital mortality also fell from 9.3\% to 4.8\%. Though they could not demonstrate a causative factor that had led to the improvements seen and tentatively concluded that the introduction of outreach teams has a favourable impact on mortality and readmission rates. Thus it would appear that nurse-led CCOTs charged with follow-up of patients discharged from ICU improve outcomes when compared to historical controls. However these two studies say little of those patients referred \textit{de novo} to the outreach service. Again, the interventions themselves are unclear.

1.6.3 \textit{Cost-effectiveness}

Bellomo \textit{et al.} performed a prospective, controlled, before and after trial examining the introduction of a MET to a large teaching hospital\textsuperscript{49}. The team evaluated and treated any surgical patient deemed to be at risk of developing an adverse outcome by nursing, paramedical or medical staff. They concluded that the introduction of the MET was associated with a significant reduction in the number of adverse events (relative risk reduction 57.8\%, $p<0.001$), post-operative mortality (relative risk reduction 36.6\%, $p=0.018$) and mean duration of hospital stay (23.8 to 18.9 days, $p=0.009$). This translated to an economic saving with an estimated decrease in hospital stay of nearly 12000 bed days per year. The authors acknowledged that the
decrease in adverse events was only partly due to the interventions performed by the MET, and that increased awareness of the signs of physiological instability by the very introduction of the MET had improved care. It is also important to point out that these were post-operative surgical patients likely to have less co-morbidity as their medical counterparts.

1.6.4 In-hospital Mortality

Mortality data in a similar study comes from Bristow et al. This group published a prospective cohort comparison between three similarly sized hospitals in Australia\(^{50}\). In one hospital the cardiac arrest team was replaced by a MET while it was retained at the other two. The study demonstrated a reduction in unanticipated ICU admissions in the hospital with the MET team (case-mix-adjusted odds ratios: Hospital 1, 1.00; Hospital 2, 1.59 (95% CI: 1.24-2.04); Hospital 3, 1.73 (95% CI, 1.37-2.16), however there was no difference in cardiac arrest rates or in-hospital death rates between the hospitals. This lack of mortality benefit seen in this study was different from that of Priestley et al. who studied the phased introduction of a CCOT in the UK over a 32 week period\(^{51}\). They demonstrated that the introduction of a CCOT in a single institution reduced in-hospital mortality in wards where it operated compared to those where it did not (odds ratio 0.52 (95% CI: 0.32 – 0.85).

1.6.5 The MERIT Study

To date the best available evidence of the effect of outreach services comes from the publication of the MERIT study in 2005\(^{52}\). In his large multicentre study 23 hospitals without previous METs or CCOTs were randomised to have a MET service introduced (n=12), or to be controls (n=11). Over a period of four months an
educational strategy was undertaken to prepare the study hospitals for the introduction of the MET. This included educating staff about calling criteria, identifying patients at risk and the importance of a rapid response once criteria had been met. Reminders continued thereafter. The MET consisted of the equivalence of a pre-existing cardiac arrest team with the addition of at least one doctor and one nurse from either the emergency department or the ICU. The results were disappointing. There were no differences in cardiac arrest (odds ratio 0.94 (95%CI: 0.79 – 1.13)); unexpected deaths (odds ratio 1.03 (95%CI: 0.84 – 1.28)) or unplanned ICU admissions (odds ratio 1.04 (95% CI: 0.89 – 1.21)). There were however three main flaws in the study which makes deriving these conclusions hazardous. Firstly, the study period was only six months which would mean that the study was inadequately powered. Secondly the cardiac arrest team in the control hospitals were often called to critical patients and thus acted as an informal MET. Even though far more calls were made to the MET team in the study hospital, many were felt to be inappropriate, thus not permitting this phenomenon to counter the effect of non-arrest calls in the control group. Finally, despite the rigorous education programme, the study demonstrated that even in the MET hospitals documentation and response to changes in vital signs were not adequate. Half of the ICU admissions were not reviewed by the MET team prior to their appropriate admission and the MET team was not contacted for 70% of cases that demonstrated MET calling criteria greater than 15 minutes prior to a cardiac arrest. This again demonstrates the need for appropriate responses to trigger generated by an early warning scoring system. The study did however demonstrate the effectiveness of the pre-intervention programme. The calling rate was higher in the MET hospitals (mean 8.7 per 1000 admissions versus 3.1 per 1000 admissions p<0.0001) and the
proportion of calls not associated with cardiac arrest or unexpected death was also higher in the MET hospitals (84% versus 48% p<0.0001). It can be implied that this increase in awareness is a positive effect of the trial, however the inadequacy of documentation and calling when there was evidence of physiological abnormality suggests that there is still problems with appropriateness of MET referring, and that some patients are still being missed.

1.6.6 Further Evidence

Most recently, Gao et al. published a multi-centre observational study utilising the case mix programme database collected by the Intensive Care National Audit and Research Centre (ICNARC)\textsuperscript{53}. This was linked to the data from the survey by McDonnell et al. above\textsuperscript{45}. They assessed 108 ICUs accounting for 240,884 admissions over eight years. They demonstrated that admissions from the wards had a higher ICNARC physiology score (sicker) and had higher hospital mortality 46.9% vs 32.6% when compared to all admissions. Introduction of CCOT brought about a significant reduction in cardiac arrest for ward patients within 24 hours before admission. Also the mean ICNARC physiology score was significantly decreased after the introduction of CCOTs. This is the first study to identify this as an endpoint, and it is important. It may imply that CCOT involvement may improve timely ICU admission or that direct intervention and stabilisation prior to admission improves the clinical state of a patient. It may also mean that patients with high ICNARC scores in whom critical care is futile are not admitted. However, like the MERIT study, there was no reduction in either ICU or in-hospital mortality.
Not all studies have focussed solely on patient outcomes. Baker-McLearn et al. evaluated the impact of CCOT from a staff perspective. Performing 100 semi-structured interviews with hospital staff, they reported the following. The introduction of CCOT had resulted in fewer referrals to the ICU and that the ICU felt more able to discharge patients to hospital wards. There was also a perceived improvement in links between ward nurses and medical teams, and improved morale among ICU nurses. Secondly, there was felt to be increased contact on the wards with critical care, resulting in more opportunities to share critical care skills. However, there remained concerns about the sustainability of improved skills and some respondents felt that junior doctors were becoming de-skilled.

1.6.7 Summary of the Evidence

There is a need for a novel approach to the care of the hospital in-patient who is critically ill, is deteriorating or is at risk. The evolution of early warning scores and CCO are significant steps to providing this change. However, the current evidence of their value and necessity is contradictory. Some of this disagreement may be borne out of the patient groups being examined. The greater part of the application of early warning scores and CCO is aimed at the care of the ward in-patient, rather than those during admission or following major elective surgery. These two groups are different. The A&E/surgical patient has a fixed starting point for their critical illness, and this point is easily definable. The timescale of the illness is usually short and as such more likely to be rapidly fulminant or rapidly reversible with a lower risk of mortality. In contrast the ward patient is frequently several hours or days after admission prior to CCO involvement. This is much later after the appearance of their initial condition and whilst some may become suddenly critically ill, it is likely that
they are in fact demonstrating an accelerating course of their initial illness. Either that or a second insult has occurred in a patient already weakened by prior illness. A sudden late increase in the aggressiveness of their therapy is therefore unlikely to reverse the longer processes. There is no literature to support observed EGDT in critically ill ward patients. It may be that initial resuscitation over a short period such as that described by Rivers et al. may be too short, too long or inappropriate for the patients attended by a CCOT. A 'one-size-fits-all' response to a trigger may not bring about the desired improvements in outcome and thus protocols and guidelines based only on current best evidence may be hazardous.

Stratification of those patients into those for aggressive management and those for palliation (DNAR) appears to be a strong influence on the outcome of the studies of CCO\textsuperscript{46, 52}. This may account for many of the benefits seen i.e. the reduction of readmission rates and reduction in unanticipated ICU admissions rates\textsuperscript{47, 48, 50}. The lack of reduction in cardiac arrest calls and unexpected deaths would seem to imply that the effect of CCO is more complex. While the focus of much of the literature and indeed this introduction has been on the efficacy of the teams, there is little information on what they do, how it works and whether it is of benefit; so-called interventions.

1.6.8 **CCOT Interventions**

One element that stands out in arguing for the provision of CCO is demonstrated by the ICNARC study reported by Gao et al. This concluded that the involvement of the CCOT improved the clinical state of the patient admitted to the ICU\textsuperscript{53}. Enthusiasts for CCOT and EGDT might suggest that prior to transfer, it is the immediate intervention
under the supervision of appropriately trained CCOT staff that brings about this result. This is therefore the key value of CCO to the patient. Indeed the perception of a CCOT among ward staff, as reported by Baker-McLearn et al., is of a team that performs specialised manoeuvres in addition to their own care. It is these techniques which lead to improvement in the patient’s condition either as part on an ICU transfer, or stabilisation if ICU admission is not required. However, how effective CCOT-guided interventions are at reversing acute illness in ward patients is not known, nor how they directly affect the outcome. What are these ‘interventions’ used by CCOT? In general they are remarkably limited (Table 1.4). Retention of trained nursing staff, trainee doctor expertise, lack of medical input to CCOT and limited level 1 and 2 bed availability all serve to restrict the possibilities. They can be roughly divided in to support and monitoring of the respiratory and cardiovascular systems. Their intent is to restore normal respiratory and haemodynamic function whilst curative therapies such as antibiotics, surgery, endoscopy, interventional cardiology etc. facilitate cure. The commonest interventions delivered on the wards at the Chelsea and Westminster Hospital are listed in Table 1.5.

These are simple tools used to improve the physiological variables that become abnormal and contribute to early warning scores. As such they are often employed to treat investigation results and improve their values in a ‘because we can’ fashion. Little is known about how these interventions perform in the sphere of ward-based critical illness. Do we fully understand the interactions between patients and even the simplest supportive measures? How they are deployed in this environment is also unclear. Are they being used appropriately in keeping with the evidence that does exist? Do they produce only a short term improvement that may delay the institution of other therapy? Do they show evidence of harm which might negate any benefit
they may confer? Can further measures be employed to improve upon their likely effectiveness?

Table 1.5 Ward interventions used by the CCOT at Chelsea and Westminster Hospital

<table>
<thead>
<tr>
<th>Physiological system</th>
<th>Intervention type</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Monitoring</td>
<td>ECG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NIBP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CVP</td>
</tr>
<tr>
<td></td>
<td>Therapy</td>
<td>Fluid therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low dose Dopamine</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Monitoring</td>
<td>Respiratory rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SpO\textsubscript{2}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermittent ABGs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermittent ScvO\textsubscript{2}</td>
</tr>
<tr>
<td></td>
<td>Therapy</td>
<td>Mask oxygen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(BiPAP)</td>
</tr>
</tbody>
</table>

ECG, electrocardiogram; NIBP, non-invasive blood pressure; CVP, central venous pressure; SpO\textsubscript{2}, pulse oximetry; ABGs, arterial blood gases; ScvO\textsubscript{2}, central venous oxygen saturation; CPAP, continuous positive airway pressure (ventilation); BiPAP, bi-level positive airway pressure (ventilation).

As an example, the advent of CCOTs has permitted the increasing use of continuous positive airway pressure ventilation (CPAP) on the general wards. It is commonly used in the treatment of hypoxia that is unresponsive to mask oxygen therapy. How the burden of respiratory disease interferes with the function of more common oxygen delivery devices \textit{in vivo} is not well documented in the literature and may play a significant role in subsequent hypoxia. The application of CPAP as a response to
this phenomenon usually results in improvement in oxygenation, yet it carries risks in the ward setting. Is this the only method of achieving such a target without such risks? Could it delay the institution of other modes of oxygenation e.g. mechanical ventilation?

Those that champion CCO believe that a major part of its remit is the clinical intervention. In other words ICU-style techniques can maintain patients on the ward without the need for transfer. A contrary view of the role of CCO is to patrol the wards in order to identify those who require ICU and facilitate timely transfer. Those not requiring ICU, or in which ICU would be felt to be futile and could be observed. If we are to embrace the former, it is important to be sure that the interventions delivered to ward patients as part of CCO are valuable. Our understanding of their mechanisms of action needs to be clear. Knowledge of current practice needs to be documented in order to ensure that delivery of such methods is appropriate with minimal risk or associated morbidity. Finally, can other methods be employed to improve on the current practice? It is from these concerns that this thesis was conceived.
1.7 Thesis Aims

This thesis hopes to examine two of the main interventions performed as part of CCO, namely oxygen delivery and fluid management.

1.7.1 Oxygen Delivery

The aim of the first experimental chapter is to document how the presence of abnormal respiratory patterns affects the performance of common oxygen delivery devices.

Chapter 4 aims to document the nature of ventilation in ward patients with respiratory distress. It is hoped that this will provide evidence for that some of the hypoxia seen in such patients is due to poor interaction between patient and oxygen delivery system.

The subsequent two chapters aim to clarify whether the improvement in oxygenation seen with the application of CPAP to ward patients is due to the change in oxygen delivery system or secondary to the direct effects of positive airway pressure.

1.7.2 Fluid Management

Chapter 7 aims to document the current practice for fluid resuscitation in the critically ill ward patient and compare it to the EGDT method as a ‘standard of care’.

Chapter 8 concludes the thesis by examining a novel cardiac output monitor which may have utility on the general wards. In comparing it to an established method, it aims to prove that the data produced is valid enough to permit its use.
This thesis could also look at the influence of CCO on DNAR orders, transfer of skills and support of ward staff, but it is the physiological aspects of intervention that I choose to focus on. It is hoped that the efficacy and mechanisms of these methods can be explored and that while answering some basic questions the thesis may indicate what other questions need to be asked about the implementation of outreach interventions in clinical practice.
1.8 References


67


47. Ball C, Kirkby M, Williams S. Effect of the critical care outreach team on patient survival to discharge from hospital and readmission to critical care: non-randomised population based study. *BMJ.* 2003 Nov 1;327(7422):1014.


Chapter 2

Materials and Methods

2.1 Introduction

The previous chapter has highlighted the evolution of critical care outreach teams and their current roles in hospitals in the United Kingdom. Most of the evidence to date summarises the effect of CCOTs on mortality and ICU readmission. Associated evidence for their necessity comes from the positive effects of early warning scores and the assumption that early intervention should lead to improvements in patient care. The increasing use of intensive care techniques on the general wards has not been specifically evaluated. It is thought that early ‘higher level’ interventions lead to better outcomes. However what can be delivered to ward patients, how effective such strategies are and how well they are delivered all remain unclear.

As alluded to previously the actual number of tools available to the Chelsea and Westminster CCOT is somewhat limited, namely: The use of early-warning scores to identify patients ‘at risk’, increasing the level of physiological monitoring, delivery of oxygen, the administration of non-invasive ventilation such as continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP), the almost ubiquitous administration of intravenous fluid and occasional use of systemic inotropes. One further ‘tool’ at the disposal of the CCOT is the ‘do-not-actively-resuscitate’ order (DNAR). This thesis is set out to assess some of these interventions.
It aims to assess the efficacy of common oxygen delivery devices in a model of respiratory distress. A clinical study to document the nature of ventilation in patients with respiratory embarrassment is also conducted to permit some degree of clinical application of the model’s findings.

It next aims to describe the effects of oxygen delivery by a high flow oxygen system and any additional effects that the application of a CPAP valve may confer. To this end the effects of this device were evaluated in a lung model and then audited in clinical practice.

The delivery and effects of intravenous fluid as an intervention is also evaluated to see when and how they are used. An obvious issue is the lack of monitoring available in the ward environment. Thus the potential use of novel cardiovascular monitoring to improve haemodynamic optimisation via fluid resuscitation is included.

The DNAR order as an ‘intervention’ whilst also considered is not included in this thesis.

2.2 Oxygen Delivery

The application of inspired oxygen is a very common intervention. However little has been documented regarding the performance of oxygen delivery devices in the presence of the respiratory patterns typical of the acute respiratory failure seen in acutely unwell patients.
2.2.1  *Assessment of Common Oxygen Delivery Systems via a Model*

The first study performed as part of this thesis utilises a model of human ventilation to simulate these patterns. The model combines a mechanical ventilator with bellows to produce ventilation that can be varied. The use of a Laerdal® Airway Management Trainer mannequin (Laerdal®, Orpington, UK) to simulate the upper airway and trachea will permit the testing of a selection of oxygen delivery devices in common use at Chelsea and Westminster Hospital. Measurement of the oxygen content of the ‘inspired gas’ delivered by the devices is performed. The aim of this study is thus to establish the effects that varying the respiratory rate has on the delivery of oxygen by the selected devices. This hopes to confirm or refute the hypothesis that with the abnormal ventilatory patterns seen in respiratory failure, oxygen delivery devices perform less well than at more normal patterns.

2.2.2  *Peak Inspiratory Flow Rates in Respiratory Distress*

The previous chapter aims to describe both *in vitro* the interaction between oxygen delivery systems and ventilation in acute respiratory disease. The next study is designed to assess whether a likely significant factor in the performance of oxygen delivery devices, peak inspiratory flow rate (PIFR), is abnormal in patients with respiratory failure. This would develop the thesis that the ward-based methods to achieve oxygenation in the critically ill succeed in greater part, due to ventilatory physics rather than pulmonary physiology.

A case-control study will be performed. ‘Cases’ are those with acute respiratory failure recruited on the wards of Chelsea and Westminster Hospital. ‘Controls’ are American Society of Anesthetesthesiology (ASA) grade I or II pre-operative elective
general surgical and orthopaedic patients. Measurements of PIFR is performed using a Vitalograph 2120® (Buckingham, UK) hand-held spirometer. The subjects undergo three maximum voluntary ventilation assessments for 14 seconds each. The plot obtained is analysed using GraphClick 2.9.2 (Arizona Software, USA). A mean PIFR can be calculated from the maximal gradient differentiated by the software. The hypothesis being tested is that patients with acute respiratory failure have a higher PIFR than similar normal subjects at rest. It is hoped that with this approach a realistic evaluation can be made of how effective commonly used systems are in delivering oxygen in vivo and provide an indication of whether, in practice, they work in the way that we think. The inspiratory flow rates may provide information about a potentially key factor in the efficiency of delivery of oxygen by these systems

2.2.3 Continuous Positive Airway Pressure

The application of CPAP as an intervention to improve oxygenation in acute respiratory failure is becoming more common on the general wards. If tolerated it usually leads to a marked improvement in oxygen saturation and as such, may convey survival benefit in selected patients. What has not been documented is whether the improvement in oxygenation is primarily due an improvement in oxygen delivery or the direct effect of positive airway pressure. Chapters 5 uses the model for oxygen delivery assessment described in Chapter 3 and applies it to a CPAP system. Then Chapter 6 provides an audit of patients being treated with CPAP in order to evaluate the effects of high flow oxygen and CPAP.
2.2.4 Assessment of CPAP via a Model

The model described in Chapter 3 is used to assess the Whisperflow® 2-60 (Phillips Respironics, Pittsburgh, PA, USA) high flow delivery system. This is the system used to deliver CPAP at the Chelsea and Westminster Hospital. Clinically it is usually used with pressures of 5cmH\textsubscript{2}O or sometimes 10cmH\textsubscript{2}O. Changes are made to the respiratory rate and the addition of 5cmH\textsubscript{2}O and 10cmH\textsubscript{2}O of PAP applied at each rate. Measurement of oxygen content is performed on the ‘inspired gas’ as a reflection of the effectiveness of oxygen delivery by the system. The aim of this study is to establish the effects that varying the respiratory rate has on the delivery of oxygen by the high flow system with or without CPAP valves. The hypothesis is that a high flow system via a sealed mask would not show the same deterioration in performance as that seen with other oxygen delivery systems.

2.2.5 Clinical Audit of the Application of CPAP to Patients

To follow this up in a clinical scenario Chapter 6 is a clinical study. It examines patients with acute respiratory failure in whom CPAP therapy is to be initiated due to hypoxia on more conventional oxygen delivery devices. The aim is to document whether a change to the Whisperflow® oxygen delivery device brings about significant improvement in oxygenation and whether the subsequent application of 5cmH\textsubscript{2}O and 10cmH\textsubscript{2}O of CPAP further increases the arterial oxygen content. Thus patients are initially treated with oxygen via a venturi system delivering an approximate FiO\textsubscript{2} of 0.6. After 10 minutes an arterial blood gas is sampled and analysed for the partial pressure of oxygen (PaO\textsubscript{2}) and carbon dioxide (PaCO\textsubscript{2}). The Whisperflow® system is then applied as per the manufacturer’s instruction without a CPAP valve attached. After a further 10 minutes a second blood gas analysis is
performed. A 5 cmH₂O Accu-PEEP (Vital Signs, Barnham, UK) is then applied and a further 10 minutes elapsed, whereupon a third blood gas analysis is performed. The patient remains on 5 cmH₂O for 50 minutes (totalling 1 hour) before further blood gas analysis and a subsequent increase in CPAP to 10 cmH₂O. Another hour elapses before a final blood gas analysis is taken. At each sampling time of the experiment, the patient is asked to assess their level of comfort regarding the method of oxygen delivery. The hypothesis of this experiment is that changing to a high flow oxygen delivery system will markedly improve oxygenation, but that the application of two levels of CPAP commonly used on ward patients does not further improve oxygenation. This lack of improvement may also be accompanied by an increase in discomfort for the patient.

2.2.6 Summary

It is hoped that these model and patient based evaluations will provide information regarding how two of the common methods of ward-based oxygen delivery work in the presence of disease. In particular it will test the previously untested hypothesis that the benefits in oxygenation from CPAP accrue predominantly from the application of pressure.

2.3 Fluid Resuscitation

The efficacy of oxygen delivery will have been addressed but the other significant and common intervention is fluid management. This is an almost ubiquitous intervention performed in any patient attended acutely by the CCOT. Many patients are treated as hypovolaemic following initial assessment and varying amounts of
intravenous fluid is administered. What is not known is how the involvement of a CCOT influences this fluid management, both in its timing, its volume and observing its treatment effect? The study by Rivers et al. highlighted the use of early well controlled fluid resuscitation in septic patients in an Emergency Room environment. This adds to the general belief that early aggressive resuscitation prevents further deterioration and should reduce mortality. As an intervention on the general wards, nothing similar to the Rivers study has been performed. There is no data that documents the use of intravenous fluid in the acutely unwell in terms of timing, volume or associated complications.

2.3.1 An Audit of Ward-based Intravenous Fluid Resuscitation

The study which will be described in chapter 7 audits the current practice of this important intervention. The study aims to document the actual practice of fluid resuscitation in the general ward patients in whom CCOT involvement was deemed necessary.

To audit this activity realistically requires a reference point and here are no studies other than that by Rivers which address this issue. Therefore, while acknowledging that there are profound differences between the Emergency Room and the ward, this audit used the Rivers criteria as the gold standard by which practice was to be assessed. Patients who were attended by the CCOT at Chelsea and Westminster Hospital and received at least a 250ml bolus of fluid within an hour are included. Data is collected on the timing of fluid administration, the volume and types of fluid used, its clinical effect and the appearance of complications associated with fluid resuscitation. The results were then compared to the above gold standard. The
hypothesis being tested is that in current practice on general wards, intravenous fluid resuscitation is often delivered later than ideal, can be excessive in volume and thus may contribute to unnecessary morbidity. It is hoped that such information would be valuable in improving the delivery of this intervention to acutely unwell ward patients. Further evaluation of efficacy is beyond the scope of this investigation but hopefully this study will provide the basic information about the delivery of fluid management that will enable evaluation of efficacy in the future.

2.3.2 Cardiac Output Monitoring

To realistically apply effective fluid management requires some form of invasive monitoring which currently is difficult in the ward environment. Chapter 7 aims to demonstrate the current ‘state-of-play’ with regards to circulatory resuscitation of the acutely unwell on the wards. In the intensive care unit, such therapy is often accompanied by additional monitoring to assess and control similar treatment. The dispersion of critical care skills to the general wards is part of the CCOT remit and as such it is reasonable to expect that ICU-type monitoring may play an increasing role in the care of ward patients. One such mode is that of cardiac output assessment but most current techniques such as pulmonary artery catheters and oesophageal doppler techniques are difficult or impossible to use in the ward. What is needed is a user friendly device that can be safely deployed in the ward. The use of pulse-contour wave analysis is ever increasing and newer, simpler equipment is available which might be suitable. One such ‘user friendly’ device is the Vigileo Flotrac® (Edwards Lifesciences, LLC, Irvine USA) and its associated MHD8 Flotrac sensor. It requires no calibration and thus can be used directly with only the need of an arterial catheter. The final study in this thesis compares this monitor with a calibrated pulse-
contour wave analysis monitor, the LiDCO®. The aim is to decide if the data produced by the uncalibrated Vigileo Flotrac® would reproduce that of a calibrated system, thus permitting its use in the wider environment.

The study recruits intensive care patients in whom pulse contour wave analysis is deemed necessary by the attending physicians. The LiDCO® is calibrated in the standard way and simultaneous readings from both machines were gathered, namely: arterial blood pressure, cardiac output, stroke volume variation. Other data included fluid administration, inotrope therapy, arterial blood gas analysis and plasma lactate concentrations. The hypothesis of this study is that in the critically ill patient, the novel uncalibrated Vigileo Flotrac® produces the same results as the calibrated LiDCO® system.

It is hoped that the approach outlined above will provide useful information about some of the interventions currently used for some aspects of acute care given to patients on the general wards when their condition is severe or deteriorating. Do the limited interventions available work well in acute illness? Is their mechanism of action fully understood? Is the delivery of such interventions optimum or can they be improved upon? Are there better ways to deliver this care in the ward such as new monitoring devices?
2.4 References

Chapter 3

The Performance of Oxygen Delivery Devices at Varying Respiratory Rates

3.1 Background

Oxygen therapy is one of the most common interventions in the ward environment. Oxygen is also commonly administered to patients as part of their routine management. In the acute situation breathlessness and hypoxaemia recorded by pulse oximetry, is often the trigger that attracts attention and hence intervention. The intention is to increase the exogenous oxygen supply. Oxygen is fundamental to aerobic metabolism. In critical illness, delivery of oxygen to the tissues may be compromised, either through the pulmonary or cardiovascular systems or both. This thesis is in greater part about the assessment of ward-based interventions commonly used to increase or optimise tissue oxygen delivery. Thus it seems reasonable to begin with the intervention, the application of supplementary oxygen, which is usually the first to be initiated. It is a key therapy used in many hospital situations and is mostly delivered by some form of mask applied to the face. The range of available masks is wide utilising differing physical characteristics depending on the needs of the recipient, be it severity of hypoxaemia (non-rebreather masks), comfort (nasal cannulae) or securing respiratory drive (low FiO₂ venturi masks). Whilst almost ubiquitous in the treatment of critical illness, each type of mask is thought to deliver a characteristic amount of oxygen for that mask. The clinician selects the mask on the basis of its oxygen delivery in relation to the requirements of the patient. It is perceived that the physical performance of the mask may be altered by
circumstances and this will result in a different, usually lower, oxygen delivery than that intended. The interaction between the patient and the mask system is complex and aspects of this interaction may result in compromise of the oxygen delivery; in particular changes in respiratory patterns and rate. The question is how much in terms of oxygen delivery, is influenced by changing patterns of breathing, or put another way how consistent are the masks in the dynamics of clinical practice?

3.1.1 Oxygen delivery

Oxygen is an important part of routine care of the sick patient. When used, the arterial oxygenation achieved is often described in terms of the concentration delivered by the specific mask system. For example a blood gas result may be put in context by describing the inspired oxygen as 60% by mask. There are many devices currently available whose performance has been documented in the literature. It is usually reported as either the actual delivery from the system, the resultant inspired concentration of oxygen, or the arterial oxygenation achieved. Mask characteristics are usually assessed in physical systems that rarely allow for changes in breathing pattern.

Measurement of the delivered FiO₂ in vivo is technically challenging as invasive procedures in the airway are required at considerable discomfort to a subject. As such, most measurements that have been reported are carried out in normal subjects breathing at rest or trained to vary their tidal volumes. Several of these studies illustrate that there are multiple factors which may compromise the performance of these devices and result in an effective FiO₂ that is less, or occasionally more than that expected. From a physics perspective the actual
concentration of oxygen delivered is determined by the interaction between the delivery system and the patient’s breathing pattern\(^5\). The factors that influence the concentration actually inspired by the patient are summarised in Table 3.1. One of the main factors in determining \(\text{FiO}_2\) is the relationship between the fresh gas flow rate and the peak inspiratory flow developed by the patient. It is likely that as the patient gets distressed the flow rates alter and this will influence entrainment. This is a physics problem and so the most practical way to assess this is by a physical model.

**Table 3.1 Factors that influence the \(\text{FiO}_2\) delivered to a patient by oxygen delivery devices\(^5\)**

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Device Factors</th>
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<tbody>
<tr>
<td>Inspiratory flow rate</td>
<td>Oxygen flow rate</td>
</tr>
<tr>
<td>Presence of a respiratory pause</td>
<td>Volume of mask</td>
</tr>
<tr>
<td></td>
<td>Vent resistance</td>
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<tr>
<td></td>
<td>Tightness of fit</td>
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</table>

### 3.1.2 Difficulties in Measuring \(\text{FiO}_2\)

There are few studies that have tried to evaluate delivery system performance in the adverse circumstances in which they are commonly used\(^{20-22}\). Practical difficulties include the instantaneous and simultaneous measurement of \(\text{FiO}_2\) and gas flow. This is compounded by the problems of identifying and accessing a suitable sampling site\(^9\). The predominant problem is the relationship between the oxygen flow into the mask, the size of the reservoir effect of the mask and the peak inspiratory flow rate, the combination of which will determine air entrainment and therefore oxygen
An alternative approach is to devise a model that could mimic spontaneous breathing patterns and to collect the mixed inspired gas from the model lungs. The mixed inspired gas would to a certain degree, represent the final concentration of inspired oxygen. This could be described as the 'effective inspired oxygen concentration' (EIOC) as it represents the resultant oxygen concentration in the model over the inspiratory phase of ventilation. This avoids many of the measurement problems of the previous methods, but remains only a model. As the oxygen delivery from these systems is largely determined by the physics of the system, the model should lend itself to providing useful information about the relative performance of oxygen delivery systems.

3.1.3 **Aims**

The aim of the study was to develop a new system from an existing lung model that would enable the effective mixed inspired oxygen concentration to be measured. Then to test how effective commonly used oxygen delivery devices are at delivering predictable concentrations of oxygen at different respiratory rates.

3.2 **Methodology**

3.2.1 **Study Design**

It would be conventional to measure inspired gas on inspiration. The unique concept behind the model devised is that as it uses the expired gas from the model lungs which will be, in effect, the same as the mixed oxygen concentration inspired. Therefore, if the expired gas could be collected the concentration measured would
be the effective overall inspired oxygen concentration. This system is considerably simpler than trying to measure simultaneously the oxygen concentration and flow.

3.2.2 The Model

An experimental rig was constructed as shown in Figure 3.1. A Laerdal® Airway Management Trainer mannequin (Laerdal®, Orpington, UK), was used to simulate the nasopharynx, larynx and trachea. The mannequin’s ‘bronchi’ where attached via a Y-piece to a set of ‘slave’ bellows. These were driven by a second set of ‘driving’ bellows by way of a connecting rod. These driving bellows had been constructed for a previous study some years earlier, but their inclusion in this rig with the use of the mannequin, and using a ventilator to provide a range of breathing patterns for the mannequin was entirely novel. The use of the airway model was included to provide a realistic simulation of the upper airway.

The driving bellows were connected to a Dräger Evita ventilator (Dräger Medical, Hemel Hempstead UK), set to deliver a square wave. This relatively sophisticated intensive care ventilator would allow changes in respiratory rate, tidal volume, I:E ratio and maximum inspiratory flow rate. As the driving bellows expand, a reciprocal negative pressure is produced in the slave bellows. This acts as ‘inspiration’. Gas is thus ‘inhaled’ into the slave bellows. Expiration is passive by way of a return spring. This spring conferred a more sinusoidal profile to the square wave ventilation delivered by the ventilator.
Figure 3.1 The experimental rig

Positive pressure from the Dräger Evita ventilator inflates the first set of bellows and via the connecting rod, causes the second set of bellows to open and draw in gas (solid arrows, diagram B). The negative pressure derived from the second set of bellows draws gas from the mannequin (dashed arrows, diagram B). During the expiratory cycle of the ventilator the gas within the second set of bellows is expelled by a return spring (solid arrows, diagram C) into a 10-l mixing chamber and then out to the environment past a Datex-Ohmeda 5120 Oxygen analyser (dashed arrows, diagram C). Direction of gas movement around the apparatus was controlled by unidirectional flow valves.
Unidirectional valves block gas return to the mannequin and conduct expired gas via a T-piece to a 10 litre airtight canister which is intended to allow adequate mixing of the ‘exhaled’ gas. This mixed gas represents the mean inspired concentration in the model and for the purpose of this study is called the EIOC. This gas was then piped past a Datex-Ohmeda™ 5120 Oxygen analyser (GE Healthcare, Chalfont St. Giles, UK), and oxygen percentages recorded. All connecting tubes were 22mm Intersurgical® Elephant Tubing.

3.2.3 Calibration

Control measurements were performed by intubating the mannequin with a 7.0mm cuffed endotracheal tube. Ventilating at a tidal volume of 300 and 500 ml; respiratory rate of 10 breaths.min⁻¹; I:E of 1:2 and no Positive End-expiratory Pressure (PEEP), the mannequin 'breathed' firstly air and then 100% oxygen via a Mapleson C system. The oxygen analyser was thus calibrated to 21% and 100% respectively. The time taken to reach saturations of 100% from 21% was assessed and found to have a mean of 4:12.3 mins and 3:05.8 mins for 300 ml and 500 ml respectively. Tidal volume measures were achieved using a Wright’s Respirometer inserted in the expiratory limb of the slave system. It’s reflection of inspiratory volume was assessed by attaching a second Respirometer to the end of the endotracheal tube. There was concordance between the two at tidal volumes of 100, 250, 500, 750 and 1000 ml at respiratory rates of 10, 20 and 30 breaths.min⁻¹.

Oxygen flow rates to the devices used were controlled by a standard BOC Carnét ball flowmeter (BOC Healthcare, Manchester, UK) inserted into wall-oxygen via a Schräeder valve at 4 bar pressure. The waist of the ball relative to the device’s scale
was used to determine the oxygen flow rate. Three flowmeters were used interchangeably during testing. Each was calibrated at the start of each testing session (3-4 hours). This was done by way of a Wright's respirometer attached to the flowmeter by a 30cm piece of connecting tubing. The flowmeter would be set at 5, 10 and 15 l.min\(^{-1}\), timed for a minute and the number of litres delivered read off the Respirometer. All three of the flowmeters had good concordance between their dialled up flow rate and that delivered. Gas output from the flowmeters appeared stable and constant, but was not specifically verified. A similar method was used to test the calibration of the in-built flowmeter of the Vapotherm\(^\circledR\) system.

3.2.4 Devices

The devices selected for study are those commonly used for oxygen delivery in our institution (Table 3.2). The manufacturer’s specifications are summarised in Appendix 2. It was felt that with the exception of the Vapotherm\(^\circledR\) system, they reflected those mask systems in common use on the wards in National Health Service; certainly those institutions in which the author had previously worked. They also reflected a variety of different physical attributes of oxygen delivery devices. For example, the presence of a reservoir in the case of the non-rebreather bag, or the utilisation of the venturi effect using the Ventimask\(^\circledR\). Hence while different masks may be used in other Institutions the range used here would reflect the range of mask characteristics likely to be available in most hospitals.

The Vapotherm\(^\circledR\) system (Vapotherm Inc., Stevensville, Maryland, USA) is a new method of delivering oxygen by nasal cannulae. It consists of a high flow air/oxygen mixer (0-50 l.min\(^{-1}\)). It requires connection to oxygen and air supplies by way of
Schräeder valves. The gas mix is humidified and warmed as it passes through the device and its warmth is maintained by a warm water jacket surrounding the piping that delivers the gases to the patient. Data provided by Vapotherm® Inc. suggest that the high flow nasal delivery system is better tolerated than conventional nasal cannulae (usually up to a maximum flow of 8 l.min\(^{-1}\)) because of the warming and humidification of the gas mix. It was included in this study as a novel device, which operated at significantly higher flow rates than other devices. It was of particular interest to see if this difference would convey significant advantage in oxygen delivery, not just improved patient comfort and compliance.

<table>
<thead>
<tr>
<th>Variable Performance Devices</th>
<th>Fixed Performance Devices</th>
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<tbody>
<tr>
<td>Nasal Cannula (Teleflex Medical®)</td>
<td>Fixed Performance mask with venturi inserts (Ventimask®, Flexicare®)</td>
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<tr>
<td>Variable Performance Hudson-type mask (Teleflex Medical®)</td>
<td></td>
</tr>
<tr>
<td>Variable Performance mask with reservoir bag and safety vent. (Teleflex Medical®)</td>
<td></td>
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<tr>
<td>Vapotherm® (Vapotherm Inc.)</td>
<td></td>
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<tr>
<td>Thermovent T2 HME (Smiths Medical®)</td>
<td>(Teleflex Medical®, High Wycombe, UK, Smiths Medical®, Hythe, UK, Flexicare® Ltd., Mid-Glamorgan, UK)</td>
</tr>
</tbody>
</table>
With each system the flow rates chosen were those in common use in the institution. The study sought to look at the performance of masks as used clinically and was not seeking to assess the performance of each delivery system under a range of flow rates that may not characterise common use.

The Thermovent T2 HME (Smiths Medical, Hythe, UK) is a novel device designed for use with tracheostomy. To examine this device the mannequin was intubated orally as we were not permitted to perform a tracheostomy on the mannequin. This device was included as an unusual, but still relevant method of oxygen delivery for specific patients.

3.2.5 Assessment

A standard regimen was executed for each of the above devices. The first sets of measurements were performed at a measured tidal volume that was fixed at 500 ml. The I:E ratio remained constant at 1:2. The value of the inspiratory flow rate delivered by the ventilator was set at the minimum required to generate the appropriate tidal volume at each respiratory rate and maintain the I:E ratio at 1:2. For each change in respiratory rate the mannequin was ventilated for 5 minutes to ensure that equilibrium had been reached at the oxygen analyser. On completion of each cycle a further period of 5 minutes ‘washout’ on air was performed before the next alteration in respiratory rate. The maximum oxygen concentrations were recorded for the devices at 10, 15, 20 and 30 breaths.min\(^{-1}\). This was thought to reflect a reasonable variety of commonly encountered respiratory rates in ‘health’ and ‘disease’. The variable performance devices were tested at oxygen flow rates of 2, 4, 6, 8, 10 and 15 l.min\(^{-1}\) as delivered by the (calibrated) BOC Carnét ball.
flowmeter(s). These rates were chosen based on pragmatic clinical experience. Nasal cannulae are commonly used at lower rates such as 2 and 4 l.min\(^{-1}\). Hudson masks often are operated between 5 and 10 l.min\(^{-1}\), whilst the responses to therapy delivered by the non-rebreather type are invariably quoted ‘at 15 l.min\(^{-1}\).’ It was felt that if this study was to have clinical relevance, then inclusion of this spectrum of flow rates would be necessary. The fixed performance devices were assessed using the oxygen flow rates for the appropriate inserts, as recommended by the manufacturer (see Table 3.3 and Appendix 2). The high flow system, the Vapotherm, was analysed at two arbitrary fresh gas flow rates, 15 and 30 l.min\(^{-1}\) and four oxygen concentrations, 30, 60, 80 and 100%. The other devices were not tested at such a high flow rate (30 l.min\(^{-1}\)) as the flowmeter by which they were driven only scaled to 16 l.min\(^{-1}\). Most wall flowmeters in current use are similar in range and so it was felt that testing at higher flow rates whilst of interest, would lack clinical application.

On completion of testing at a tidal volume of 500 ml, the whole experiment was repeated at 300 ml. This was done as it was felt that in respiratory failure, tidal volume may fall as respiratory rate rises. Testing at a lower tidal volume than ‘normal’ for adults would thus convey more clinical relevance to the model.

Each device was tested at each respiratory rate, each oxygen flow rate (variable performance devices) and both tidal volumes. ‘Runs’ of testing were performed on different days and at different times. The observer was always the same. Three models of each device were tested: two from the same batch of devices, and one from a new batch several months later.
3.2.6 Statistical Analysis

For every model of the device, three runs were performed and a mean and standard deviation (SD) calculated and examined for inter-device variability by way of an analysis of variance (ANOVA). The results for each model of each device were combined into a total mean and SD per flow rate, respiratory rate and tidal volume (nine runs). This too would reflect significant device variability if it existed. Comparisons between EIOCs at different respiratory rates, at the same oxygen flow rate (variable performance systems) or FiO₂ (fixed performance systems) were also analysed by an ANOVA test. Significance was defined as a p value <0.05.

3.3 Results

Summary data is presented in this result section.

3.3.1 Inter-device variability

On comparing the inter-device variability, no significant difference between individual masks was detected p=0.95). The two different batches of masks did not differ significantly across time p=0.9.

3.3.2 Variable Performance Systems

The variable performance systems that were analysed were the Hudson mask with and without the non-rebreathing reservoir bag attachment, nasal cannulae, and the Thermovent HME.
3.3.2.1 Hudson mask

The Hudson mask showed evidence of deterioration of performance as the respiratory rate increases both at tidal volumes of 300 ml and 500 ml. At a respiratory rate of 10 breaths.min\(^{-1}\) the mask delivers a mean EIOC of 94.67% and 88.33% at 15 l.min\(^{-1}\) oxygen flow rate for tidal volumes of 300 ml and 500 ml respectively. This reduces to mean of 75.67% and 63.33% when the respiratory rate is raised to 30 breaths.min\(^{-1}\) (p<0.001). The reduction in performance is greater at 500 ml tidal volume (38.30%) than at 300 ml (20.07%). (Figures 3.2 and 3.3).

3.3.2.2 Hudson non-Rebreathing Mask

The addition of a reservoir bag and flap valves over the orifices does not improve the performance of the Hudson mask. The mean EIOC delivered by the non-rebreather system at 15 l.min\(^{-1}\) oxygen flow rate and 10 breaths.min\(^{-1}\) respiratory rate is 85.67% and 79.33% for 300 ml and 500 ml tidal volume respectively. In fact for all oxygen flow rates the non-rebreather system fails to perform as well as the standard Hudson mask, across all respiratory rates and at both tidal volumes. It also shows deterioration in performance as the respiratory rate increases. For example at an oxygen flow rate of 15 l.min\(^{-1}\) the mean EIOC falls from 85.67% to 68.33% (20.2%) and 79.33% to 59.67% (24.78%) at 300 ml and 500 ml tidal volume. p<0.001 in both cases (Figures 3.4 and 3.5).
Figure 3.2 Hudson mask. Effective inspired oxygen concentration (EIOC) achieved by a Hudson Mask at four oxygen flow rates: 2 litres.min\(^{-1}\) (☐), 6 litres.min\(^{-1}\) (◇), 10 litres.min\(^{-1}\) (△) and 15 litres.min\(^{-1}\) (○), across a range of respiratory rates at a tidal volume of 300 ml. Error bars represent +/- 2 SD. (n= 9 measurements per plot).
Figure 3.3 Hudson mask. Effective inspired oxygen concentration (EIOC) achieved by a Hudson Mask at four oxygen flow rates: 2 litres.min\(^{-1}\) (□), 6 litres.min\(^{-1}\) (◇), 10 litres.min\(^{-1}\) (△) and 15 litres.min\(^{-1}\) (◇), across a range of respiratory rates at a tidal volume of 500 ml. Error bars represent +/- 2 SD. (n= 9 measurements per plot).
Figure 3.4 Hudson non-Rebreather Mask. Effective inspired oxygen concentration (EIOC) achieved by a Hudson non-Rebreather Mask at four oxygen flow rates: 2 litres.min$^{-1}$ (□), 6 litres.min$^{-1}$ (◇), 10 litres.min$^{-1}$ (△) and 15 litres.min$^{-1}$ (○), across a range of respiratory rates at a tidal volume of 300 ml. Error bars represent +/- 2 SD. (n= 9 measurements per plot).
Figure 3.5 Hudson non-Rebreather Mask. Effective inspired oxygen concentration (EIOC) achieved by a Hudson non-Rebreather Mask at four oxygen flow rates: 2 litres.min$^{-1}$ (□), 6 litres.min$^{-1}$ (◊), 10 litres.min$^{-1}$ (∆) and 15 litres.min$^{-1}$ (○), across a range of respiratory rates at a tidal volume of 500 ml. Error bars represent +/- 2 SD. (n= 9 measurements per plot).
3.3.2.3 Nasal Cannulae

The Nasal Cannulae achieved the highest EIOC of all the variable performance systems. This was maintained across all oxygen flow rates and both tidal volumes. In particular, at 15 l.min\(^{-1}\), a respiratory rate of 10 breaths.min\(^{-1}\) and a tidal volume of 300 ml, the mean EIOC was 97.33%, approaching the holy grail of 100% in a self-ventilating patient. The cannulae did, however, also demonstrate deterioration in performance as the respiratory rate increased at both tidal volumes. At an Oxygen flow rate of 6 l.min\(^{-1}\): 87.67% to 69.33% (20.92%) and 81.33% to 54.67% (14.75%), 300 ml and 500 ml. P<0.001 in both cases (Figures 3.6 and 3.7).

3.3.2.4 Thermovent H2 HME

As with the above oxygen delivery systems, the Thermovent system in the intubated mannequin showed deterioration in performance at higher respiratory rates. Unlike the previous systems, at lower oxygen flow rates the performance was more consistent (2 l.min\(^{-1}\) \(\text{O}_2\) flow rate Vt 500 ml: 10 breaths.min\(^{-1}\) 31.67%, 30 breaths.min\(^{-1}\) 25.67%). This was however still statistically significant (p=0.04). The change in tidal volume had less of an influence on the EIOC (4 l.min\(^{-1}\) \(\text{O}_2\) flow rate 30 breaths.min\(^{-1}\): Vt 300 ml 32%, Vt 500 ml 31.33%) (Figures 3.8 and 3.9).
Figure 3.6 Nasal Cannulae. Effective inspired oxygen concentration (EIOC) achieved by nasal cannulae at four oxygen flow rates: 2 litres.min$^{-1}$ (□), 6 litres.min$^{-1}$ (○), 10 litres.min$^{-1}$ (△) and 15 litres.min$^{-1}$ (○), across a range of respiratory rates at a tidal volume of 300 ml. Error bars represent +/- 2 SD. (n= 9 measurements per plot).
Figure 3.7 Nasal Cannulae. Effective inspired oxygen concentration (EIOC) achieved by nasal cannulae at four oxygen flow rates: 2 litres.min\(^{-1}\) (□), 6 litres.min\(^{-1}\) (◊), 10 litres.min\(^{-1}\) (△) and 15 litres.min\(^{-1}\) (○), across a range of respiratory rates at a tidal volume of 500 ml. Error bars represent +/- 2 SD. (n= 9 measurements per plot).
Figure 3.8 Thermovent T2 HME. Effective inspired oxygen concentration (EIOC) achieved by a Thermovent T2 HME at four oxygen flow rates: 2 litres.min⁻¹ (□), 6 litres.min⁻¹ (◊), 10 litres.min⁻¹ (△) and 15 litres.min⁻¹ (○), across a range of respiratory rates at a tidal volume of 300 ml. Error bars represent ± 2 SD. (n= 9 measurements per plot).
Figure 3.9 Thermovent T2 HME. Effective inspired oxygen concentration (EIOC) achieved by a Thermovent T2 HME at four oxygen flow rates: 2 litres.min⁻¹ (□), 6 litres.min⁻¹ (◇), 10 litres.min⁻¹ (△) and 15 litres.min⁻¹ (○), across a range of respiratory rates at a tidal volume of 500 ml. Error bars represent +/- 2 SD. (n= 9 measurements per plot).
3.3.3  *Fixed Performance System*

The fixed performance system that was tested was the Venturi mask and inserts supplied by Flexicare®.

3.3.3.1  *Venturi System*

The Venturi system showed consistent performance at the lower oxygen concentration inserts at both tidal volumes examined. They mean EIOC measured was close to that expected by the insert. For example at 30 breaths.min\(^{-1}\) with a tidal volume of 500 ml the 24% and 28% inserts delivered a mean EIOC of 23.67% (p=0.79) and 26% (p=0.80) respectively. There was, however, some reduction in the EIOC at the higher oxygen concentration inserts, particularly at 500 ml tidal volume. (Vt 300 ml 60% insert 10 breaths.min\(^{-1}\) 59.67%, 30 breaths.min\(^{-1}\) 53.33%. Vt 500 ml 60% insert 10 breaths.min\(^{-1}\) 57.33%, 30 breaths.min\(^{-1}\) 50.33%. Both were statistically significant (p<0.001) (Figures 3.10 and 3.11).
Figure 3.10 Venturi Mask. Effective inspired oxygen concentration (EIOC) achieved by each Venturi Mask insert: 24% (×), 28% (□), 35% (◇), 40% (△) and 60% (○), across a range of respiratory rates at a tidal volume of 300 ml. Error bars represent +/- 2 SD. (n= 9 measurements per plot).
Figure 3.11 Venturi Mask. Effective inspired oxygen concentration (EIOC) achieved by each Venturi Mask insert: 24% (×), 28% (□), 35% (◇), 40% (△) and 60% (○), across a range of respiratory rates at a tidal volume of 500 ml. Error bars represent +/- 2 SD. (n= 9 measurements per plot).
3.3.4 **High Flow, High Concentration Systems**

The High Flow, High Concentration System that was tested was the Vapotherm® system.

3.3.4.1 **Vapotherm®**

The Vapotherm system had additional analysis at two gas flow rates 15 and 30 l.min\(^{-1}\). The oxygen concentration was selected on the dial on the system. In terms of consistent performance, this system showed very little reduction in EIOC as the respiratory rate. At tidal volumes of 300 ml there was no change in EIOC at all oxygen concentrations, as the respiratory rate increased. Doubling of the gas flow rate also had little influence on the EIOC. With the tidal volume set at 500 ml, however, there was a slight reduction in EIOC at 15 l.min\(^{-1}\) gas flow (FiO\(_2\) 100%, 10 breaths.min\(^{-1}\) 71.67, 30 breaths.min\(^{-1}\) 67.67) and this did not reach statistical significance (p=0.10). This was abolished when the gas flow rate was increased to 30 l.min\(^{-1}\). Of most interest was that in this model the Vapotherm® is not able to deliver the dialled FiO\(_2\). For example, at both 300 ml and 500 ml tidal volume the maximum EIOC achieved for ‘100%’ FiO\(_2\) 78.67% and 76.67% respectively. Increasing the gas flow rate did improve delivery, particularly in the 500 ml assessment, but only by a maximum of 7%. (30 breaths.min\(^{-1}\) 100% FiO\(_2\) Vt 500 ml) (Figures 3.12 and 3.13).
Figure 3.12 Vapotherm. Effective inspired oxygen concentration (EIOC) achieved by the Vapotherm for four different oxygen concentrations at 30 l.min⁻¹ gas flow: 30% (□), 60% (◊), 80% (△) and 100% (○) across a range of respiratory rates at a tidal volume of 300 ml. Error bars represent +/- 2 SD. (n= 9 measurements per plot)
Figure 3.13 Vapotherm. Effective inspired oxygen concentration (EIOC) achieved by the Vapotherm for four different oxygen concentrations at 30 l.min⁻¹ gas flow: 30% (□), 60% (◇), 80% (△) and 100% (○) across a range of respiratory rates at a tidal volume of 500 ml. Error bars represent +/- 2 SD. (n= 9 measurements per plot).
### 3.4 Discussion

The model clearly demonstrates a reduction in the effective inspired oxygen concentration (the mixed oxygen concentration from the entire inspiratory phase) with the variable performance masks as the respiratory rate increases while at a fixed tidal volume. This varied between delivery systems. For example, nasal cannulae with an oxygen flow rate of 4 l.min\(^{-1}\), deliver an EIOC from 69.67% to 48% when the respiratory rate increases from 10 breaths per minute to 30 and the tidal volume is 500 ml.

With the fixed performance systems, the impact of altered ventilation is substantially diminished especially at the lower concentrations. The 24% venturi mask shows no reduction in performance. At higher ‘fixed’ concentrations there is deterioration. The 60% mask does deteriorate from 57.33% at 10 breaths per minute and a tidal volume of 500 ml, to 50.33% at 30 breaths per minute, behaving increasingly like a variable performance system as the venturi orifice diameter increases.

The Vapotherm\(^\circledR\), which is a high flow rate system, shows minimal change across the range of respiratory rates. Interestingly changing the gas flow rate from 15 l.min\(^{-1}\) to 30 l.min\(^{-1}\) only has a minimal effect on EIOC and neither produces the value that is selected on the oxygen:air mix dial, particularly at the higher FiO\(_2\). The system is known to achieve 99% humidification and this would compromise the EIOC, however this could only account for a drop of approximately of 5% with fully saturated air.
Table 3.3 Manufacturers recommendations for oxygen flow rates and resultant oxygen concentrations for the variable performance device\textsuperscript{23} (see Appendix 2).

<table>
<thead>
<tr>
<th>Oxygen Delivery Device</th>
<th>Oxygen Flow Rate (l.min\textsuperscript{-1})</th>
<th>Resultant Oxygen Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hudson mask \textsuperscript{(Teleflex Medical\textsuperscript{®})}</td>
<td>5 – 6</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>7 – 8</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>9 – 10</td>
<td>60</td>
</tr>
<tr>
<td>Hudson Nonrebreather \textsuperscript{(Teleflex Medical\textsuperscript{®})}</td>
<td>10 – 12\textsuperscript{*}</td>
<td>80-100</td>
</tr>
<tr>
<td>Nasal Cannulae \textsuperscript{(Teleflex Medical\textsuperscript{®})}</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>44</td>
</tr>
<tr>
<td>Thermovent\textsuperscript{®} T2 HME \textsuperscript{(Smiths Medical)}</td>
<td>1 – 10</td>
<td>27 – 60</td>
</tr>
<tr>
<td>Ventimask\textsuperscript{®} \textsuperscript{(Felxicare\textsuperscript{®})}</td>
<td>2 (24%)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>4 (28%)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>6 (31%)</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>8 (35%)</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>10 (40%)</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>15 (60%)</td>
<td>60</td>
</tr>
<tr>
<td>Vapotherm\textsuperscript{®} \textsuperscript{(Vapotherm Inc.)}</td>
<td>8 – 40</td>
<td>30 – 100</td>
</tr>
</tbody>
</table>

\textsuperscript{*}May require higher flows. The flow should be adjusted so that the reservoir bag does not deflate more than one third during inspiration.
Table 3.3 summarises the manufacturer’s recommendations for oxygen flow rates for their variable performance devices tested, and the resultant oxygen concentration to be expected. The study performed here, in a model, suggests that with many currently used oxygen delivery systems this predicted performance is unpredictable.

3.4.1 Clinical Implications

This has significant clinical implications. Oxygen therapy is often first line treatment of those with acute problems in the ward environment and is also a significant part of the armament available to the outreach and other ward teams. If the model results are extrapolated to the critically ill patient, then knowledge about the impact of altered respiratory pattern on the oxygen delivery being achieved will be important in deciding which delivery system to use. Furthermore it may well be that in many cases where the target of arterial oxygenation, be it $\text{SpO}_2$ or $\text{PaO}_2$, is not achieved because of the performance of the oxygen mask, a simple increase in the oxygen concentration set or alteration of the flow rate delivered to these systems may correct the problem. The second issue is that interpretation of results may be affected. Lower patient values than expected as a result of predicting a higher oxygen delivery than is actually being achieved may influence clinical judgement as to the severity of the problem. There may be a lower than desired $\text{SpO}_2$, and a clinician may thus institute more invasive forms of ventilation such as continuous positive airway pressure (CPAP), bi-level positive airway pressure or even mechanical ventilation based on this interpretation. Escalating to these more sophisticated forms of oxygen delivery may be entirely appropriate and as shall be discussed later in this thesis, be desirable for certain specific conditions. However unnecessary escalation based on the delivery of lower than expected oxygen
concentrations may be counterproductive in terms of comfort and the need for a higher intensity environment. Both CPAP and BiPAP may be difficult to deploy and are not without complications when used in a ward environment. If this can be circumvented by the use of a more effective system then that would be an advantage. Comfort in particular is likely to have a significant influence on the time any oxygen system stays on the patient. Using or developing more ‘comfortable’ systems is important as it may provide more reliable continuous delivery, a fundamental factor of oxygen therapy.

If the desired end-point is a ‘normal’ SpO$_2$ or PaO$_2$ then predictable and effective oxygen delivery is needed. An understanding of what can be achieved by each system is not just academic, but vital if unnecessary use of more invasive systems is to be avoided. For example, this study demonstrates that at higher respiratory rates, the Hudson non-rebreather mask delivers much lower oxygen concentrations that many would assume (many clinicians believe it to be able to deliver 100%). A low SpO$_2$ in such a situation may be seen as an indication for CPAP or urgent mechanical ventilation. However to achieve the desired end-point, maybe a better design or mode of oxygen delivery is all that is required, thus reducing the potential hazards of more aggressive techniques. Following on from these studies and an increased awareness of these issues, there has resulted a proliferation of the use of the Vapotherm® system in the ward environment and a reduction in the use of CPAP. It subjectively appears to be effective simply by delivering the oxygen concentration that is required. This requires further evaluation.

Another potential benefit may be that most of the masks and delivery systems in common use, with the exception of Vapotherm® are relatively old systems that were developed years ago. The information from this model may allow a new innovative
approach to developing more dependable systems by looking at ways of altering the effective reservoirs in the breathing systems as well as altering flow. The model may also be of use in testing the efficacy of these systems.

3.4.2 Mechanism of Failure

The actual FiO$_2$ that is inspired by the patient and reaches the distal airways is difficult to predict for several reasons (see Table 3.1). The entrainment of environmental air will be influenced by the relationship between oxygen gas flow through the system, the inspiratory pattern of the patient, the effective reservoir within the mask system itself and to some degree the dead space of the mask and pharynx. The single most important factor is probably the relationship between the tidal volume, the peak inspiratory flow rate (PIFR), and at what point this exceeds the available volume of undiluted oxygen within the mask and pharynx. In sick patients the respiratory pattern is often altered and tends towards relatively lower tidal volumes at an increased respiratory rate and hence a high PIFR. Respiratory rates in excess of 30 breaths per minute are not uncommon and may be associated with PIFR’s of greater than 30 lmin$^{-1}$ and loss or diminution of the respiratory pause. This will increase entrainment of environmental air which combined with rebreathing of dead space gases will dilute the inspired oxygen concentration.

Attempts to measure this in the past have focused upon trying to instantaneously measure FiO$_2$ and gas flow$^9$. This has been hampered by the sampling site, flow and oxygen concentration measurement and aligning these electronically. Sampling in patients needs to be as far down the airway as possible, which again poses a difficult. The accuracy of the pneumotachograph is problematic and its presence will
invariably alter the mechanics of the delivery system itself. Rapid real time oxygen concentration analysis has been difficult, and even now, when available, would have to synchronise with flow measurement to provide the amount of oxygen delivered.

An alternative approach is this model that mimics spontaneous breathing patterns. It may produce a more realistic indication of how these delivery systems function in adverse circumstances. This contrasts with most previous models which have evaluated the concentration of the oxygen flowing through the delivery system without looking at the interplay between delivery and respiratory pattern\(^4\).

3.4.3 *The Model as a Reflection of Real Life*

There are problems with the model. It is far from a perfect representation of human ventilation. The mannequin is synthetic and whilst anatomically correct, does not behave as the more pliable human airway. Snug mask fitting on the face is an issue although the same can be said for the human subject. The more rigid mannequin permits predictable increases in PIFR as the radius of the airway remains constant. *In vivo*, respiratory distress and tachypnoea with a high work of breathing could collapse of the upper airway. This would reduce the airway radius, potentially leading to increased airway resistance and reduced PIFR. Air entrainment would thus be less and so the performances of the oxygen systems may be maintained. The respiratory cycle employed in the model may also differ from that seen *in vivo*. Fixing the I:E ratio at 1:2 at all the respiratory rates has two potential confounding effects. First, the respiratory pause is likely to be maintained at far higher respiratory rates than that seen clinically. This serves to maintain mask performance at higher rates in the model. Second, the I:E is not constant in respiratory distress. Expiratory time is
reduced *in vivo*, and although it will also decrease at high rates with the model the pattern may be different. As with the loss of respiratory pause this would further serve to cause a lower oxygen delivery as there would be less time for any reservoir to be replenished.

Models are able to look at the physics of the ventilation and will never really approximate the physiology of the lungs. In these studies it is really the physics of oxygen concentration during inspiration that is of interest and the model can look at these far more easily than physiological studies. The magnitudes of the changes seen are large. While they may not be exactly the same as occurs *in vivo* the magnitude of change clearly illustrates the trends one would see clinically and it and does fit with the hypothesis that air entrainment changes with increasing respiratory rate to the detriment of inspired oxygen concentration.

Similarly in terms of gas composition, the results obtained from this model are not directly applicable to the clinical setting. There is an absence of the contribution that carbon dioxide and water vapour (with the exception of the Vapotherm®) make to the concentration of oxygen in the inhaled gas. There is no nasopharyngeal humidification and no carbon dioxide production in the inhaled gas. Indeed, the rebreathing of any exhaled gas is prevented by the effects of the unidirectional valves passing ‘inhaled’ gas to the oxygen analyser.

The contribution of the dead space gases to $\text{FiO}_2$ can, however, be estimated by making an assumption about the proportion dead space contributes to tidal volume, oxygen uptake and CO$_2$ production. A relatively simple formula can be derived to predict further reduction in the measured EIOC values caused by the presence of dead space gases (see Appendix 1). These are however only estimates and cannot
accurately predict FiO$_2$ based on this model's data, because of the complexity of pulmonary physiology. The variation in anatomical and physiological dead space and changes in oxygen consumption and CO$_2$ production, particularly in acute illness, make the derived values in Appendix 1 only approximations. The model cannot mimic physiology but it does illustrate the physics of oxygen delivery by these systems and the trends present in the model would be expected to be present in the patient.

In only one of the delivery systems did the model produce an unexpected result. When the nasal cannulae are used the effective inspired oxygen was higher than with the Hudson mask which was not an intuitive result. In the model the oxygen is delivered into the nose of the manikin and even though the mouth was open, it is possible that it effectively produces a pharynx full of oxygen resulting in a high inspired oxygen value. It is impossible to say if this represents the situation clinically.

Using this model, an indication of the performance of different oxygen delivery systems has been achieved. The variable performance systems, including those with a rebreathing bag, appear to deliver lower than predicted mixed inspired oxygen concentrations as the respiratory pattern deteriorates with tachypnoea, at least in this model. Thus in clinical practice oxygenation assessments assuming an inspired oxygen concentration may be quite misleading. The fixed performance systems are better, but only up to 60% oxygen, which may be inadequate. The high flow system performed well across the circumstances tested. Anxieties about comfort and airway drying may be misplaced$^{24}$. The results found here indicate not only the changes in performance already described but suggest the model could be used to produce realistic tables of oxygen delivery system performance across the entre range of oxygen delivery systems.
3.4.4 Conclusions

The model demonstrates that as respiratory rate increases, a fall off in performance, in terms of the mean inspired oxygen concentration, is observed in most of the commonly used oxygen delivery systems used at this Institution. It demonstrates the need for an appreciation of the physical capabilities of these systems in the presence of abnormal respiratory patterns. It would appear from this study that when higher inspired oxygen requirements need to be met in the ward environment, a high flow system (e.g. Vapotherm®) may have a more predictable performance.

If higher intensity ward care is to be meaningfully deployed it would seem appropriate to seek better designs to deliver high oxygen concentrations, whilst maintaining the simplicity of an easily applicable mask. Based on this data, it is reasonable to suggest a trend towards high flow systems as a strategy. As stated previously this is a model but the physics should be the same in vivo. A key assumption is that a high PIFR occurs in respiratory distress and this is a/the significant contributor to the reduction in performance of open mask systems. Proving that this occurs in the clinical setting is important to help explain the findings of this chapter and if advances are to be made in the delivery of oxygen to patients who are critically unwell. The following chapter attempts to demonstrate whether or not PIFR increases in respiratory distress.


23. Teleflex M. Hudson RCI Therapy Products. 2006

Chapter 4

Peak Inspiratory Flow Rates in Respiratory Distress

4.1 Background

4.1.1 The Relationship between Inspiratory Flow and Oxygen Delivery

The previous chapter concluded that there is a drop off in the performance of oxygen delivery systems and postulated that the most likely mechanism by which the deterioration in performance occurs is that of entrainment of environmental air due to an increase in peak inspiratory flow rate (PIFR). What is not clear is whether this phenomenon is present in the clinical setting. As described in Chapter 3, demonstration of a significant fall off in performance of oxygen delivery devices is technically difficult in vivo. In order to evaluate the different techniques of oxygen therapy some form of in the clinical validation of the model is required. It is assumed that inspiratory flow rate changes in many disease states but it may be that whilst respiratory rate increases in most forms of acute respiratory disease, alterations in tidal volume, minute ventilation, respiratory pause time and inspiratory:expiratory (I:E) ratio may cause no significant change in inspiratory flow. This should be assessed directly as a significant alteration in flow rates would lend some circumstantial credence to the hypothesis that entrainment is a key feature of mask performance. Any further innovation in oxygen delivery systems, as shall be discussed in the following chapters, requires some knowledge of the physical interaction between patient and system and elaboration of the mechanisms by which
performance is altered. Thus, this chapter aims to evaluate the \textit{in vivo} inspiratory flow rates in health and acute respiratory illness.

4.1.2 \textit{Literature Review}

It was anticipated that there would be considerable literature on inspiratory flow rates in acute clinical circumstances. In fact there is a real scarcity of literature that examines spirometric changes in acute shortness of breath secondary to respiratory illness. In the field of sports medicine high levels of exercise and high workloads are associated with very high peak inspiratory flow rates\textsuperscript{1, 2}. Other data from the realm of high altitude medicine has reported raised inspiratory flow rates in climbers both at rest and exercising\textsuperscript{3}. A study by Depledge \textit{et al.} modified a Wright’s respirometer to measure peak inspiratory flow rate (PIFR) in normal subjects\textsuperscript{4}. Whilst remarking that his innovation had potential for ward usage in patients unable to attend formal spirometric examination, there is no further literature that this method was ever applied in the acute setting. Finally, there is information from studies examining inhalational drug delivery that quote values for peak inspiratory flow rates (PIFR). In stable patients PIFRs up to 400l.min\textsuperscript{-1} have been described\textsuperscript{5-7}. In disease, a study by Dhuper \textit{et al.} looked at detecting room air entrainment as an explanation for the failure of Heliox treatment in asthma\textsuperscript{8}. They studied acute asthmatics and normal controls breathing 70% Heliox. The study demonstrated a significant fall in helium concentration at both tidal ventilation and during an asthma attack (46.2% and 27.5%) this was counteracted by an additional gas supply being piped into the mask. Whilst not directly measuring inspiratory flows, they hypothesised that this change and its reversibility, was due to entrainment of environmental air. They demonstrated
that a flow rate into a plastic mask of 25 l.min\(^{-1}\) is required to maintain a helium concentration of 70%.

It is easy to comprehend why similar data has not been gathered in the patient group with respiratory failure. Static spirometry is cumbersome and potentially hazardous for the acutely unwell subject. Hand-held spirometers are in general basic; measuring only forced expiratory volume in 1 second (FEV\(_1\)), forced vital capacity (FVC) and peak *expiratory* flow rates on single vital capacity manoeuvres. Some models will document a PIFR following a VC, but not during tidal ventilation. It is abnormal tidal breathing that is of interest in order to explain the findings so far.

4.1.3 *Hypothesis*

The hypothesis of this study is that PIFRs are significantly higher in patients with acute respiratory failure when ‘at rest’, compared to similar healthy subjects.

4.1.4 *Aims*

The study had two aims. Firstly to document PIFRs in healthy subjects both at rest and during exercise. This would permit comparison of the experimental technique to the current literature and thus prove its adequacy. Secondly, to measure and compare PIFRs in patients with acute respiratory failure to those of similarly matched control patient subjects.
4.2 Methodology

4.2.1 Study Design

Two similar studies were performed. The first using normal subjects and the second using patients and matched controls.

4.2.2 Study 1: Normal subjects

Recruitment of 10 volunteers was achieved from the anaesthetic and intensive care staff at the Chelsea and Westminster Hospital. The group consisted of medical staff, nursing staff and physiotherapists. Inclusion criteria consisted of physical fitness to climb six flights of stairs and verbal consent to participation in the study. Exclusion criteria were chronic lung disease with the exception of asthma at British Thoracic Society treatment level 1; inter-current upper or lower respiratory illness, pregnancy, orthopaedic or rheumatological illness; a history of syncope or arrhythmia either spontaneous or exercise-induced9.

4.2.3 Study Equipment

In order to immediately assess the peak inspiratory flow rate of the subjects during non-forced ventilation, a hand-held spirometer was used. The Vitalograph® 2120 (Buckingham, UK) was chosen as the most appropriate tool. Connected to a laptop PC it can record more complex spirometric values using the accompanying Spirotrac® 4.24 software. In particular the maximum voluntary ventilation (MVV) function produces a graph of volume against time for 14 seconds. This plot can be converted to a JPEG file and analysed using GraphClick 2.9.2 (Arizona Software,
USA). This software performs a point differentiation, thereby giving a value for flow rate. The spirometer was calibrated by Vitalograph® technicians, and was maintained in good working order. Use of the spirometer by the subjects required a bacterial filter and a disposable cardboard mouthpiece.

The steps from the basement to the 5th floor of the hospital were used as the exercise test. Each flight was 13 steps (26 per floor) and this approximated 9 metabolic equivalents (METs).

4.2.4 Testing of normal subjects

The selected volunteers underwent MVV testing using the spirometer both at rest and following rigorous exercise. The subjects were required to sit quietly for 15 minutes. They then performed an MVV test and a single breath vital capacity enabling documentation of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁). Subsequently each of the subjects were asked to walk (not run) as fast as possible from the basement to the 5th floor without stopping. As soon as they arrived they underwent a second MVV test. The graphs obtained were converted to JPEG format and a mean peak inspiratory flow rate was calculated from three of the breaths displayed on the graph. Demographic data of age, gender, height and weight, were also gathered.
4.2.5 Study 2: Patients

This was an open non-blinded case-control observational study. Patients were recruited from the intensive care unit, general wards and emergency department of the Chelsea and Westminster Hospital.

Inclusion criteria were as follows:

- Age > 16 years
- Presence of oxygen therapy.
- Tachypnoea of greater than 20 breaths per minute.
- Onset of symptoms within 48 hours.
- Evidence of hypoxia $\text{SpO}_2 \leq 92\%$ breathing room air or a partial pressure of arterial oxygen ($\text{PaO}_2$) of $\leq 8.0 \text{ kPa}$.

It was important that these values were reversed to an $\text{SpO}_2$ of $\geq 95\%$, by the application of mask oxygen via a Venturi mask delivering a fraction of inspired oxygen ($\text{FiO}_2$) of 0.6.

Exclusion criteria were:

- Excessive oxygen requirements as defined by a fall in $\text{SpO}_2$ of $\geq 5\%$ within 30 seconds of removal of oxygen and/or desaturation below 90% whilst receiving oxygen, at any time.
- Patient refusal.
- Reduced level of consciousness.
- Confusion.
- Inability to tolerate cushioned mask.
- Vomiting.
• Abnormal facies or facial fractures/injuries.
• Pregnancy.
• Refusal by attending physicians.

4.2.6 Controls

Controls of similar age to the patients being investigated were recruited from the surgical wards at both Chelsea and Westminster Hospital and Northwick Park Hospital. They were studied from prior to elective general and orthopaedic surgical procedures and were required to be independently graded as American Society of Anesthesiology (ASA) I and II with no history of chronic lung disease (except asthma treated to BTS guidelines level 1) or inter-current respiratory illnesses. They were required to describe a normal exercise tolerance defined as being able to climb two flights of stairs without stopping or experiencing significant shortness of breath. Their SpO\textsubscript{2} needed to be ≥95% whilst breathing room air. Cigarette smoking was not an exclusion criterion unless there was evidence of chronic obstructive airways disease.

4.2.7 Testing of patients and controls

The patients underwent three measurements of MMV using the hand-held spirometer, three to five minutes apart with oxygen re-applied between tests. The examination was terminated if desaturation occurred during testing or the patient failed to regain an SpO\textsubscript{2} of ≥95% for one minute before repeating. The control patients underwent exactly the same testing procedure including the use of oxygen between tests. They were tested on the ward pre-operatively, prior to any pre-
medication or medical intervention. Essentially, an in-patient group who were otherwise well.

4.2.8 Data Collection
Measurement of PIFR was performed using the method outlined earlier. Demographic data was also collected including the diagnosis made by the attending physicians.

4.2.9 Statistical Analysis
All statistical analysis was performed using SPSS 14.0 (LEAD Technologies Inc., USA). In Study 1, a mean PIFR was calculated in order to validate the method with previous studies that looked at high workload exercise. For Study 2 comparisons of PIFR measurements between the two groups was performed using Mann-Whitney U test. Demographic data was analysed using a student t-test for continuous data and a Chi² for categorical data.

4.2.10 Sample Size
A sample size of 32 patients and 15 controls permits detection of a difference of a PIFR of >36 l.min⁻¹ with a power of 80% and a 5% significance. This value is well within the values achieved by healthy volunteers, as outlined in the above introduction (up to 400 l.min⁻¹). Data from Study 1 detected a mean PIFR at rest of 30.29 l.min⁻¹ (SD 2.54 l.min⁻¹). Pilot data with 5 patients (included in the overall results) detected a median PIFR of 84.66 l.min⁻¹ (IQR 38.4 l.min⁻¹). Thus a value of
>36 l.min\(^{-1}\) would represent an approximate doubling of PIFR and approximate the pilot data.

4.3 Results

4.3.1 Study 1: Normal subjects

Table 4.1 demonstrates the demographics of the normal subjects taking part in the validation study. They are all young (mean age of 30.29 (SD 2.54) and all had a normal body habitus with normal lung function. One subject smoked approximately five cigarettes per day and another require salbutamol therapy as required for mild seasonal asthma.

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>FEV(_1) (l.min(^{-1}))</th>
<th>FVC (l.min(^{-1}))</th>
<th>FEV(_1)/FVC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>M</td>
<td>185</td>
<td>79</td>
<td>4.82</td>
<td>6.11</td>
<td>78.89</td>
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<tr>
<td>2</td>
<td>32</td>
<td>M</td>
<td>184</td>
<td>78</td>
<td>4.91</td>
<td>6.23</td>
<td>78.81</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
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<td>28</td>
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<td>4.82</td>
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<td>5.28</td>
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<tr>
<td>10</td>
<td>34</td>
<td>M</td>
<td>182</td>
<td>78</td>
<td>4.62</td>
<td>5.67</td>
<td>81.48</td>
</tr>
</tbody>
</table>

FEV\(_1\), Forced expiratory volume in 1 second; FVC, Forced vital capacity
Table 4.2 The mean peak inspiratory flow rates in normal subjects at rest and at peak exercise.

<table>
<thead>
<tr>
<th>Subject number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIFRrest (l.min⁻¹)</td>
<td>27.22</td>
<td>31.48</td>
<td>33.65</td>
<td>26.35</td>
<td>29.16</td>
<td>27.83</td>
<td>30.27</td>
<td>32.93</td>
<td>32.33</td>
<td>31.69</td>
</tr>
<tr>
<td>PIFRexercise (l.min⁻¹)</td>
<td>282.1</td>
<td>290.2</td>
<td>246.4</td>
<td>306.5</td>
<td>211.5</td>
<td>236.7</td>
<td>215.8</td>
<td>241.7</td>
<td>294.9</td>
<td>278.4</td>
</tr>
</tbody>
</table>

PIFR, peak inspiratory flow rate.

Figure 4.1 The change in peak inspiratory flow rate in 10 normal subjects on climbing 6 flights of stairs.

Table 4.2 and Figure 4.1 demonstrate the values for peak inspiratory flow rate for the 10 normal subjects at rest and after 6 flights of stairs. The data was normally distributed with a means of 30.29 l.min⁻¹ (SD 2.54) and 260.41 l.min⁻¹ (SD 34.12) for
rest and exercise respectively. These values are in keeping with the published
literature\textsuperscript{1-4}.

4.3.2 Study 2: Patients

A total of 47 subjects were recruited to Study 2. 32 were patients with the inclusion
criteria. 15 were enrolled as normal controls. Their demographics are summarised in
Table 4.3. The actual PIFR data is presented in Table 4.4 and summarised in Figure
4.2. The distribution of PIFR values in the patient group was non-parametric and
showed a leftward skew. As such a mean value for PIFR was not able to be
calculated and a median calculated instead. In the control group, much like the
normal subjects in Study 1, the distribution of PIFR values was normally distributed.
The groups were well matched in terms of age and gender and there were significant
differences in the respiratory rates and the SpO\textsubscript{2} values when breathing room air.
The median PIFR in the patient group was 76.5 l.min\textsuperscript{-1} (interquartile range 51.25
l.min\textsuperscript{-1}). This compared to a median of 30.00 (interquartile range 6.00 l.min\textsuperscript{-1}) in the
control group (p<0.0001).
Table 4.3 Characteristics of patients with respiratory failure and controls.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=32)</th>
<th>Controls (n=15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) +/- SD</td>
<td>62.8 +/- 16.6</td>
<td>59.73 +/- 12.7</td>
<td>p=0.500(^a)</td>
</tr>
<tr>
<td>Male sex n (%)</td>
<td>53.1%</td>
<td>40.0%</td>
<td>p=0.401(^b)</td>
</tr>
<tr>
<td>Diagnosis/Surgical procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute asthma</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute lung injury</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atelectasis</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Chest trauma</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Haemothorax</td>
<td>1</td>
<td></td>
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<tr>
<td>Pancreatitis</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Severe sepsis</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral pneumonitis</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Cholecystectomy</td>
<td></td>
<td></td>
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<tr>
<td>Herniorrhaphy</td>
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<tr>
<td>Haemorrhoidectomy</td>
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</tr>
<tr>
<td>TKR</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Varicose veins</td>
<td></td>
<td>2</td>
<td></td>
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<tr>
<td>Knee arthroscopy</td>
<td></td>
<td>2</td>
<td></td>
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<tr>
<td>THR</td>
<td></td>
<td>1</td>
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<td></td>
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<td>1</td>
<td></td>
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<tr>
<td>Mean respiratory rate (bpm) +/- SD</td>
<td>27.21 +/- 3.75</td>
<td>12.67 +/- 2.12</td>
<td>p&lt;0.001(^a)</td>
</tr>
<tr>
<td>Peripheral oxygen saturation on air (%) +/- SD</td>
<td>90 +/- 1.72</td>
<td>97 +/- 1.69</td>
<td>p&lt;0.001(^a)</td>
</tr>
</tbody>
</table>

\(^{a}\)2-tailed Student t-test p value; \(^{b}\)Chi-squared test p value; SD, standard deviation; COPD, chronic obstructive airways disease; bpm, breaths per minute.
Table 4.4 Mean peak inspiratory flow rates and respiratory rates for patients and controls

<table>
<thead>
<tr>
<th>Patients</th>
<th>RR (breaths.min⁻¹)</th>
<th>PIFR (l.min⁻¹)</th>
<th>Controls</th>
<th>RR (breaths.min⁻¹)</th>
<th>PIFR (l.min⁻¹)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>75</td>
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</table>
Figure 4.2 A box and whisker plot demonstrating the difference in peak inspiratory flow rates between the patients and controls. \( p < 0.0001 \)

4.4 Discussion

This small study examining the effect of acute respiratory failure on the peak inspiratory flow rate demonstrates that shortness of breath is associated with an increase in the PIFR when compared to a control group of similar age healthy subjects without acute respiratory disease. It was clearly impossible to select normal subjects prior to acute respiratory failure and while the pre-operative group may have been different, potentially with less co-morbidity, it did provide an idea of the flow rates in similar age groups under normal circumstances. It would be very unlikely
that the patients in acute respiratory failure, as a group, would have particularly high resting peak inspiratory flow rates.

The spread of inspiratory flow rates is wide with a maximum value of 293 l.min\(^{-1}\) achieved by a young man with severe pneumonia. The patient group also had a significantly increased respiratory rate. It was not possible with the software used, to measure the area under the curve from the MVV traces and obtain tidal volumes. However visual examination and comparison with those of the normal subjects during exercise implied that the tidal volume had fallen. It is impossible to say whether this represented the same minute ventilation at a higher respiratory rate, however it does suggest a double-negative effect as far as a patient's interaction with an open oxygen delivery system. Firstly the high PIFR could cause functional failure of the oxygen delivery device as demonstrated by the model \textit{in vitro}. Secondly, falling tidal volume would increase the proportion of dead space ventilation with an associated reduction in alveolar ventilation and worsening of ventilation perfusion match. Finally, there is clear loss of the respiratory pause in the patient group when compared to the controls. This too would compromise oxygen delivery.

4.4.1 \textit{Clinical Implications}

If the change in peak inspiratory flow is the cause of entrainment then there may be methods of circumventing the problem. This could be achieved by using systems that provide a method for matching the PIFR at all times or by providing a suitable and adequate reservoir throughout the inspiratory phase of ventilation. For example, continuous positive airway pressure (CPAP) systems either run at high flow rates
(140l.min\(^{-1}\)) or have reservoirs so that peak flows can be easily met. Thus no entrainment as evidenced by deteriorating delivery, is seen with these systems. According to the data presented here, these technologies should perform well enough to match the PIFR in most cases. It also helps explain why in a few cases closure of the CPAP valve can occur in inspiration despite full fresh gas flow in the system. This phenomenon has been reported by Glover et al. who also developed a model of abnormal ventilation. They used it to assess the mask pressure achieved by a CPAP flow generator\(^{10}\). They found that at high inspiratory flow rates this pressure could reach atmospheric leading to valve closer, a potentially hazardous event for the patient. The flow generators that incorporate a reservoir, e.g. Dräger® CF800, are less likely to encounter this problem, and they may yet prove a better system than the less bulky non-reservoir flow generators.

This study was made deliberately simple in order to minimise the risk to the patient. However it has several weaknesses. Firstly it was unblinded and this could lead to observer bias or even lead-time bias when the patient will participate only when feeling improved. Secondly the use of peak inspiratory flow rate rather than mean inspiratory flow rate (MIFR) is a potential criticism. PIFR occurs in the midpoint of inspiration and is brief. This is usually the time of peak flow so that the area under the curve is large. So although the period of air entrainment into an oxygen mask is likely to be short, it is unlikely to be offset by a longer time within the inspiratory time period when inspiratory flow rate is much lower.

It could be argued that the nature of the surgery that the control group were to undergo was particularly unlikely to have an impact on their respiratory function (e.g. herniorraphy, varicose vein excision). This potential selection bias could lead to an unduly significant result when compared to the patient group. However, with the
exception of the three patients with established COPD (only one of which could be described as severe), all the patient groups would have fulfilled ASA I or II status prior to their acute illness. As such it is probably reasonable to use these controls as a comparison group. Finally the control group were not directly matched. Mean ages were comparable, but gender, whilst non-significant appears different. Closer matching would prove logistically more difficult in a single centre and would not be likely to significantly change the results obtained. Indeed, in an observational study such as this, it is questionable if the need for a control group is required at all.

4.4.2 Conclusions
In conclusion, this study demonstrates *in vivo* that there is indeed a marked increase in PIFR in patients in acute respiratory failure when compared to similar patients without acute respiratory illness. As such it confirms the findings reported in Chapter 3 and could be considered as providing support and some associated clinical validation of its findings. This study is a further contribution to proving the hypothesis that hypoxia seen with some oxygen masks may be in part due to failure of the system. As is studied in the following two chapters, the beneficial effects of more sophisticated oxygen systems not studied in Chapter 3 may be due to the physics of delivery demonstrated here, rather than physiological effects they are believed to convey.

In the clinical environment the use of oxygen as a major intervention in hypoxia is necessary and vital. These first two chapters have demonstrated that persistent hypoxia that can be seen with simple oxygen delivery systems is due to a mismatch in the mask-patient interface. This is convincingly abolished by the use of CPAP. In
the ward environment the advent of MET/CCO has increased the use of CPAP as a method for achieving the goal of appropriate oxygenation of the arterial blood. However, how much of this is physical and how much is physiological is unclear and is examined in the following two chapters.
4.5 References


Chapter 5

Continuous Positive Airway Pressure

5.1 Background

The previous two chapters have examined the interaction between the delivery of oxygen and the respiratory pattern of the patient. As stated at the start of Chapter 3, the delivery of oxygen to critically unwell patient is often an urgent intervention, and in such a setting. The actual oxygen delivery has been shown to be unpredictable using some of our standard oxygen delivery methods. The data suggest that in respiratory distress, the use of common mask systems often leads to a deterioration in oxygen delivery just when it would be desired to be optimal. Clinically, as the patient with ongoing hypoxaemia is at risk, recourse to more intensive interventions is warranted. The clinical situation may require endotracheal intubation and mechanical ventilation, but often continuous positive airway pressure (CPAP) or non-invasive ventilation may be attempted in a bid to prevent immediate or unnecessary escalation to this very major intervention. The easiest method to apply in the ward is CPAP. The object of this strategy is not to ventilate the lungs, rather to maintain the patency of and/or recruit respiratory units which in turn should help preserve functional residual capacity. The net effect should be enhanced oxygen delivery and uptake. A more sophisticated approach is non-invasive ventilation by Bi-level positive airway pressure (BiPAP), where there is ventilation of the lungs by the application of two levels of positive pressure. This may be patient triggered or mandatory in nature and is also delivered via a tightly sealing cushioned mask.
BiPAP is, in this Institution, usually applied in high dependency areas and as such is not really a ward based intervention yet and so is beyond the remit of this thesis.

CPAP is an increasingly common intervention used to deliver oxygen in the ward environment. Previously it was the reserve of a higher dependency area such as an intensive care or coronary care unit. It used to be delivered under the supervision of respiratory physiotherapists, but now CPAP is very much within the repertoire of the general wards and is commonly delivered by nursing staff. Its benefits in congestive cardiac failure are well described as well as in some other forms of respiratory failure where reduction of the work of breathing may be helpful but its use has been extrapolated to a wider range of respiratory failure where the evidence is poor or non-existent. The reason for this is that it can be easily applied and it is often effective in improving oxygenation.

There is no doubt that CPAP commonly achieves its goal of increasing patient oxygenation in acute respiratory failure, but what remains relatively unclear is which aspects of this technique leads to this result. Is it the effect of positive airway pressure on the lower respiratory tract, or is it more an effect of the method of oxygen delivery? The following two chapters aim to explore this question.

5.1.1 History

Continuous positive airway pressure (CPAP) was first described as long ago as 1936 by Poulton, who treated a pulmonary oedema patient with high flow oxygen via an anaesthetic mask\(^1\). He constructed the oxygen generator by reversing the flow on a domestic vacuum cleaner. It was subsequently developed for use in children by way of head-boxes, and came into adult practice as a clinical intervention, in the late
1970s\textsuperscript{2-5}. Its use has now diversified into a wide range of clinical situations. In the acute setting this is invariably for the treatment of hypoxia from many causes. Chronic domiciliary CPAP use is increasingly common for the treatment of obstructive sleep apnoea and other disorders associated with sleep and obesity. This chapter will not cover this indication further.

5.1.2 \textit{Mechanism of Action}

It is said to have a clinical effect in several ways. It improves oxygenation but is also believed to have intrinsic benefits to the mechanics of breathing and as such reduces the work of breathing. This has the secondary effects of reducing the breathing rate and improving efficiency as seen by increased inspiratory force and larger tidal volumes. This is achieved through alterations in compliance as the relatively small positive pressure results in increased lung volume, possibly with either some recruitment or avoidance of de-recruitment, thereby a better position on the pulmonary compliance curve\textsuperscript{6-8}. The net effect may be to minimise alveolar collapse, improve compliance, decrease the work of breathing and improve ventilation/perfusion matching\textsuperscript{9}.

5.1.3 \textit{Clinical Uses of CPAP}

The clinical uses of CPAP have been studied widely in many situations where pulmonary function is impaired. As stated above the main goals of CPAP treatment are to minimise alveolar collapse, improve compliance, decrease the work of breathing and improve ventilation/perfusion matching\textsuperscript{9}. This improves oxygenation.
The most enthusiasm for CPAP has come from treating acute cardiogenic pulmonary oedema (ACPO).

Bersten et al. demonstrated that the use of CPAP rather than oxygen therapy alone reduces the respiratory rate, improves oxygenation and acid-base status at 30 minutes in 39 patients with ACPO\textsuperscript{10}. There was a significant reduction in the rate of intubation and mechanical ventilation in the CPAP group. Interestingly, however these indices returned to parity at 24 hours, and there was no differences in mortality between the groups, although this was a small study not powered to detect mortality. Subsequent studies have confirmed the findings of rapid resolution of symptoms and hypoxia, particularly if applied early\textsuperscript{11}. Indeed one study looked at application of CPAP by a mobile intensive care unit, prior to hospital admission\textsuperscript{12}. They demonstrated significant improvements in oxygenation, respiratory rate, heart rate and systolic blood pressure. The trial was however retrospective, and thus it was not possible to compensate for other therapies delivered in the pre-hospital environment such as glyceryl trinitrate or morphine.

These smaller studies have shown physiological improvements and reductions in intubation rates in ACPO, but there still remains controversy as to whether CPAP confers a mortality benefit for this condition. Park et al. published a study of 80 patients randomised to receive either oxygen by face mask, CPAP or BiPAP\textsuperscript{13}. They also documented improvements in symptoms and physiology, but in addition demonstrated a significant reduction in mortality for the CPAP and BiPAP patients at 15 days when compared to the patients who received oxygen alone. This was not persistent and mortality was similar at 60 days. The study was prospective, but with small numbers in each group. A meta-analysis by Peter et al. looked at 23 trials that compared CPAP to oxygen therapy or BiPAP\textsuperscript{14}. They concluded that in ACPO,
CPAP reduces the need for mechanical ventilation and mortality when compared to oxygen therapy alone (relative risk 0.59, (95% CI 0.38-0.90, p=0.015)). It failed to demonstrate a superiority of BiPAP over CPAP.

Following this and other work\cite{15}, the use of CPAP for ACPO as an additional therapy has become commonplace. However a recent large multi-centre study by Gray \textit{et al.}\cite{16} was unable to demonstrate a mortality benefit in ACPO\cite{16}. They randomised 1069 patients with ACPO to receive either oxygen therapy, CPAP or BiPAP. They found no difference in mortality at 7 days between the groups. They were also unable to demonstrate a reduction in intubation rates, improvement in oxygenation at 1 hour or respiratory rate between the groups. Only an improvement in a dyspnoea score and arterial pH proved to be significantly different. This paper is of major interest. It was a well conducted trial with a large study population. It could not show any mortality benefit in the specific condition of ACPO with either mode of non-invasive ventilation (NIV).

Much of the theorising that had occurred prior to this publication had focussed on a cardiovascular benefit by the application of PAP. Raising intrathoracic pressure would reduce cardiac preload, and by reducing the work of breathing, reduce myocardial stress\cite{17,18}. There is also echocardiographic data of patients receiving CPAP for ACPO that supports a reduction in end-diastolic left ventricular volume compared to patients on oxygen alone\cite{17}. Despite this evidence, the paper by Gray \textit{et al.} does not demonstrate that this transfers to a survival benefit.

CPAP has also been shown to convey benefit in the treatment of post-operative atelectasis and hypoxia. Squadrone \textit{et al.} performed a multi-centre randomised controlled trial of 209 patients with post-operative hypoxia following major elective
abdominal surgery\textsuperscript{19}. Patients were either assigned to receive oxygen by face mask, or CPAP. They reported a lower intubation rate (relative risk (RR), 0.099; (95\% CI, 0.01-0.76; p=0.005)) and had a lower occurrence rate of pneumonia (RR, 0.19; 95\% CI, 0.04-0.88; p=0.02), infection (RR, 0.27; 95\% CI, 0.07-0.94; p=0.03), and sepsis (RR, 0.22; 95\% CI, 0.04-0.99; p=0.03) in the CPAP group as compared to the oxygen group. Whilst other studies have not reported such a significant reduction in post-operative pulmonary complications, they have demonstrated a significant improvement in radiographical evidence of atelectasis\textsuperscript{20-22}. A recent meta-analysis of CPAP use in post-operative hypoxia concluded that ‘although the effect on mortality remains to be evaluated in larger studies, CPAP decreases post-operative pulmonary complications (sic), atelectasis, and pneumonia; supporting its use in the clinical practice\textsuperscript{23}.

The benefit of CPAP in other forms of respiratory failure such as pneumonia, asthma and chronic obstructive pulmonary disease (COPD) is less clear. Despite its widespread use for the treatment of other the common causes of acute respiratory failure, there are few studies that examine its benefits in conditions other than ACPO. There is evidence that it may confer a survival benefit in the treatment of pneumocystis carinii pneumonia associated with HIV infection\textsuperscript{24}, although the treatments for HIV have changed immeasurably since this small trial was performed in 1992. Delclaux \textit{et al.} have performed the only substantial clinical trial into the use of CPAP to treat all-cause respiratory failure\textsuperscript{25}. They randomised 123 patients with a PaO\textsubscript{2}/FiO\textsubscript{2} of <300 mmHg with a normal PaCO\textsubscript{2} to receive either oxygen therapy alone or CPAP. Approximately half had pneumonia, and one third cardiac disease. After 1 hour of treatment, oxygenation was improved in the CPAP group (PaO\textsubscript{2}/FiO\textsubscript{2} 203 mmHg, (95\% CI: 45-431) vs PaO\textsubscript{2}/FiO\textsubscript{2} 151 mmHg (95\% CI: 78-432) p=0.02).
No other differences in respiratory indices were observed between the groups. Treatment with CPAP failed to reduce the endotracheal intubation rate, hospital mortality or ICU length of stay and it was associated with a higher number of adverse events 18 vs 6; p=0.01). This trial demonstrated that which is commonly observed: the immediate improvement in oxygenation in all-cause respiratory failure.

5.1.4  *Complications of CPAP*

CPAP in the acute setting is not a benign therapy. Whilst many of the trials described above have not shown significant complication rates, there are many case reports of the complications of CPAP listed below in table 5.1\textsuperscript{26-32}. In particular those that give the greatest concern to clinicians are the failure to tolerate as this leads to failure of oxygen delivery; cutaneous effects, or effectively damage from the tight fitting mask, which can limit the time that CPAP can be used and has been reported as requiring surgical treatment. Impairment of cough as this could potentially lead to retention of secretions and bronchial obstruction, communication difficulties which can make management difficult for both patient and clinician. The advent of the CPAP helmet has gone some way to improving some of these problems. They remain a relatively new method, and there is no evidence that they convey any treatment benefit over a mask system, although they may be better tolerated\textsuperscript{33, 34}. Outside of the diagnosis of ACPO the evidence of benefit of PAP in terms of mortality is weak, but the improvement in oxygenation is documented\textsuperscript{25}.  

144
Table 5.1 Recognised complications of CPAP

<table>
<thead>
<tr>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to tolerate</td>
</tr>
<tr>
<td>Cutaneous damage</td>
</tr>
<tr>
<td>Impairment of cough</td>
</tr>
<tr>
<td>Communication difficulties</td>
</tr>
<tr>
<td>Haemodynamic disturbances</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Pneumocephalus</td>
</tr>
<tr>
<td>Pneumopericardium</td>
</tr>
<tr>
<td>Otorrhagia</td>
</tr>
<tr>
<td>Increased in physiological dead space</td>
</tr>
</tbody>
</table>

Many of the important complications associated with CPAP in acute respiratory failure occur because of the mask. In the community where CPAP is applied either nasally or via a full face mask, the mask complications are negligible, but not unreported\(^{35,36}\). Yet in the hospital environment they are appreciable. Why this should be is subject to conjecture. Community delivered CPAP masks are technologically sophisticated and are patient-applied with a high degree of supervision by specifically trained practitioners. They are commonly only applied at night with the daytime for recovery. The patient group is usually otherwise well and
highly motivated. In contrast, the patient with acute respiratory failure has the mask applied by less experienced attending staff, has little input into the choice and fitting of the mask and in general, the masks lack the sophistication of their community counterparts. The CPAP masks still used in the acute setting are cheaper disposable type with little facial contouring and a fixed air pressure within the seal. They remain applied as continuously as tolerated with little break for tissues at risk to recover. Over-tight application of such masks, in a bid to prevent gas leak, may explain the higher incidence of cutaneous injury. This complication is common and is directly due to the need to seal the airway to the system to provide the perceived benefit of positive airway pressure (PAP). Whilst the use of more improved mask designs which reduces the need for such a tight fit is ever increasing, cost implications in particular are likely to limit their widespread introduction in most hospitals. For example a Respironics® ComfortGel mask costs approximately £110, whereas the Intersurgical® CPAP mask is priced at under £1.00 if ordered in bulk.

There has been little or no basic assessment of how CPAP masks work in terms of oxygen delivery. They will deliver what is required as entrainment is impossible. Improvement seen when a patient is changed from a standard mask to CPAP is usually attributed to the physiological benefits from CPAP but this has not been studied. It is possible that a large proportion of the improvement seen with CPAP is due to the improvement in oxygen delivery above that of an open mask potentially interfacing poorly with a patient’s respiratory pattern. A sealed system with high flow oxygen has little to no capacity for entrainment of environmental air and delivers the FiO₂ set on the flowmeter. The high gas flow rate or presence of a compliant reservoir negates those effects of high inspiratory flow rates seen in the previous chapter, with a few exceptions⁳⁷. Could it be that as an intervention, the influence of
CPAP on oxygenation is mainly due to improved oxygen delivery compared to open oxygen systems, rather than the more physiological explanations related to the PAP? If so would better open mask design achieve similar physical properties without the potential complications associated with CPAP in the acute setting?

5.1.5 Aims
The following two chapters seek to examine the first of these questions. Firstly by employing the model used in Chapter 3 (see Figure 3.1) we aim to demonstrate that a CPAP system does indeed maintain its oxygen delivery in a predictable manner across the same ranges of respiratory rates and tidal volumes as with the open oxygen systems. Secondly in Chapter 6, to examine the effect of a staged introducing a CPAP system to patients in respiratory failure. Thus the aims of the following two chapters are:

1. To demonstrate the effect of varying respiratory rate and tidal volume on oxygen delivery of a high flow CPAP system.
2. In patients with respiratory failure, to describe the effect on arterial oxygenation of changing from an open mask system to a closed CPAP system and the subsequent application of increasing PAP.

5.2 Methodology
The same model system as Chapter 3 was used to test a standard CPAP high flow system. The lung model was set up and calibrated in the same way as for testing the oxygen delivery devices. The CPAP system used was the same that is used
clinically at the Chelsea and Westminster Hospital, both on the ICU and the general wards. This consisted of a flow generator (Whisperflow® 2-60. (Philips Respironics, Pittsburgh, PA, USA) connected to the wall oxygen supply at 4bar. The flow generator was then connected to a t-piece via a specific CPAP circuit of 22mm corrugated tubing (Intersurgical, Wokingham, UK), passing over a water bath humidifier (Fisher & Paykel, Maidenhead, UK). The t-piece inserted into a cushioned size 4 CPAP mask (Intersurgical, Wokingham, UK). The third limb of the t-piece had a further 100cm of corrugated tubing attached. Two levels of CPAP valve were used +5 cmH₂O and +10 cmH₂O (Accu-PEEP, Vital Signs, Barnham, UK). The CPAP mask was applied to the mannequin using the standard harness. All other elements of the model were as outlined in the previous chapter. Two flow generators were used at different times. They were maintained in good working order. Calibration of the oxygen analysers was performed by Philips Respironics technicians and as per the manufacturer’s instructions (see Appendix 2).

The model with the CPAP system attached was tested in the same way as previously. The flow rate on the generator was set to deliver at maximum (140 l.min⁻¹ according to the manufacturer’s specifications – Appendix 2).

Calibration of the driving ventilator and the oxygen analyser within the test rig was performed as outlined before. The experiments were performed at two FiO₂ settings on the generator 0.6 and 1.0. Trails were run at both a Vt of 500mls and 300mls, and the respiratory rates were varied from 10, 15, 20 and 30 breaths.minute⁻¹. Each respiratory rate was examined three times and a mean EIOC and standard deviation were determined.
In addition to the reproduction of the methods of Chapter 3 applied to the CPAP system. An assessment of pressure within the system was performed. This was measured using a 14G Abbocath® inserted in both the inspiratory and expiratory limbs of the system. Pressure was assessed using a standard vascular pressure transducer set (Tru-wave®, Edwards Lifesciences, Newbury, UK) and a Hewlett-Packard Merlin ICU monitor (Hewlett-Packard, Bracknell, UK). Measurements of pressure were taken in the inspiratory and expiratory limbs in both inspiration and expiration. The mannequin was ventilated at 10 breaths.min⁻¹ with a tidal volume of 500 ml. The flow generator was set to deliver 100% oxygen at a flow rate of 140 l.min⁻¹ Assessments were made with the system without a CPAP valve and with 5 cmH₂O attached. The process was performed on three separate occasions for each of two identical flow generators, using new tubing and valves on each occasion. The mean pressures were calculated for each limb in both of the ventilatory movements.

5.2.1 *Statistical Analysis*

All data was analysed using SPSS 14.0 (LEAD Technologies Inc. USA). As in Chapter 3 comparisons between EIOCs at different respiratory rates and FiO₂ were analysed by an analysis of variance. Significance was defined as a p value <0.05. The null hypothesis was that there was no difference in EIOC between the different respiratory rates at the same FiO₂. A comparison between the EIOC of a venturi mask system and the CPAP system without the valve at the same minute ventilation and FiO₂. This was done by way of an unpaired two-tailed t-test.
5.3 Results

The CPAP system tested in this model showed no deterioration in performance as the respiratory rate increased, either at a Vt of 300 ml or 500 ml (p=0.89 & 1.0 respectively). The CPAP system delivered oxygen at the expected FiO₂. There was no change in EIOC at either FiO₂ examined and the addition of 5 cmH₂O or 10 cmH₂O PAP made no difference to the EIOC detected (p=0.95 & 0.90 respectively) (Figures 5.1 to 5.4).

The results of the pressure measurements within both limbs demonstrated a non-significant ΔP across the mask. With no valve attached the mean inspiratory pressure was 1.4 cmH₂O and 1.2 cmH₂O for the inspiratory and expiratory limbs respectively (SD 0.3 cmH₂O) p=0.75. With the 5 cmH₂O valve attached this rose to 6 cmH₂O and 5 cmH₂O respectively (SD 0.4 cmH₂O) p=0.56. Similar results were found in expiration. Without the valve the mean pressure in both limbs were 1.6 cmH₂O and 1.3 cmH₂O (SD 0.3 cmH₂O) p=0.83. Attachment of the 5 cmH₂O valve resulted in pressures across the mask of 6.2 cmH₂O and 5.4 cmH₂O (SD 0.4 cmH₂O) p= 0.78 (Figure 5.5).
Figure 5.1 Effective inspired oxygen concentration delivered by the CPAP system at 3 PEEP settings, across a range of respiratory rates Tidal volume of 300ml. FiO₂ 0.6. (n=6 measurements per plot) p=0.89
Figure 5.2 Effective inspired oxygen concentration delivered by the CPAP system at 3 PEEP settings, across a range of respiratory rates Tidal volume of 500ml. FiO$_2$ 0.6. (n=6 measurements per plot). P=1.0
Figure 5.3 Effective inspired oxygen concentration delivered by the CPAP system at 3 PEEP settings, across a range of respiratory rates Tidal volume of 300ml. FiO$_2$ of 1.0. (n= 6 measurements per plot). P=0.95
Figure 5.4 Effective inspired oxygen concentration delivered by the CPAP system at 3 PEEP settings, across a range of respiratory rates Tidal volume of 500ml. FiO₂ of 1.0. (n=3 measurements per plot) p=0.90
Figure 5.5 Mean pressures within the inspiratory and expiratory limbs of the CPAP system when attached to the model ventilating at 10 breaths.min$^{-1}$ with a Vt of 500ml. (n= 6 for each data point) Error bars represent +/-2SD.
5.4 Discussion

This very simple experiment has demonstrated that the high flow CPAP system attached via a sealed mask, delivers an $\text{FiO}_2$ as expected to a model of human respiration. Changes in respiratory rate and by virtue, minute ventilation have no effect on this delivery. This is true for two tidal volumes.

The most likely mechanisms at play in this experiment are a combination of high oxygen flows that can match the inspiratory flow rates even at high minute ventilation, and the lack of entrainment of environmental air achieved by sealing the airway with a close fitting mask. Also, the contribution of the 100 cm of 22 mm corrugated tubing in the expiratory limb of the CPAP system is notable. This was included even though many systems only require the application of the CPAP valve directly to the mask itself. One major reason was that this was a precursor study to the audit of the effect of CPAP in the patients treated at Chelsea and Westminster Hospital described in Chapter 6. The use of such a limb had evolved historically and was formally summarised in the CPAP protocol particular to this institution. The protocol was also the reason for the selection of 5 cmH$_2$O and 10 cmH$_2$O as the values for PAP in this study and that in the following chapter. Indeed most studies use between 5 cmH$_2$O to 15 cmH$_2$O as their settings and most institutions that publish their protocols online start at 5 cmH$_2$O$^{10,16,38,39}$. Direct reproduction of the clinical technique used at this institution was important in allowing conclusions to be drawn about the in vitro and in vivo results. In addition, the efferent limb in a high flow system, in effect adds an additional reservoir which, combined with the flows, preclude rebreathing. The wide diameter of the tubing also precludes a significant increase in resistance and hence is unlikely to increase intrinsic pressure in the system (Figure 5.5).
It could be argued that a CPAP system without an expiratory limb or a CPAP valve may permit the entrainment of air through the mask port. This study cannot provide such data, however based on the data from Chapter 4 with a median PIFR of 75l.min\(^{-1}\), a high flow system delivering 140l.min\(^{-1}\), this seems unlikely for most subjects. However the same may not be true for CPAP systems that utilise a reservoir such as the Dräger’s CF800 system. It may be that if the use of a high flow oxygen delivery device without a valve is to be advocated, then the inclusion of an expiratory limb may be warranted.

5.4.1 *Clinical Implications*

In clinical practice it is desirable to set the oxygen flow rate at such a level as to maintain a small leak of air through the valve during inspiration. This optimises the function of the valve in delivering positive airway pressure, but the recognition that sealing the face to prevent entrainment of air is not new. This phenomenon was recognised during World War Two in oxygen delivery systems for pilots where a tight fitting mask was essential to maintain oxygen concentrations at altitude. Also in combat conditions the respiratory pattern of pilots was known to change and so entrainment could become an issue if the masks were not well fitting. The same is true today in modern fighter aircraft. It is of interest that in commercial aviation, oxygen masks for passengers are not designed to fit tightly, and at a standard 2 l.min\(^{-1}\) oxygen flow rate are ineffective in delivering enough oxygen if decompression occurs at the usual altitudes of commercial airliners. However the flight crew do have appropriately fitting masks in the cockpit.
The high oxygen flow rate used in this experiment is probably the most important factor in achieving the results demonstrated. What could also be done is to explore the effect of a staged reduction in the flow rate with or without the attached expiratory limb. Is there a threshold in this model at which oxygen entrainment occurs and how does this compare to open system? If the valve were to be attached, entrainment would lead to its closure during inspiration – a potential patient hazard. However a system without the valve and an expiratory limb – essentially an Ayre’s T-piece – may have significant capacity for flow reduction (2-3 times minute ventilation), thus reducing potential detrimental effects of high flow such as airway drying and noise. The model would lend itself well to such an examination.

Figure 5.5 amalgamates data from this study and that of Chapter 3. It demonstrates the effect of changing from a venturi system to a CPAP system with no valve attached, both set to deliver an FiO₂ of 0.6. The respiratory rate (and therefore minute ventilation) is high and there is a marked increase in EIOC on changing from the venturi to the CPAP system. This is statistically significant (t-test p<0.001) for both tidal volumes. It demonstrates, in this model, that the performance of the CPAP system is superior to that of the venturi at this relatively extreme of ventilation. It further underlines the physical properties of these two systems and, whilst the venturi system is the ‘best’ of the commonly used open systems, it cannot deliver oxygen as predictably as its CPAP counterpart.
Figure 5.6 The effect on EIOC on changing from a venturi system to a CPAP system with no valve at 2 tidal volumes. FiO₂ 0.6, Respiratory rate 30 breaths.min⁻¹. (n=9 measurements per plot for venturi, 6 measurements for CPAP) Student t-test p<0.001.
5.4.2 Problems with the Model

In general this is a good model to test a CPAP system for oxygen delivery, but not for the potential physiological effects of CPAP. The realistic mannequin permits a relatively good assessment of ‘mask-seal’ although its plastic construction is less compliant than the human face. This might mean that a seal is well maintained in the model at higher PAP values, when a leak might be expect in real life. As in Chapter 3 the relative rigidity of the upper airway simulator may not simulate the effect of PAP on the human version. Any local effects of enhanced airway pressures in the upper airways which may be relevant in some uses of CPAP, for example sleep apnoea, would not be seen. Similarly any changes in airway diameter cannot be simulated.

In other ways the application of PAP in this model was irrelevant as the model has no capacity for recruitment of alveoli or alterations in V/Q matching. This was borne out by the demonstration that the addition of PAP at 5 cmH$_2$O and 10 cmH$_2$O had no effect on the oxygen concentration delivered. However the absence of PAP did not reduce the oxygen concentration delivered.

Again as with Chapter 3, the respiratory patterns generated by the ventilator and bellows may be similar to those seen in vivo but will never be identical. However, the main features of the patterns are reproducible. What the model offers is a close examination of the physics of oxygen delivery not the physiology.

5.4.3 Conclusions

These two in vitro experiments (chapters 3 and 5) pose the question that is not clear from the literature. Is the rapid improvement in patient oxygenation seen with the application of CPAP due to the alveolar recruitment, prevention of de-recruitment
and improvement of the position on the compliance curve; or is it a physical phenomenon achieved by the delivery system itself improving oxygen delivery in the place of a failing open oxygen system? The model provides convincing evidence that entrainment is an issue with the masks tested and that CPAP has no entrainment. It suggests the effects are of some magnitude and may be a part of the explanation for the increase in oxygenation seen with CPAP. To test this requires examination of these systems in patients with respiratory distress and see if there is an initial increase in oxygenation but also to see if oxygenation improves with either time or with different levels of pressure on the CPAP. The following chapter describes an audit of practice in a patient population with acute respiratory failure starting CPAP therapy, in which these questions can be examined from the use of these systems in vivo.
5.5 References


Chapter 6

The Effect of Continuous Positive Airway Pressure on Oxygenation in Acute Respiratory Failure.

6.1 Introduction

The issue being described in the previous chapters is that the set inspired concentration of oxygen in a mask system may be different from that actually received by the patients during different breathing patterns. The previous chapter demonstrated in a model of human ventilation, that a CPAP system maintains its set oxygen delivery regardless of the minute ventilation, or pattern of breathing. As such it performs better than the other systems tested in Chapter 3. With the exception of the Vapotherm® and the Venturi system at low FiO₂ settings, all other systems show deterioration in function as minute ventilation rises. The venturi system used at a higher FiO₂ shows decreased FiO₂ in the model with increasing minute ventilation as its physical characteristics come to match those of a variable performance system. The Vapotherm® showed good maintenance of oxygen delivery as the respiratory pattern changed, but the delivered values of FiO₂ within the model were not the same as the settings on the oxygen:air mixer. Thus of the systems tested, only a CPAP system delivers the desired FiO₂ across a range of respiratory patterns in this model. This is likely due to the complete prevention of the entrainment of environmental air by the sealed mask and hence the delivery of oxygen to the lungs at suitably high flow to match the ventilatory pattern in abnormal ventilation.
6.1.1 *Physiological Effects of CPAP*

The effect of CPAP on oxygenation in the clinical setting has physiological as well as physical characteristics. The model with no lung tissue was unable to demonstrate the physiological effects CPAP may confer, and it may be that the bulk of the improvement in oxygenation seen in humans is due to an improvement in lung physiology. There is experimental evidence of the potentially beneficial physiological effects of CPAP in the literature summarised in Table 6.1.

**Table 6.1 Beneficial physiological effects of CPAP**

<table>
<thead>
<tr>
<th>Physiological Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimising alveolar collapse</td>
</tr>
<tr>
<td>Improving pulmonary compliance</td>
</tr>
<tr>
<td>Decreased work of breathing</td>
</tr>
<tr>
<td>Improved ventilation: perfusion matching</td>
</tr>
<tr>
<td>Reduces extra-vascular lung water</td>
</tr>
</tbody>
</table>

Abboud *et al* demonstrated that the administration of CPAP of both 5 cm H$_2$O and 11 cmH$_2$O significantly improved mean total lung capacity, functional residual capacity, and residual volume in healthy volunteers$^1$. Closing capacity remained unchanged. The differences between 5 cmH$_2$O and 11 cmH$_2$O were small. Anderson *et al.* experimenting with excised human lung reported superior re-inflation of simulated atelectasis with the application of CPAP compared to simulated normal breathing$^2$. They also commented that collateral non-bronchial channels had a significant role in the re-inflation of the lung and postulated that ‘this route of re-expansion also has a
potential secretion clearing effect in that pressure is built up distal to an obstruction'.
The lungs used were post-mortem and structurally normal. How much these suppositions can be applied in vivo remains conjecture.

Work by Roseler et al in intubated patients after major gastrointestinal surgery demonstrated that CPAP of 11 cmH\textsubscript{2}O significantly improved blood oxygenation and reduced the work of breathing\textsuperscript{3}. This study strongly implies a physiological effect as the possibility of entrainment had been eliminated by intubation. However these were post operative elective surgery patients and as has been described previously do often have some atelectasis, contributing to shunt, which is more likely be improved by the application of CPAP. A further detail is that ventilation in the intubated patient bypasses some of the physiological PEEP engendered by the upper airway. This could in theory, increase the probability of CPAP being beneficial. Another consideration when discussing the use of CPAP in post-operative patients both in this study and that by Squadrone et al. referenced in the previous chapter is the use of Nitrous oxide (N\textsubscript{2}O) as part of the anaesthetic management\textsuperscript{4}. Nitrous oxide is more soluble in blood than nitrogen, and by replacing nitrogen in the alveoli is thought to lead to more extensive ‘absorption atelectasis’\textsuperscript{5}. The literature suggests that N\textsubscript{2}O does not lead to greater atelectasis than using nitrogen, but may produce a more rapid onset\textsuperscript{6-9}. At termination of anaesthesia dissolved N\textsubscript{2}O rapidly comes out of solution into the alveoli, displacing the other gases, namely nitrogen, oxygen and to a lesser extent carbon dioxide. This ‘third gas’ effect reduces the concentration of the other alveolar gases especially oxygen, leading to arterial hypoxia. This phenomenon can be circumvented by maintaining a high FiO\textsubscript{2}, but at the risk of worsening atelectasis.
Preventing atelectasis may be more effective than reversing atelectasis with positive pressure. It is likely that recruitment manoeuvres using far higher pressures than standard post-op CPAP (5-10 cmH₂O) is required to overcome the surface tension forces of collapsed alveoli. Subsequent application of CPAP might then be expected to maintain alveolar patency. This may be why the data from Pasquina et al. suggests a superiority of non-invasive pressure support ventilation to CPAP in improving radiological evidence of post-operative atelectasis, although it did not convey any other clinical benefit. However, a recent randomised controlled trial of recruitment manoeuvres and CPAP versus neither in patients undergoing elective surgery was unable to demonstrate a difference in terms of alveolar to arterial oxygen gradient. Whether or not CPAP is of real use in the treatment of post-operative atelectasis remains a subject of debate but it is clear that upper gastrointestinal, cardiac or thoracic surgery will continue to present a significant risk of causing atelectasis so methods of preventing atelectasis are important.

Several studies have demonstrated that CPAP reduces the inspiratory work of breathing by offloading the inspiratory muscles. However there is little data that describes the effects of expiratory work of breathing. Anecdotal reports suggest breathing out ‘feels’ more difficult in volunteers and may involve an active component. This is usually a passive function, and though reductions in inspiratory work of breathing may reduce symptoms of breathlessness, there is no evidence that this reduces oxygen consumption (VO₂). Indeed one study suggested that the application of CPAP in respiratory failure increases VO₂. Whether this could be detrimental is unclear.

The physiological phenomena, described in Table 6.1, are likely to improve oxygenation but are unlikely to have immediate effects. Yet the improvement in
oxygenation seen when a patient is transferred from mask oxygen to CPAP is almost instant. It is thus reasonable to hypothesise that at least part of the improvement in oxygenation in acute respiratory failure is due to a physical effect such as an improvement in oxygen delivery.

6.1.2 Aims

It is obvious that after the application of CPAP in the ward situation, oxygenation often improves. The protocol of instituting CPAP at the Chelsea and Westminster Hospital is standardised but has never been audited. The aims of the following audit were to see if auditing standard practice could demonstrate when the application of a high flow sealed oxygen system improves oxygenation in acute respiratory failure patients already receiving oxygen via a 0.6 FiO₂ venturi mask? Does the addition of standard practice CPAP valve to that system further improve the oxygenation achieved by the high flow system alone?

6.2 Methodology

An unblinded observational audit was performed as part of the institution of a new protocol for the delivery of CPAP in patients with non-hypercarbic respiratory failure. The study was carried out both on the ICU and general wards at the Chelsea and Westminster Hospital. It was an observational audit conforming to the written Hospital protocol for the introduction and monitoring of CPAP in the ward environment and is summarised in Table 6.2 and Figure 6.1. This had been developed jointly by the intensive care unit and the critical care outreach team.
Table 6.2 Summary of the Chelsea and Westminster written protocol / guideline for the introduction of continuous positive airway pressure for the treatment of acute non-hypercarbic respiratory failure. In the final column is detailed the measurements made during the study for each stage of the protocol.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Ventilation Mode</th>
<th>FiO₂</th>
<th>Time</th>
<th>Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Venti-mask</td>
<td>0.6</td>
<td>10 minutes</td>
<td>ABG, RR &amp; Comfort score</td>
</tr>
<tr>
<td>2</td>
<td>CPAP system: 0 cmH₂O</td>
<td>0.6</td>
<td>10 minutes</td>
<td>ABG, RR &amp; Comfort score</td>
</tr>
<tr>
<td>3</td>
<td>CPAP system: 5 cmH₂O</td>
<td>0.6</td>
<td>10 minutes</td>
<td>ABG, RR &amp; Comfort score</td>
</tr>
<tr>
<td>4</td>
<td>CPAP system: 5 cmH₂O</td>
<td>0.6</td>
<td>50 minutes</td>
<td>ABG, RR &amp; Comfort score</td>
</tr>
<tr>
<td>5</td>
<td>CPAP system: 10 cmH₂O</td>
<td>0.6</td>
<td>60 minutes</td>
<td>ABG, RR &amp; Comfort score</td>
</tr>
</tbody>
</table>

Ethical approval was given but did not require written consent as it was deemed part of ‘acute’ care. Verbal permission was sought.
Figure 6.1 Sequential change in oxygen delivery device delivered to the participating subjects (as per Hospital protocol/guideline). (A = Venti-mask system, B = CPAP system with no PEEP valve – T-piece, C = CPAP system with PEEP valve applied (pressure 5 or 10 cmH₂O))
Patients were recruited if they fulfilled the following inclusion/exclusion criteria:

6.2.1 *Inclusion criteria:*

- Adults >16 years
- Acute (<48 hours) Type I respiratory failure:
  - $\text{PaO}_2 < 8.0$ kPa when breathing room air.
  - $\text{PaCO}_2 < 6.0$ kPa (not deemed suitable in the presence of CO2 retention).
- A decision to apply the CPAP system had been made by the attending physicians.
- Maintenance of $\text{SpO}_2 > 93\%$ when breathing oxygen via a Ventimask with an FiO$_2$ insert of 0.6.

6.2.2 *Relative exclusion criteria were those for applying CPAP in the ward:*

- Patient delirium or low conscious level
- Evidence of clinical suspicion of raised intracranial pressure.
- Vomiting
- Facial injury or abnormality preventing good mask fitting.
- Imminent endotracheal intubation.
- Patient refusal.
- Refusal by the attending physician.

All clinical decisions relating to the patient’s ongoing care were made by the attending physicians. The study observer had no influence on the delivery of CPAP, nursing care or any medical decisions.

Patients were given the option of separate arterial blood gas (ABG) measurements or insertion of an arterial catheter under local anaesthetic. In some cases a catheter was inserted by the medical team, or was already *in situ*. All patients were monitored with $\text{SpO}_2$, non-invasive or invasive (if arterial line *in situ*) blood pressure and single
lead electrocardiography. The subjects were either seated in a chair or in bed. Additional monitoring such as central venous catheterisation was dictated by the nature of the clinical condition and preferences of the attending medical staff. Once the timescale outlined in Table 6.2 had been completed, the care and further management was returned to the medical team.

6.2.3 Data collection

At each stage in the protocol three measurements were made:

1. An arterial blood gas (ABG) sample recording PaO$_2$ and PaCO$_2$.

2. An enquiry as to their level of ‘comfort’ on a scale of 1 to 10 where 10 is very comfortable and 1 is extremely uncomfortable. A comfort score.

3. Respiratory rate.

In addition to the ABG, comfort score and respiratory rate data, patient demographics, the clinical diagnosis made by the attending physicians and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score were documented$^{19}$.

6.2.4 Statistical analysis

All data was analysed using SPSS 14.0 (LEAD Technologies Inc. USA). Where appropriate the data was analysed on an intention-to-treat basis. To detect statistical significant differences in oxygenation and respiratory rate between the different stages of the protocol, a two way analysis of variance was performed with a Bonferroni correction to allow for multiple testing. Assessment of the ordinal data of
the comfort score was performed using a Kruskal-Wallis test. Detection of location of differences was performed using repeat Mann-Whitney U tests. Analysis of demographic data, diagnosis and APACHE II score was performed using a Student’s t-test for continuous data and a Chi\(^2\) test for categorical data. Repeated Measures analysis of variance was carried out as part of a sub-group analysis to look at whether age, gender, diagnosis or APACHE II score had additional influence on oxygenation. A p value of 0.05 was taken to represent a significant finding.

6.2.5 Sample Size

Although this was a audit it was assumed, from experience, that CPAP would improve oxygenation and a power analysis was performed. A sample size of 53 patients was required to detect a 2.5 kPa increase in PaO\(_2\) with a significance of 0.05 and a power of 80% (assuming a common \(\sigma\) of 6 kPa).

6.3 Results

53 patients were audited. Their demographic data is represented in Table 6.3. They were a heterogenous group of patients with a variety of pulmonary causes for acute respiratory failure. The age range was 22-93 years (mean 61 SD +/- 20 years). 2 of the patients were intolerant of CPAP prior to completing the 1 hour (stage 4 – see Table 6.3). 1 patient became intolerant to the mask at 10 cmH\(_2\)O (stage 5). 1 further patient deteriorated on treatment and was intubated and ventilated prior to completion of stage 5. The results are presented in Tables 6.3 – 6.8 and figures 6.2 – 6.5. Stage 5 is not always appropriate and so there are fewer patients (n=31), and
3 of this group had already either become intolerant of CPAP, 2, or required intubation, 1.

Table 6.3 Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (yr)</td>
<td>60.89 (+/- SD 20.36)</td>
</tr>
<tr>
<td>Male Gender</td>
<td>26 (49.1%)</td>
</tr>
<tr>
<td>Apache II score</td>
<td>17.74 (+/- SD 4.58)</td>
</tr>
<tr>
<td>Mean PaO$_2$ recruitment criterion (kPa)</td>
<td>7.87 (+/- SD 0.76)</td>
</tr>
<tr>
<td>Mean PaCO$_2$ recruitment criterion (kPa)</td>
<td>4.86 (+/- SD 0.71)</td>
</tr>
<tr>
<td>Respiratory rate (breaths.min$^{-1}$)</td>
<td>29 (+/- SD 6)</td>
</tr>
</tbody>
</table>

Table 6.4 Clinical diagnoses of aetiology of acute respiratory failure in audit subjects

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia (%)</td>
<td>22 (41.5%)</td>
</tr>
<tr>
<td>Cardiogenic pulmonary oedema</td>
<td>11 (20.9%)</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>7 (13.2%)</td>
</tr>
<tr>
<td>Pulmonary oedema (hypervolaemic)</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Haemothorax</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Viral pneumonitis</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td><em>Pneumocystis carinii</em> pneumonia</td>
<td>1 (1.9%)</td>
</tr>
</tbody>
</table>
Table 6.5  Mean PaO$_2$ in patients with respiratory failure

<table>
<thead>
<tr>
<th>Oxygen system</th>
<th>Venturi</th>
<th>T-piece</th>
<th>CPAP 5cmH$_2$O</th>
<th>CPAP 5cmH$_2$O</th>
<th>CPAP 10cmH$_2$O</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO$_2$</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Time</td>
<td>10 min</td>
<td>10 min</td>
<td>10 min</td>
<td>50 min</td>
<td>60 min</td>
</tr>
<tr>
<td>Mean PaO$_2$ (kPa)</td>
<td>10.37</td>
<td>21.06</td>
<td>21.13</td>
<td>21.16</td>
<td>19.56</td>
</tr>
<tr>
<td>Range (kPa)</td>
<td>7-22</td>
<td>11.05-44.05</td>
<td>10.76-42.92</td>
<td>10.98-36.6</td>
<td>11.1-32.67</td>
</tr>
<tr>
<td>St Dev (kPa)</td>
<td>2.83</td>
<td>7.067</td>
<td>7.53</td>
<td>6.54</td>
<td>5.98</td>
</tr>
</tbody>
</table>

Figure 6.2  Mean PaO$_2$ in patients with respiratory failure at each stage of the CPAP protocol. Error bars represent +/- 2SD (n=53 up to CPAP 5 cmH$_2$O, n=31 for CPAP 10 cmH$_2$O). P<0.001 (ANOVA)
Table 6.6 Mean PaCO₂ in patients with respiratory failure

<table>
<thead>
<tr>
<th>Oxygen system</th>
<th>Venturi</th>
<th>T-piece</th>
<th>CPAP 5cmH₂O</th>
<th>CPAP 5cmH₂O</th>
<th>CPAP 10cmH₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>FlO₂</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Time</td>
<td>10 min</td>
<td>10 min</td>
<td>10 min</td>
<td>50 min</td>
<td>60 min</td>
</tr>
<tr>
<td>Mean PaCO₂ (kPa)</td>
<td>4.86</td>
<td>4.93</td>
<td>4.91</td>
<td>4.93</td>
<td>5.04</td>
</tr>
<tr>
<td>Range (kPa)</td>
<td>3.45-6.20</td>
<td>3.51-6.47</td>
<td>3.43-6.31</td>
<td>3.54-6.55</td>
<td>3.73-6.38</td>
</tr>
<tr>
<td>St Dev (kPa)</td>
<td>0.71</td>
<td>0.75</td>
<td>0.76</td>
<td>0.72</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Figure 6.3 Mean PaCO₂ in patients with respiratory failure at each stage of the CPAP protocol. Error bars represent +/- 2SD (n=53 up to CPAP 5 cmH₂O, n=31 for CPAP 10 cmH₂O). P=0.87 (ANOVA)
Table 6.7 Median respiratory rate in patients with respiratory failure

<table>
<thead>
<tr>
<th>Oxygen system</th>
<th>Venturi</th>
<th>T-piece</th>
<th>CPAP 5cmH₂O</th>
<th>CPAP 5cmH₂O</th>
<th>CPAP 10cmH₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO₂</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Time</td>
<td>10 min</td>
<td>10 min</td>
<td>10 min</td>
<td>50 min</td>
<td>60 min</td>
</tr>
<tr>
<td>Mean Resp. Rate (breaths.min⁻¹)</td>
<td>29.4</td>
<td>29.1</td>
<td>28.9</td>
<td>26.6</td>
<td>25.5</td>
</tr>
<tr>
<td>Range (bpm)</td>
<td>14-40</td>
<td>16-40</td>
<td>16-39</td>
<td>15-39</td>
<td>12-32</td>
</tr>
<tr>
<td>St Dev (bpm)</td>
<td>6.05</td>
<td>5.86</td>
<td>5.89</td>
<td>5.16</td>
<td>4.71</td>
</tr>
</tbody>
</table>

Figure 6.4 Mean respiratory rates in patients with respiratory failure at each stage of the CPAP protocol. Error bars represent +/- 2SD (n=53 up to CPAP 5 cmH₂O, n=31 for CPAP 10 cmH₂O). P=0.04 (ANOVA)
Table 6.8 Median comfort scores for patients with respiratory failure

<table>
<thead>
<tr>
<th>Oxygen system</th>
<th>Venturi</th>
<th>T-piece</th>
<th>CPAP 5cmH₂O</th>
<th>CPAP 5cmH₂O</th>
<th>CPAP 10cmH₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIO₂</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Time</td>
<td>10 min</td>
<td>10 min</td>
<td>10 min</td>
<td>50 min</td>
<td>60 min</td>
</tr>
<tr>
<td>Median Comfort score</td>
<td>9</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Range</td>
<td>6-10</td>
<td>2-9</td>
<td>1-9</td>
<td>1-8</td>
<td>3-8</td>
</tr>
<tr>
<td>IQR</td>
<td>1</td>
<td>1.75</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 6.5 A box and whisker plot of the comfort score expressed by patients with respiratory failure at each stage of the CPAP protocol. (n=53 up to CPAP 5 cmH₂O, n=31 for CPAP 10 cmH₂O). P<0.001 (Krukal-Wallis).
The results of this audit in patients with acute type 1 respiratory failure demonstrate a significant improvement in PaO$_2$ on changing from the Ventimask$^\text{®}$ to the CPAP system (mean change 10.69 kPa (SD 5.14 kPa)). The addition of the PEEP valve either at 5 cmH$_2$O or 10 cmH$_2$O did not result in an increase in the mean PaO$_2$. The mean value of PaCO$_2$ was unaffected by either the change from Ventimask to the T-piece or on the application of the PEEP valve at either 5 cmH$_2$O or 10 cmH$_2$O. (p=0.87). However, there was statistically significant difference in the respiratory rate, a decrease, on the application of the 5 cmH$_2$O PEEP valve (p=0.04). Further increases in the value of the PEEP valve did not significantly reduce the respiratory rate.

The comfort score was significantly reduced on the application of the CPAP system from the Ventimask$^\text{®}$. (p=0.047). However, though the reduction in the comfort score across the whole protocol was statistically significant (p<0.001, Kruskal-Wallis test), differences between the subsequent stages were not apparent.

The diagnosis was considered albeit in a small number of patients. The general pattern of early improvement in oxygenation was seen throughout. In the 11 patients with a diagnosis of cardiogenic pulmonary oedema the pattern appeared the same.

6.4 Discussion

In patients being put on CPAP for a range of causes of acute respiratory failure there is a significant increase in oxygenation on changing from a Ventimask$^\text{®}$ to a CPAP system despite no change in the fractional inspired oxygen. The subsequent addition of pressure of either 5 cmH$_2$O or 10 cmH$_2$O appears to have no immediate further
benefit in terms of an increase in oxygenation over the following hour, or two hours in
the patients followed for that time period. It should be noted that the respiratory rate
did fall on CPAP.

This audit of the oxygenation of a heterogenous group of patients in respiratory
failure, being treated with CPAP had some interesting findings. On changing from
the Ventimask® to the CPAP system it appears that a significant improvement in
oxygenation occurs during instigation when there is no CPAP valve and hence
negligible system pressure (the intrinsic pressure in the open CPAP system at these
flow rates, measured on a lung model, is between 1.2 and 1.6 cmH₂O). There then
appears to be no further improvement in oxygenation on application of the CPAP
valves to produce positive airway pressure (PAP), either 5 cmH₂O or subsequently
10 cmH₂O. There was however a gradual reduction in respiratory rate over the two
hours on CPAP (p= 0.027). The changes after one hour are not significant although
this may reflect relatively small numbers.

The implication is that the immediate improvement in oxygenation is rapid,
independent of pressure and probably reflects a higher inspired oxygen
concentration with a closed system than with the Ventimask®. As the effect occurs in
a heterogenous group of patients it suggests a physical characteristic of the system
rather than anything related to any specific disease process. The subsequent
application of pressure has no further immediate effect on oxygenation, even at 1
hour, although 5 cmH₂O did appear to result in a decrease in respiratory rate. This
latter effect implies an improvement in the pattern of breathing which could be
because of better oxygenation. Alternatively it may be due to a physiological effect
such as a change in the work of breathing, altered compliance or increased FRC but
this is conjecture. The patients were also undergoing treatment for their condition in
parallel to these observations and this cannot be excluded from interpretation of this observation.

It is hard to align the decrease in respiratory rate with the potential for further improved oxygenation when no further improvement in oxygenation is seen albeit over a limited time period. It is therefore possible the rate effects are due to the initial oxygenation effect and not related to more complex physiological corrections such as recruitment or changes in ventricular function which one might expect to see by one hour. One argument might be that these high flow systems generate their own intrinsic pressure but this was measured, on a model, and is only approximately 1.4 cmH$_2$O which seems highly unlikely cause such impressive effects.

There was no obvious effect on the carbon dioxide which is reassuring. Comfort has always been an issue with CPAP systems and so this simple comfort score was used as a very basic assessment tool. It has always been known that patients find CPAP uncomfortable and this simple score appears to confirm that.

6.4.1 Critique of the Audit

The numbers are too small to draw any conclusions from the diagnostic categories. Albeit post priori, the differential diagnoses were evaluated. It was the younger patients with pneumonia that appeared to have the greatest improvement in oxygenation and this was borne out statistically. While it had been expected that the patients with congestive cardiac failure would show dramatic improvement with the application of pressure, this was not obvious. In such patients the initial improvement in oxygenation with CPAP was without any pressure as with the patients with other diagnoses. The argument has long been that CPAP benefits congestive failure
through the effects of the positive pressure. The oxygenation effect seen in this audit occurs before the pressure is applied and so seems to be pressure independent. If the physiological effects are genuinely important in terms of oxygenation then, as some of these patients were followed for two hours, a hypothesis needs to be generated to explain when one might expect to see the benefits of these effects. The current literature does not suggest a timescale for the effects of PAP to act on the lung. The surrogate approach of detecting when the maximal improvement in oxygenation occurs would suggest a one to two hour period\textsuperscript{20-24}. This was part of the reasoning behind limiting the audit to two hours. The other was more pragmatic. It was felt that continuous therapy with CPAP was most likely to detect the influence of PAP on the primary endpoint, oxygenation. Maintaining continuous therapy without a break is difficult much beyond two hours, thus a 2 hour limit was set to try to evaluate the immediate effects of CPAP. Only two of the 53 patients found CPAP intolerable within those two hours and it might be that the audit could have been continued longer without significant drop-out. The use of sophisticated masks may improve comfort and compliance with treatment, but have a significant cost implication. This needs to be formally studied and a future study could attempt longer periods of assessment, such as four or six hours. As a final point, it is interesting that the respiratory rate was significantly decreased after the application of CPAP even within this short time-scale, although it did take longer to become apparent than in the literature. Summaries of the mechanical aspects of the physiological rationale for non-invasive ventilation (including CPAP) imply an almost immediate effect. Thus work of breathing, pulmonary compliance and FRC all improve early in treatment which is reassuring when drawing conclusions from the observations reported here\textsuperscript{25}. 
There are several other limitations to this audit. It is observational nature and the attention of the team and the nature of the equipment may affect these results. A study randomising patients to a T-piece or CPAP would improve the quality of this data but this poses dilemmas in consent in patients who are clinically at risk.

A further issue is that this is a relatively small audit with a wide distribution of data. An endpoint of a 2.5 kPa increase in PaO$_2$ between the different stages of the protocol would be considered a significant change and this value is based on the literature from studies in ACPO when CPAP is introduced following mask oxygen therapy.$^{24}$ Would such an increase be expected by introducing a CPAP valve to the open CPAP system be reasonable? Clinically such an increase would be desirable, as for example, an improvement in PaO$_2$ of 7.9 kPa to 10.5 kPa would be viewed by most clinicians as an effective, but moderate intervention. In the future bigger numbers may allow greater confidence in the information and permit any data from subgroups such as diagnosis to become more obvious. Indeed, whilst the heterogeneity of the subject’s pathology makes this data more easily applicable to clinical practice, it may hide signals specific to certain patients groups.

It could be argued that CPAP was not the appropriate treatment for the respiratory failure in some of these patients. If this were the case, and it is clearly a matter of opinion, then it shows that even in this relatively small group of patients, CPAP is being used successfully for patients with evidence of significant hypoxia regardless of cause. This is an issue which played a significant part in the inception of this audit. If one were to limit the audit to conditions where there is strong evidence from the literature of CPAP being of benefit e.g. ACPO or possibly post-operative atelectasis, then whilst more scientifically acute, the results would not reflect its use in the
medical community, making the results much less applicable. A large prospective trial is needed.

The trigger for consideration for CPAP was a clinician deciding it was needed and was dependent on a clinician led diagnosis. This may have added a degree of subjectivity. Maybe a more formal assessment of the diagnostic data by independent clinicians would allow for greater diagnostic accuracy in a future trial.

There was a low rate of endotracheal intubation when compared to the literature (1.89%). These were mainly ward patients and the decision to use CPAP was entirely in the hand of their clinicians and the Outreach team. Though blinded to the presence of audit when deciding to institute CPAP, this may reflect earlier intervention in this institution.

6.4.2 Clinical Implications

This audit demonstrates that the CPAP system, with or without pressure, is clearly superior in delivering oxygen to the available open mask system. However as mentioned in the introduction and as demonstrated by the findings with the comfort score, it is uncomfortable for some patients. If its main effects are in fact secondary to physics rather than physiology, there is an argument for improving the performance of non-sealed mask systems. One can postulate that the seal of CPAP system is only required because the reservoirs of commonly used oxygen masks are insufficient. Without the necessity of being able to pressurise the system it would be easier to design far more comfortable oxygen delivery systems that enable better coughing and physiotherapy and even drinking and eating without detriment to
oxygenation. It is therefore very important that the mechanism of oxygenation in CPAP is investigated further.

6.4.3 Conclusions

In patients in acute respiratory failure, CPAP achieved a higher inspired oxygen concentration than a Ventimask® at the same set inspired oxygen fraction but the main changes occur prior to the application of the valve and hence the pressure. In this simple observational audit it appears the immediate effects of CPAP on oxygenation in patients is pressure independent. This challenges existing concepts on how CPAP works in the critically ill. This needs urgent examination in a formal study.


Chapter 7

An Audit of Fluid Resuscitation of Ward Patients

7.1 Background

The means by which the ward outreach services can intervene in the ward are limited and to this point the main focus has been on oxygen delivery to the patient. The other significant area of intervention is fluid management and dealing with ‘on the ward’ fluid resuscitation.

A very common problem is haemodynamic disturbance and in particular hypotension. Goldhill et al. demonstrated that ward patients have a higher mortality with critical illness than patients presenting to the emergency department or via the operating theatre\(^1\). The emphasis was on detecting problems early, the implication being that earlier implementation of treatment may avert deterioration and should improve outcome. Hence the advocacy for track and trigger scores. The Critical Care Outreach Team (CCOT) and the ward based staff are in the ideal position for early identification of fluid management issues and therefore well placed for early intervention. To date the areas that have been investigated have been either the means of early detection and development of early warning systems, or the efficacy of the team approach\(^2-7\). This includes CCOT and MET (Medical Emergency Team) and has focused on dealing with ward problems using early warning systems linked to team management and then hard outcomes such as cardiac arrest. There is very little or no information about specific interventions such as when and what fluid management is instituted and whether it is effective, even though it is a significant
part of the interventions that are likely to be instituted. The study by Rivers et al. where they applied early goal directed therapy in the emergency department and demonstrated improved outcomes seems to be a good potential model for ward intervention\(^8\). While clearly this is a very different environment, it seems intuitive, that early intervention elsewhere such as the ward should also be beneficial. The earlier the better is not dissimilar to the concept of the ‘Golden Hour’ so familiar in the treatment of trauma\(^9\). In practice this has not yet been shown in the ward environment.

This chapter is intended to provide an idea of what is happening currently in one institution to try to develop a picture of fluid management as a ward based intervention.

### 7.1.1 Hypotension and Early Circulatory Failure

The intervention of fluid administration is hard to define. In the ward environment a patient may become unwell for a wide range of reasons. The early warning signs of tachycardia, hypotension, alterations in perfusion and tachypnoea may be indicators of hypovolaemia or relative hypovolaemia. Depending on the cause and its natural history this may, if left untreated, progress towards a shock state. Shock is defined loosely as failure of the circulation to adequately meet the body’s metabolic demands. It classically comes in several guises outlined in Table 7.1.
Table 7.1 Physiological classification of circulatory shock

<table>
<thead>
<tr>
<th>Type of Shock</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distributive</td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>LV failure</td>
</tr>
<tr>
<td></td>
<td>Severe valvular disease</td>
</tr>
<tr>
<td>Hypovolaemic</td>
<td>Haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Heat stroke</td>
</tr>
<tr>
<td>Obstructive</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>Cardiac tamponade</td>
</tr>
</tbody>
</table>

Once established it may require relatively sophisticated interventions to treat shock including invasive cardiovascular monitoring to guide fluid and inotrope management which may necessitate Intensive Care and is not feasible in the ward. Paradoxically early simple interventions in the wards, before shock becomes established may be relatively more effective than late intervention in Intensive Care. Therefore in the ward environment, focusing on the clinical events that may be a clue to evolving shock is probably more useful in terms of intervention than once shock has become established and more aggressive measures will almost certainly be needed. The evidence that exists currently demonstrates beyond reasonable doubt, that failure to deal with these problems early is associated with poor outcome and that early warning systems do detect the problems earlier. As yet hard data confirming that early intervention in the ward is effective is lacking. As mentioned few, if any, studies address the specific interventions being used and tend to focus on the systems being employed such as CCO or MET.
The techniques currently available to treat or support early signs of circulatory insufficiency in the ward are limited to intravenous fluid resuscitation in various forms. Some ward areas permit low dose inotropes (e.g. Dopamine), but in general, the initial resuscitation of the acutely shocked patient is limited to the administration of fluids. These may be in the form of crystalloid, colloid and/or blood products. The monitoring available is also very limited with central venous monitoring often unavailable in the early stages when the CCOT is called.

7.1.2 Intravenous Fluid Resuscitation

In the ward situation, with limited facilities fluid resuscitation is commonly the first approach to improving the circulation. While it is simple and rapid and is often beneficial it is not innocuous. In resuscitation, it has long been associated with problems although the literature tends to come from resuscitation environments or from management of the critically ill. In 1977 Lucas et al. demonstrated that high volumes of fluid resuscitation in trauma (mean of 9.3 litres blood and 17.4 litres of crystalloid) lead to a syndrome of hypertension and a raised cardiac output with respiratory insufficiency in 18 of the 35 patients studied. Further information suggesting the potential negative effect of excessive fluid administration comes from a study by Wiedemann et al. this time in patients with acute lung injury. In the very sick, a conservative fluid strategy in cardiovascularly stable patients reduced intensive care stay and time of mechanical ventilation and suggested liberal fluid management may be detrimental in the critically ill with pulmonary complications. There is no doubt that in these scenarios excess fluid administration is hazardous but can it be extrapolated to the ward? The work of Goldhill and others suggest that some patients on the ward are becoming critically ill and need early intervention and
so, while the studies are not available, it is reasonable to assume that while the ward situation may be different the dilemma as regards fluid administration is the same. The lesser severity of illness may be balanced by the paucity of monitoring.

Under these circumstances the mode in which fluids are administered is unclear. Generally it takes two forms. In the dehydrated patient who may be considered to be behind on fluid, a general increase in fluid administration may be indicated which is a relatively minor alteration in the management already in place. This would be very hard to detect as a step wise intervention, in an audit. Alternatively if the patient is considered hypovolaemic, through changes in blood pressure perfusion or urine output, the administration of boluses of fluid may be initiated. Defining a bolus is complex. In studies a ‘bolus’ is usually defined in terms of both volume and rate of administration. In the ward there is no set definition and circumstances may dictate both the size and rate of administration of a bolus. This makes it difficult to define what constitutes a bolus.

A reasonable broad encompassing definition might be, “An incremental volume of fluid being given far more rapidly than would be usual for normal intravenous fluid administration and being given for a specific indication.”

In the studies that have been published such as those of Rivers et al. in the emergency setting or those in the high risk surgical population, the environments allowed invasive monitoring. This included monitoring of central venous pressure, lactate concentration and the ScvO₂ in the Rivers study and the use of central catheters and cardiac output monitors with high risk surgical patients\textsuperscript{17-19}. In those studies it is clear that the use of intravenous fluid to resuscitate the shocked patient needs to be timely, appropriate and well monitored if the goals of resuscitation are to
be achieved with the least associated morbidity. In the ward environment these monitors are not readily, if ever available and in patients found by early warning systems, would need to be initiated rather than being in place. While a ubiquitous practice, it would seem after an extensive search of the literature, that the use of fluid resuscitation on the wards of a general hospital has never been studied. It has certainly not been studied in the manner in which it is currently used by CCOTs as one of the few interventions available to them.

This is the context in which a preliminary audit to assess the accessibility of this intervention to study, was established. In this Institution CCO services are functional and are called to the ward to assess and institute early intervention which often involves fluid management. The aim of the audit was to acquire a general picture of current practice with regard to fluid intervention for haemodynamic instability in the ward environment. There was no obvious comparator at the time of this audit but it was considered wise to use a comparator, a ‘gold standard’. The nearest approach is that by Rivers et al. using the early goal directed therapy guidelines albeit in a very different environment where patients are seen de novo and management instituted rapidly, often with fluids. At the time of this audit Rivers protocol for early goal directed therapy was being considered for implementation in the ward environment. Although there are clear limitations to the comparison it theoretically provided a known standard against which the audit could be compared and had the potential advantage of looking at the practicality of its implementation.
7.2 Methodology

This was a prospective audit of the use of fluid intervention for haemodynamic instability in the ward and was observational in nature. The observer had no influence on clinical care and decision making. The audit was carried out on the general wards of the Chelsea and Westminster Hospital. The population of patients audited were identified by the following criteria:

7.2.1 Inclusions

- Adults >16 years
- Entry to the audit was triggered by referral to CCOT for opinion about the management of a predefined haemodynamic abnormality or ‘target’ (Table 6.2). This was required to be either:
  - A new referral.
  - A minimum of 5 days since a previous review by ICU/CCOT.
  - A minimum of 5 days after discharge from ICU.
- The need for fluid resuscitation.
- They had to be ward based in-patients with a duration of admission > 24 hour, i.e. not new admissions

7.2.2 Exclusions

Patients from level 2 and 3 beds were excluded, as well as patients attending the emergency department. It was felt sensible to exclude patients in the maternity or paediatric departments and those suffering cardiac arrest.
7.2.3 Definitions

**Intravenous fluid resuscitation:** A bolus was loosely defined as: “An incremental volume of fluid being given far more rapidly than would be usual for normal intravenous fluid administration and being given for a specific indication.”

For the purpose of this audit and to be inclusive, intravenous fluid resuscitation (IFR) was defined the use of a bolus as an intake of greater than or equal to 250ml of intravenous fluid in 60 minutes as an individual and specific intervention separate from the prescribed fluid administration.

**Target (feature of haemodynamic instability):** In each situation the indication for IFR was recorded, the ‘target’ was haemodynamic instability necessitating intervention. An assessment made of whether treatment of the target was satisfactory (reversed) by the administration of intravenous fluid. This did not necessarily mean that the indication chosen had returned to ‘normal’ but rather that its ongoing treatment with IFR was not required further.

**Complications:** The detection of complications of intravenous fluid was attempted by recording variables associated with predictable complications of hypervolaemia. These were new signs of peripheral oedema, rales on auscultation. New chest x-ray signs of infiltration consistent with oedema and with no other cause. Lastly, a CVP greater than 15 mmHg.

**Comparison with goal directed therapy.** Data was also gathered, where possible, on targets sought in the ward which were comparable to those described by the study by Rivers et al. on EGDT, as evidence of systematic goal-directed treatment. This could be used as a comparator albeit from a different environment.
7.2.4 Practical Application of the Method

A patient from the ward was included on referral to the CCOT. The admission criterion to this study was the need for fluid to treat haemodynamic instability as outlined above.

The time from the first appearance in the patient’s documentation of the target abnormality was recorded. The time of the institution of IFR was documented to assess the response time after the appearance of the target. The time from its appearance to calling the CCOT was also documented.

If IFR was required already, on the advice or the direct action of the CCOT, an assessment of the specific indication for IFR was made. This then became the target and its reversal an endpoint, as was its failure to effect reversal. This was used to define success or failure of the IFR. The definitions of target are summarised in Table 7.2. Each patient was reviewed at 6, 24, 48 and 72 hours. A range of other available physiological data pertaining to the perceived success of IFR was also gathered on each occasion. The baseline data recorded and the subsequent review data are summarised in Table 7.3.

Time 0 was defined as the time of the first fluid bolus. When two or more measurements of infrequently sampled variables e.g. pH by arterial blood gas analysis (ABG) were present within a time interval, the sample closest to the review time was recorded. Complications of fluid management were sought by the assessment of the variables thought to be indicative of fluid overload (Table 7.3).
Some measurements from the early goal directed therapy (EGDT) protocol as described by Rivers et al. were chosen as a standard with which to compare the results in the audit. Thus data was gathered to detect adherence to the protocol published in the New England Journal of Medicine\(^8\) (Figure 7.1). This took the form of examining, at 6 hours, measurements obtained from central venous catheters.
(CVC) and their subsequent use of ScvO₂ and the maintenance of a haematocrit above 0.3.

The use of vasoactive agents was not relevant as this was almost impossible in the ward environment. Other patient endpoints were defined as ICU admission, death and the initiation of a ‘Do not actively resuscitate’ (DNAR) order. Data collection was ceased if the patient was admitted to the ICU, died or was transferred to another institution. Death in hospital was recorded.

**Table 7.2 Definitions of targets for IVR**

<table>
<thead>
<tr>
<th>Target</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low mean arterial pressure (MAP)</td>
<td>MAP &lt; 65 mmHg</td>
</tr>
<tr>
<td>Increased heart rate (HR)</td>
<td>HR &gt; 100 beats.min⁻¹</td>
</tr>
<tr>
<td>Low urine output (UO)</td>
<td>UO &lt; 0.5 ml.hr⁻¹</td>
</tr>
<tr>
<td>Raised creatinine</td>
<td>Creatinine &gt; 120 μmol.l⁻¹ when thought to be previously normal</td>
</tr>
<tr>
<td>Worsening acidosis</td>
<td>pH &lt; 7.36 and unacceptable to the attending team</td>
</tr>
<tr>
<td>Abnormal base deficit (BE)</td>
<td>BE &lt; -2 and unacceptable to the attending team</td>
</tr>
<tr>
<td>Abnormal lactate</td>
<td>Plasma lactate &gt; 2 mmol.l⁻¹ and unacceptable to the attending team</td>
</tr>
<tr>
<td>Other</td>
<td>Any other cause thought by the attending team to require IVR.</td>
</tr>
</tbody>
</table>
Table 7.3 Data recorded during audit at baseline and reviews at 6, 24, 48 and 72 hours.

<table>
<thead>
<tr>
<th>Baseline data recorded</th>
<th>Review data recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td><strong>IVR</strong></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>Fluid volume</td>
</tr>
<tr>
<td>Male gender</td>
<td>administered (ml)</td>
</tr>
<tr>
<td>DOA (days)</td>
<td>Fluid type(s) used</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Fluid balance (ml)</td>
</tr>
<tr>
<td>APACHE II (0-71)</td>
<td>MMODS (0-20)</td>
</tr>
<tr>
<td>MMODS (0-20)</td>
<td>Target achieved? (Y/N)</td>
</tr>
<tr>
<td><strong>Target and response</strong></td>
<td><strong>Complications</strong></td>
</tr>
<tr>
<td>Target</td>
<td>New bilateral rales</td>
</tr>
<tr>
<td>Time of abnormality (hr)</td>
<td>(Y/N)</td>
</tr>
<tr>
<td>Time of response (hr)</td>
<td>New CXR infiltrates</td>
</tr>
<tr>
<td>Time to call CCOT (hr)</td>
<td>(Y/N)</td>
</tr>
<tr>
<td></td>
<td>New clinical oedema</td>
</tr>
<tr>
<td></td>
<td>(Y/N)</td>
</tr>
<tr>
<td></td>
<td>CVP &gt; 15mmHg (Y/N)</td>
</tr>
<tr>
<td></td>
<td>RRT for fluid overload</td>
</tr>
<tr>
<td></td>
<td>(Y/N)</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td><strong>Cardiovascular</strong></td>
</tr>
<tr>
<td>HR (beats.min⁻¹)</td>
<td>HR (beats.min⁻¹)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>MAP (mmHg)</td>
</tr>
<tr>
<td>CRT (s)</td>
<td>CRT (s)</td>
</tr>
<tr>
<td>CVC (Y/N)</td>
<td>CVC (Y/N)</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>CVP (mmHg)</td>
</tr>
<tr>
<td>ScvO₂ (%)</td>
<td>ScvO₂ (%)</td>
</tr>
<tr>
<td>Use of inotropes (drug</td>
<td>Use of inotropes (drug</td>
</tr>
<tr>
<td>and dose)</td>
<td>and dose)</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>Haematocrit</td>
</tr>
</tbody>
</table>
Table 7.3 (contd.) Data recorded during audit at baseline and reviews at 6, 24, 48 and 72 hours.

<table>
<thead>
<tr>
<th>Baseline data recorded</th>
<th>Review data recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td>Respiratory rate (breaths.min(^{-1}))</td>
<td>Respiratory rate (breaths.min(^{-1}))</td>
</tr>
<tr>
<td>Oxygen therapy (Y/N)</td>
<td>Oxygen therapy (Y/N)</td>
</tr>
<tr>
<td>NIV/CPAP (Y/N)</td>
<td>NIV/CPAP (Y/N)</td>
</tr>
<tr>
<td>FiO(_2)</td>
<td>FiO(_2)</td>
</tr>
<tr>
<td>SpO(_2) (%)</td>
<td>SpO(_2) (%)</td>
</tr>
<tr>
<td>ABG? (Y/N)</td>
<td>ABG? (Y/N)</td>
</tr>
<tr>
<td>PaO(_2) (kPa)</td>
<td>PaO(_2) (kPa)</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td><strong>Metabolic</strong></td>
</tr>
<tr>
<td>pH</td>
<td>pH</td>
</tr>
<tr>
<td>BE</td>
<td>BE</td>
</tr>
<tr>
<td>Lactate (mmol.l(^{-1}))</td>
<td>Lactate (mmol.l(^{-1}))</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td><strong>Renal</strong></td>
</tr>
<tr>
<td>Urinary catheter (Y/N)</td>
<td>Urinary catheter (Y/N)</td>
</tr>
<tr>
<td>UO (ml.kg.hr(^{-1}))</td>
<td>UO (ml.kg.hr(^{-1}))</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Creatinine</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>On ward? (Y/N)</td>
<td></td>
</tr>
<tr>
<td>ICU (Y/N)</td>
<td></td>
</tr>
<tr>
<td>Died (Y/N)</td>
<td></td>
</tr>
<tr>
<td>DNAR (Y/N)</td>
<td></td>
</tr>
</tbody>
</table>

IVR, intravenous fluid resuscitation; DOA, duration of admission; APACHE II, acute physiological and chronic health score\(^{21}\); mMODS, modified multi-organ dysfunction score\(^{22}\); CCOT, critical care outreach team; CXR, chest X-ray; CVP, central venous pressure; RRT, renal replacement therapy; CVC, central venous catheter; ScvO\(_2\), oxygen saturation of central venous blood; NIV, non-invasive ventilation; CPAP, continuous positive pressure ventilation; FiO\(_2\), fraction of inspired oxygen; SpO\(_2\), pulse oximetry oxygen saturation; ABG, arterial blood gas; PaO\(_2\), partial pressure of arterial oxygenation; BE, base deficit; UO, urine output; ICU, intensive care unit; DNAR, do not actively resuscitate order.
7.2.5 Statistical analysis

Descriptive statistics are presented as mean $\pm$ standard deviations (SD) for continuous data and median and inter-quartile range (IQR) or range for non-parametric data. Testing of relationships between different time intervals for fluid balance and rate of administration was performed using a Kruskal-Wallis test. Differences between separate time intervals were assessed using multiple Mann-Whitney U tests. All statistical analysis was performed on SPSS v14.0 (LEAD Technologies Inc. USA).

7.3 Results

7.3.1 General observations

84 non-consecutive patients were identified as suitable for entry to the audit over the study period of 12 months. Only those referred for haemodynamic instability were included. Complete documentation of medical observations, blood results, blood gas results etc. were sought. These were found to be deficient due to a variety of problems such as nursing documentation, lost samples, absence of CCOT cover at night, in 30 of the eligible patients and so these patients were excluded. This resulted in a cohort of 54 patients.

The indications for fluid resuscitation are summarised in Figure 7.2. The two most frequent indications were a urine output below $0.5 \text{ ml.kg}^{-1}.\text{hr}^{-1}$ or a mean arterial pressure of less than 65 mmHg.

A summary of the admission duration of the subjects is displayed in Figure 7.3. Median length of stay was 3 days (IQR 7 days). The baseline characteristics of the patients in the study are summarised in Table 7.4. The range of diagnoses was large
reflecting the heterogeneity of the disciplines that the CCOT cover. Diagnoses including such diversity as a ruptured ectopic pregnancy, massive epistaxis, Addisonian crisis and metformin overdose, preclude a readable table of diagnoses. The reasons or indications for fluid therapy are described in Table 7.1 and Figure 7.4.

All patients received at least 6 hours IFR with one exception where the patient was transferred out to another institution for specialist care. 39 patients had not reached a final end point (ICU admission, death or discharge) point at 24 hours, 35 by 48 hours. By 72 hours this decreased to 26 patients remaining in the audit, the rest having reached a final endpoint.

Figure 7.2 The indications for the institution of IVR – the Target. (UO, low urine output; MAP, low mean arterial pressure; BE, abnormal base defecit; HR, abnormal HR; pH, abnormal pH; azotaemia, rising creatinine; lactate, raised lactate. Criteria defined in Table 7.2).
Figure 7.3 Length of stay for the patients prior to the institution of IVR.

Figure 7.4 Causative pathophysiology underlying the conditions of the patients in the audit.
Table 7.4 Baseline characteristics of the patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (yr) +/- SD</td>
<td>57.9 +/- 18.3</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>44.4</td>
</tr>
<tr>
<td>Mean Heart rate (beats.min⁻¹) +/- SD</td>
<td>108.4 +/- 16.7</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg) +/- SD</td>
<td>59.96 +/- 15.2</td>
</tr>
<tr>
<td>Capillary refill time of &lt;2 seconds (%)</td>
<td>46.3</td>
</tr>
<tr>
<td>Mean Respiratory rate (breaths.min⁻¹) +/- SD</td>
<td>23 +/- 6.4</td>
</tr>
<tr>
<td>Mean SpO₂ (%) +/- SD</td>
<td>96.98 +/- 2.4</td>
</tr>
<tr>
<td>Median APACHE II Score (IQR)</td>
<td>20 (12.8)</td>
</tr>
<tr>
<td>Median mMOD Score (IQR)</td>
<td>4.5 (5.8)</td>
</tr>
</tbody>
</table>

SpO₂, pulse oxygen saturation; APACHE II, acute physiological and chronic health score²¹; mMODS, modified multi-organ dysfunction score²².

7.3.2 First involvement of the CCOT

Figure 7.5 summarises in a box and whisker plot the timeline from the first appearance of the target abnormality and the initial delivery of IFR (delineated by the box and whisker on the left). Median time was 3 hours (IQR 3 hours). The plot on the right records the timescale of the involvement of the CCOT with the appearance of an abnormal physiological target. Median time for referral to the CCOT is 5 hours (IQR 4 hours).
Figure 7.5. Response times from first appearance of target abnormality.

(Time IVR = Time delay to the initiation of IFR after appearance of the target abnormality; Time CCOT = Time delay before contact with the CCOT after appearance of the target abnormality). X axis = timeline Y axis = time in hours.

7.3.3 Ward patients compared to those in the Rivers EGDT study.

In this group of ward patients approximately 35 patients (64%) would have been eligible for consideration in the Rivers trial. However there were also three cases of gastrointestinal haemorrhage, two of status asthmaticus and two of acute pulmonary oedema, which were exclusion criteria in the original study. It was intended to use the Rivers trial as a comparator to have some standard for comparison. The issues being evaluated can be summarised as follows;
Treatment of the Problem within 1 hour of the Problem Being Recognised

The evidence is demonstrated in Figure 7.5. It clearly took far longer to identify and treat ward patients than those presenting to an emergency department.

Administration of Oxygen and/or Intubation

9/53 patients (16.7%) did not receive supplemental oxygen within the first 6 hours. However the SpO₂ was with one exception, adequately saturated on breathing room air.

Central Venous Catheterisation (CVC) and IFR to a CVP of 8-12 mmHg

This was rather central to the Rivers study and clearly was easily achieved. The ward environment in most general hospitals in the UK is far less conducive to placing central venous access. Despite this, 13/53 (24%) patients underwent central venous cannulation during the first 6 hours and a further 6/53 patients already had central catheters in situ prior to inclusion in the audit.

In terms of use of these for measurement the situation was unclear. Documentation was scarce, and the CVP values were often not recorded, or only every 4 hours. There was no evidence of a graded response to the CVP measurement, and its use in guiding the fluid management. Where there was a record of the measurement, 10/19 patients with CVC’s in situ did not achieve a CVP of 8 mmHg, 6/19 had CVP measurements within the range with 3 of these patients above 12 mmHg at 6 hours.
ScvO\textsubscript{2} Measurement

5/53 patients had an ScvO\textsubscript{2} measurement taken in the first 6 hours. Each had one sample taken and none had repeated measurement. All were below 70\% (range 59-69\%). No patients went on to receive dobutamine as this was not possible but one patient in severe cardiogenic shock did receive adrenaline.

Maintenance of Haematocrit (Hct) above 0.3 to Improve Oxygen Delivery

19/53 patients had a Hct less than 0.3. Of the patients who received blood, all, 9/9, were known to have an acute haemorrhagic condition and be actively bleeding but only 5 of these had Hct less than 0.3. 14 of the 19 patients with a haematocrit ≤0.3 did not receive blood.

7.3.4 Resolution of the Target Indication for Intervention

The indication for IFR, or target, was assessed for a return to haemodynamic normality as defined by the trigger values over the 72 hour period of the patient audit. This is summarised in Table 7.5. Of the 54 patients included, 9 had resolved their target by six hours, 14 by 24 hours, 5 by 48 hours and 5 by 72 hours. In total, 33 of the 54 patients had resolved their targets by 72 hours. 4/54 patients had not resolved their target at 72 hours, and had not either died or been admitted to the ICU (16/54 – see below).
Table 7.5 Resolution of target abnormality

<table>
<thead>
<tr>
<th>Time interval (hr)</th>
<th>6</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=54)</td>
<td>9</td>
<td>14</td>
<td>5</td>
<td>5</td>
<td>33 (62)</td>
</tr>
<tr>
<td>MAP target (n=16)</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>9 (56)</td>
</tr>
<tr>
<td>BE target (n=6)</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3 (50)</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; BE, base deficit.

Table 7.5 also summarises some sub-group analysis for the targets of MAP <65 mmHg and BE < -2. 9/16 patients with MAP as their target resolved the problem with IFR alone. Of the remainder 4/7 who failed to respond to fluid were admitted to ICU, 2/7 were palliated and 1/7 died. With regards to BE as a target, 3/6 resolved the problem within 24 hours. Of the remainder, 2 were admitted to ICU and 1 was palliated.

7.3.5 Poor Patient Outcomes

21 patients did not have resolution of their haemodynamic problems with fluid administration. Of these 13/20 were admitted to the ICU and 1 patient was transferred to a specialist centre. 3 patients died on the ward within 24 hours – with 2 suffering cardiac arrest. 1 patient was made DNAR and palliated. There were a remaining 4 patients who did not resolve but did remain on the wards after the 72 hour interval. One patient with an unresolved target remained actively treated, resolved slowly and was discharged home. In the remaining 3 patients the decision
was made to go to a DNAR status with appropriate palliation. Therefore 13 patients failed to resolve and required further treatment. There is inadequate information to assess whether the ward interventions were helpful in preventing further deterioration prior to ICU admission. These 13 patients were admitted to the ICU, 11 were admitted within 6 hours and the remaining 2 within 24 hours. 5/13 died on the ICU and 2/13 after discharge to the ward. There were 6 survivors.

7.3.6 Complications associated with fluid administration.

Potential complications associated with IFR are summarised in Table 7.6.

Oedema was defined as the subjective presence of new generalised peripheral oedema. Overall almost half the patients had oedema. Rales were defined as bilateral inspiratory crepitations typical of pulmonary oedema observed by the attending team.

X-ray changes. New infiltrates were defined as the appearance of bilateral alveolar shadowing on any chest x-ray that was taken during the 24 hour period and was not thought to be directly related to other pathology affecting the patient.

A CVP > 15 mmHg was also recorded for the 19 patients who had a CVC in situ or inserted during the audit period. The number 15 mmHg was arbitrary; chosen as 3 mmHg above the recommended target from the Surviving Sepsis Campaign\textsuperscript{23}. 
Table 7.6 Complication rates and the time of their appearance.

<table>
<thead>
<tr>
<th>Time interval (hr)</th>
<th>6 (n=54)</th>
<th>24 (n=39)</th>
<th>48 (n=35)</th>
<th>72 (n=26)</th>
<th>Total (%) (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rales</td>
<td>18</td>
<td>10</td>
<td>4</td>
<td>0</td>
<td>32 (59)</td>
</tr>
<tr>
<td>CXR changes</td>
<td>14</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>25 (46)</td>
</tr>
<tr>
<td>Oedema</td>
<td>1</td>
<td>6</td>
<td>11</td>
<td>8</td>
<td>26 (48)</td>
</tr>
<tr>
<td>CVP &gt; 15 mmHg</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>7 (37)</td>
</tr>
<tr>
<td>No Complications (%)</td>
<td>31 (57)</td>
<td>16 (41)</td>
<td>12 (34)</td>
<td>11 (27)</td>
<td></td>
</tr>
</tbody>
</table>

Table 7.7 Results for fluid volumes and rates administered over the 4 time intervals.

<table>
<thead>
<tr>
<th>Time interval (hr)</th>
<th>6</th>
<th>24</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median rate of fluid administration (ml.hr⁻¹) [range]</td>
<td>300 [83 - 667]</td>
<td>200 [63 - 338]</td>
<td>120 [42 - 167]</td>
<td>102.8 [63 - 148]</td>
</tr>
</tbody>
</table>
7.3.7 Volumes and Rate of Fluid Delivery

The volumes, rate of delivery and balance of fluid administered are summarised in Table 7.7. The median amount of fluid administered to those who remained on the wards for the duration of the audit was 9847 ml [range 7506-13660 ml]. There was also a statistically significant rise in fluid balance for the time intervals 24, 48 and 72 hours (p<0.001). The initial volume of fluid in the first 6 hours is 2000 ml, but delivered at a median rate of 300ml.hr^{-1}. Both volume and rate reduced over time (p<0.001).

7.4 Discussion

7.4.1 Summary

This audit sought to describe fluid interventions by the CCOT in patients in the ward environment. It proved an extremely difficult subject to audit and highlighted a large number of difficulties in investigating this type of ward intervention and indeed of assessing the efficacy of a ward based CCOT.

The range of patient diagnoses was too large to easily demonstrate in a table and this illustrates the breadth of the remit of a ward based CCOT. In this audit the median APACHE II score was 20 which is high for a ward environment and may suggest that ICU admission is likely.

The specific findings were as follows:

The response time from target trigger to initiation of fluid resuscitation was a median of 3 hours (IQR 3 hours) while the median time to referral to the CCOT was 5 hours.
(IQR 4 hours) suggesting that fluid resuscitation was often instituted before the arrival of the CCOT.

Of the patients receiving fluid therapy as an intervention, 34/54 were successful but it is hard to pinpoint the cause of failure in the remainder.

The cumulative amount of fluid given over 72 hours to those that remained on the wards was 9847 ml [7506 – 13660 ml]. The cumulative fluid balance at 72 hours was a median value of 5730 ml [1150 – 11419 ml].

Potential complications were common with the appearance of oedema of the lungs and tissues in approximately 50% of the patients. The pulmonary complications appeared early phenomenon.

7.4.2 Comparison with the EGDT Protocol of Rivers et al

As an audit, the comparison with the Rivers et al. study is problematic and will be discussed below needs to be discussed. The decision to use the Rivers study as a comparator was clearly erroneous creating more problems than it solved.

For example, from the point of inclusion in the study the entry trigger was referral to the CCOT but IFR was often initiated prior to referral to CCOT as can be seen by the time delays so that the use of CCOT referral as a method of selecting patients clearly excluded some patients. This was not comparable to the Rivers study where each patient in a casualty department is assessed on admission and so is seen immediately. This contrasts with ward patients who present randomly in a wide range of ways and the specific illnesses are not usually de novo primary illnesses. In the ward patients there was a delay in the institution of IFR and in the involvement of the
specialist team. This could really only be assessed against other ward based environments but there are no such studies.

Oxygenation was not a primary goal in this audit while it was central to the Rivers study. Most patients did not have oxygen therapy instituted rapidly. At the review of the diagnosis the target abnormality was invariably haemodynamic to be included in this audit rather than respiratory. The \( \text{SpO}_2 \) was with one exception, adequately saturated on breathing room air. This therefore was not a helpful endpoint to consider.

The use of CVP measurements was far less in the ward patients. This information is interesting but not helpful. In the Rivers study it was perceived that a target CVP value was essential and hence all have that monitoring. In the ward environment the CVP could have been used diagnostically but it is unlikely with such a wide range of patients that a specific CVP for all patients is either a realistic or even sensible goal for management. However this part of the audit does indicate that CVP is used more than was probably expected although it casts no light on how it is used.

This use of ScvO\(_2\) is of interest because it was a novel interventional measurement at the time. Although only 5 patients had such data recorded, it at least demonstrates an awareness of its potential value. There was no written evidence of how it was used if at all. More interesting is more recent work by Rupert Pearse (personal communication) showing that the range of normal ScvO\(_2\) is wide and although 59\% may be outside the normal range for Rivers, the patients may have fallen within a normal range. Reliance on ScvO\(_2\) as a sole measurement without the clinical background is probably fraught with difficulty.
In the Emergency department the focus on haematocrit is almost certainly appropriate but in the ward environment protecting a haematocrit of 0.3 is difficult in the context of a restrictive transfusion policy. While many would argue that in any acute illness a higher haematocrit is both safe and sensible the evidence is not yet there. Hence in both ICU and the wards a haematocrit less than 0.3 might even be perceived as good practice. In any event it makes comparison impossible.

These were the main comparators used and it clearly demonstrates the difficulties in using values or criteria from a rather specific trial in a very different environment. As a comparator it is useless but it did clearly illustrate some issues that might not otherwise have been aired, such as the use of haematocrit and of ScvO$_2$.

Of interest is the severity of illness. The APACHE score in the audit had a median value of 20. This does suggest the severity of illness of patients in the ward environment is in some respects comparable with that in a published trial albeit from an emergency department. It needs to be mentioned that this was not the way in which the APACHE score was originally described but it does still provide some indication of severity of illness. It may not be the optimal score for such an audit in future and possibly the SOFA score might be more appropriate.

7.4.3 Response Time

The response time is important. The delay in the response time to the institution of IFR is disappointing especially when compared to the study by Lundberg et al. whose ward patients had a median time to delivery of fluid of only 27 minutes$^{24}$. In this audit, the difference between the time of initiation of treatment and the time to referral to the CCOT imply that start of therapy was by the attending team. This
study was performed before the introduction of the Chelsea Early Warning Scoring System (CEWSS), so one might have assumed that awareness would now be higher and responses faster. Nevertheless a median of 3 hours from appearance of the problem to the first bolus of fluid is disappointing. It is probably relevant to consider the targets that triggered a response. A MAP of 52 mmHg in a 24 year old man (a defined target in this audit) is probably judged differently from the same value in a 76 year old. A BE of -10 may is more likely to trigger a rapid response than a UO of 20 ml.hr\(^{-1}\). This is an area that needs to be addressed.

7.4.4  The Efficacy of the Intervention

This audit shows that this relatively simple intervention was effective in reversing the problem much of the time. If one excludes those patients in whom the intervention resulted in a change of management, such as palliation it would appear that the majority of those with hypotension responded, 9/14. Those who failed either died, 1, or were admitted to ICU indicating the magnitude of the problem was greater than could be averted in the ward. Using base excess as an indicator with the same exclusions, then 3/5 responded to fluid. This would suggest in a limited series that these interventions are actually successful in a significant number of patients. It implies that IFR is an effective treatment for a significant number of patients with the defined targets. However for those that do not respond, how much of this is due to delays remains unknown.

Of those that later needed admission to intensive care this raises a series of questions about the ward interventions. It is presumably important to know whether the interventions allowed ICU admission and prevented further deterioration or even
death in the wards but detailed analysis of these cases would be needed to make this assessment. The ICU admission rate was similar to that of the MERIT study\textsuperscript{7} with an ICU mortality rate similar to that of Goldhill \textit{et al}. This data would suggest that CCOT involvement in fluid management will be ineffective in some patients who are likely therefore to need ICU. It would be of value to know if they were genuinely considered salvageable at the time of admission to Intensive Care. It would also be useful to know the nature of the underlying problem and the degree of genuine reversibility. It is important to appreciate that more patients did respond to treatment than did not and that in those that did not their failure to respond may be an indication of severity of illness. It is interesting that 11 patients admitted to ICU were transferred within 6 hours of the institution of IFR. With no easily identifiable control group as a comparison, it is difficult to say whether or not this relatively brisk resolution of a problem is related to the input of the CCOT.

6/54 patients died during this audit. 2 suffered cardiac arrest, but 4 had a new DNAR order applied as a consequence of the need for IFR, when it and other measures’ were observed to be failing. Whilst struggling for improvements in mortality is an important role of CCOT, the recognition of inevitable failure and appropriate withdrawal of ‘critical care’ is potentially as valuable, but harder to define and measure.

7.4.5 \textit{Fluid management}

Table 7.7 is interesting. Firstly the cumulative amount of fluid and the fluid balances certainly confirm the assertion made earlier that most practitioners err on the side of more rather than less fluid. For those that remained on the ward for the full 72 hours
a fluid balance of up to 10 litres is of concern, particularly in view of the complications documented. Secondly the median rate of fluid administration seems lower than might be expected, particularly in the first 6 hours. This may be due to a more cautious approach by non-CCOT personnel or by the affect of the 9 patients that reversed their target in the first 6 hours with only small amounts of fluid.

7.4.6 Complications of Fluid Management

Overall this appears to be high. It was the complications in part that inspired the inception of this audit. It is important to break down the complications as they were assessed. Oedema was common and increased with time. The difficulty in this sign is that while it is associated with fluid administration it is also associated with severity of illness and the two cannot be easily separated. The same is true of pulmonary rales. Both are suggestive, neither is definitive. The presence of new pulmonary oedema on a chest X-ray may be a slightly harder endpoint and this was also substantially increased.

The use of a high CVP value was taken as an objective sign of fluid overload and used because it was part of the Rivers study. Its value in assessing potential complications is very limited. As can be easily seen those with high values which should be a positive feature in the Rivers study yet potentially a negative feature here, are very small in number.

Overall one would have to comment that there is circumstantial evidence of some fluid overload. The appearance of pulmonary congestion appears to be greatest early in the resuscitation period with the greater proportion of clinical and radiographical evidence documented with in the first 48 hours. In this audit no patient
had an overt clinical complication from fluid overload but clearly there is potential for this to happen. As a large number of patients did resolve their haemodynamic problems the apparent cost benefit lies in favour of fluid administration. Nevertheless, although it cannot be directly stated from the results, it would seem obvious that most of this fluid administration is done without monitoring and this presumably increases the potential risk. There is a place for trying to improve monitoring in the ward environment to facilitate fluid management.

7.4.7 Limitations of the Audit

This was an over-ambitious project aimed at providing information about a common ward intervention about which there is currently no in evidence at all. An audit of this type covers a large number of wards and a wide range of patients. The intention was to focus on fluid intervention. It is difficult to capture these incidents. The use of referral to CCOT seemed the only realistic way of approaching the problem but it is quite clear that most interventions were initiated before the CCOT were involved. This was in contrast to the study of CPAP in Chapter 6 where only the CCOT and ICU were able to implement CPAP, so intervention was limited to those two teams. While using the referral as a trigger allowed those interventions to be found and tracked, inevitably an unknown but almost certainly large number of minor interventions with no referral were lost. It is also a major consideration that at the time of the audit the CCOT functioned during an extended day but overnight and weekend events could easily be missed. Documentation was generally very poor and made this audit difficult in particular determining why an intervention was initiated. Follow up also posed problems over the time period of the audit and after wards.
Another major issue is that this audit makes the assumption that fluid therapy is the appropriate treatment for the targets outlined. These were chosen as signs of circulatory insufficiency. The administration of fluid as a treatment for these signs supposes that fluid will reverse the problem. Clearly that is not true in practice. The treatment of the underlying condition is intricately associated with the likelihood of success of supportive measures. Some patients were destined to fail because of the severity and nature of the condition and the effectiveness and rapidity of its specific treatment. Defining success of CCOT or fluid resuscitation by fluid management alone is a large weakness in this study.

The use of the Rivers study as a comparator has already been discussed and while at the outset it seemed not only a reasonable standard but also the only standard that had been evaluated it became clear most aspects of the study were not comparable. It should be mentioned that at the time of planning CCOT were discussing trying to implement Rivers approach in the ward environment in part.

The numbers appear small but belie the logistical difficulties of collecting the data.

7.4.8 Conclusions

In summary this audit was a difficult project to do, and as such should be considered a pilot study that has highlighted a number of difficulties that should lead to better methodology. It identified the problems of studying the efficacy of interventions performed on a large, very diverse group of patients. More importantly it clarifies why there has been no effective study of interventions commonly used in almost every hospital ward. This must be addressed.
It is difficult to define end points for interventions. Reducing mortality and ICU admission represent just the tip of the iceberg when describing the role of CCOT. Indeed of the patients who died, three quarters had a new DNAR order. This too is a valuable intervention. Looking only at the response to a single intervention not usually curative in its own right, ignores the influence of treatment of the underlying condition. In the Surviving Sepsis Campaign, antibiotics are to be given within 1 hour. In this diverse group of diagnoses such a requirement would be difficult to enshrine.

This audit does demonstrate slow response times and potentially excessive amounts of poorly monitored fluid administration. Better ways of improving response to a trigger still need to be sought even in this era of track and trigger. More robust methods need to be developed to measure the effect of CCOT on ward patient’s treatments. Trying to delineate the effect of one supportive intervention on outcome has proved very difficult and the data produced does not permit significant conclusions to be drawn. Expanding studies into other interventions and looking for positive effects of CCOT may prove difficult and expensive but as it constitutes such a large part of daily ward based practice and as the outcomes are of such consequence it does deserve attention.

Fluid therapy in the wards is common, is performed in a range of ways for diverse reasons and seems to be effective in a high proportion of cases but with the potential for complications. In those in whom it fails the mortality is high. There has been no significant work on these interventions and their efficacy. In other environments fluid management is guided by monitoring but this is rarely the case in the wards. One area that urgently needs evaluating is whether user friendly monitoring systems are available that would be helpful in the ward environment for fluid administration.
7.5 References


Chapter 8

The Comparison of an Uncalibrated Cardiac Output Monitor with a Dye Dilution Pulse Contour Method

8.1 Background

The previous chapter which considered fluid administration included the observation that fluid was often given as a treatment, but monitoring of how much was needed was a problem. A cardiac output monitoring system would presumably assist those in the ward environment but at present these techniques, which are invasive and complex are restricted to higher dependency areas. A simple user-friendly technique for use in the ward which is reliable in terms of correlation with more invasive methods both in accuracy and consistency could be a useful adjunct to ward management.

8.1.1 Oxygen Delivery

The need for disciplined cardiovascular support is increasingly important in the care of the critically ill. A stable circulation permits the effective delivery of oxygen and nutrients to the tissues, whilst permitting removal of the waste products of metabolism. The delivery of oxygen is vital for aerobic cellular metabolism. This efficient mode of cellular energy production is desirable. More cellular energy presented as adenosine tri-phosphate (ATP), is produced per molecule of glucose than by anaerobic metabolism (36 molecules of ATP to 2). Cellular integrity is energy
dependent, especially membrane potential maintenance and acid-base control. Failure of oxygen (and nutrient) delivery obliges cells to convert to anaerobic metabolism compromising energy production and thus risking cellular integrity and function, which in turn can impair organ and thus whole body function. In critical illness there is a need to maintain delivery, particularly of oxygen, to the tissues. This function is for the greater part served by the circulation. Consisting of the heart as the pump and the vessels as the conduits, oxygen is carried to the cells. The majority is carried bound to haemoglobin. Put simply, Oxygen delivery (DO₂) is dependent of the amount of oxygen contained in the blood (CaO₂) and the circulation propelling it to the tissues – reflected as the cardiac output (CO). Indeed DO₂ is calculated as CO x CaO₂. What DO₂ is required to maintain normal homeostasis in critical illness is an important question? It was thought reasonable to match the DO₂ to the consumption of oxygen (VO₂). This can increase markedly in conditions such as severe sepsis. Matching DO₂ to VO₂ would be physiological and that increasing cardiac output to achieve this, or even exceed this target would improve outcome. However as outlined in Chapter 1 the studies of Gattanoni and Hayes did not demonstrate this to be a beneficial strategy¹,². Indeed it can be argued that this technique ignores a much more complex reality both at a circulatory and cellular level. Looking at the global effects may be considered simplistic as in illness, regional blood flow is often disordered, but from a pragmatic viewpoint the maintenance of an adequate circulation to optimise at least a normal DO₂ is still seen as an important part of critical care. It is likely that the earlier it’s restoration, the greater the likelihood of a favourable outcome³.
8.1.2 *Interventions to Improve DO$_2$*

Manipulating DO$_2$ can be achieved by intervention at most points on the oxygen cascade. Oxygen delivery to the alveoli has been discussed and examined already in this thesis. The concentration of haemoglobin needed in critical illness remains debated but is a component of oxygen delivery and is important to survival$^{4, 5}$. Optimising the cardiac output is also a key strategy employed. This is commonly achieved by either fluid or inotropes or both. Fluid management is a simple intervention deliverable on the ward. It has been demonstrated to be both life saving if given appropriately, but also detrimental if given in excess$^{3, 6}$. As demonstrated in the previous chapter, control of fluid management is very variable when delivered to patients on the ward. Yet the simple clinical end points assessed on the wards such as peripheral skin temperature, jugular venous pressure and base deficit are themselves surrogate and prone to misinterpretation. Grissom *et al.* demonstrated associations with physical examination findings and cardiac output measurements, but they correlated poorly$^{7}$. Vincent *et al.* demonstrated that whilst peripheral temperature is of use in low cardiac output states, it correlates poorly with cardiac output in septic shock. A recent review by Schey and Williams concluded that skin temperature assessment of cardiac output is at least equivocal$^{8}$. The insertion of a central venous catheter is time honoured, but often of questionable value and more recently the use of central venous oxygen saturation (ScvO$_2$) as a guide to circulatory adequacy is widespread but is also controversial$^{7, 9, 10}$. More invasive devices such as the pulmonary artery catheter are inappropriate in the ward are not without risk$^{11, 12}$. If DO$_2$ is a sensible end-point to be assessed in order to control fluid management, then would it not be better to assess the end-point – cardiac output
more formally, than other markers? The issue is then, which monitors are available and which can be used on the ward?

8.1.3 Cardiac Output Monitoring

Cardiac output monitoring devices have been in common use for many years in the intensive care unit. The high nurse to patient ratio and the highly skilled nature of the critical care nurse enables these techniques to be used in a relatively safe environment. Methods currently employed to measure cardiac output and other haemodynamic parameters are outlined in Table 8.1.

In the ICU, cardiac output monitoring has been used in a variety of ways and attention has focussed on its overall impact on outcome. In that respect its use for monitoring fluid administration is subsumed in its general use. Despite its frequent use in the intensive care unit, the case for monitoring cardiac output remains unclear. Any monitor that can be considered of use will need to demonstrate that the treatments initiated by the results it produces, convey a benefit. In critical care this will invariably require a benefit in mortality. As yet this has not been demonstrated in a large trial. The PAC-Man trial of 2005 is the largest to date and focussed on the pulmonary artery catheter (PAC)\textsuperscript{13}. Concern over the safety of the device had been raised by the publication of a cohort study by Connors \textit{et al.} which demonstrated an excess mortality for ICU patients treated with the aid of a PAC (odds ratio 1.24 (95% CI 1.03 – 1.49)\textsuperscript{12}. The PAC-Man study enrolled 1041 patients and randomised them to receive a PAC or not. The study was unable to demonstrate an excess mortality or an increased survival and the authors concluded that further studies are required to.

‘Ascertain whether management protocols involving PAC use can result in improved
<table>
<thead>
<tr>
<th>Method of measurement</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transthoracic echocardiography</td>
<td>Non-invasive. Requires high technical expertise.</td>
</tr>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td>Transoesophageal echocardiography</td>
<td>Invasive. Requires high technical expertise. Risk of upper GI complications</td>
</tr>
<tr>
<td>Pulmonary artery catheter</td>
<td>Invasive. Thermodilution technique. Intermittent. Remains gold standard</td>
</tr>
<tr>
<td>Transthoracic bolus injection (PiCCO, LiDCO, Modelflow)</td>
<td>Requires central and arterial access. Thermo/dye-dilution technique</td>
</tr>
<tr>
<td>Pulse contour wave analysis</td>
<td>Continuous, Most require calibration. May require special catheters</td>
</tr>
<tr>
<td>Oesophageal doppler</td>
<td>Invasive. Continuous. Simple to use, but can be difficult to focus.</td>
</tr>
<tr>
<td>Aortovelography</td>
<td>Non invasive. Questions over accuracy. Intermittent.</td>
</tr>
<tr>
<td>Thoracic bioimpedence</td>
<td>Non invasive. Low signal to noise ratio. Reflects changes rather than absolute values.</td>
</tr>
</tbody>
</table>
outcomes in specific groups if these devices are not to become a redundant technology.

Connors and PAC-Man examined the impact of one type of cardiac output monitor on survival of heterogenous ICU patients. More specifically, there is data supporting its use in early goal-directed therapy high risk surgery. Pearse \textit{et al} used a lithium dye dilution method to goal direct a DO$_2$ of 600 ml.kg.min$^{-1}$ in high risk post operative patients admitted to the ICU. The results were a significant reduction in post-operative complications and hospital length of stay, but no mortality benefit\textsuperscript{14}. Boyd \textit{et al}. using a PAC demonstrated a 75\% reduction in mortality for high risk surgical patients (5.7\% vs 22.2\%; $p$=0.015) by maintain the same DO$_2$ with dopexamine\textsuperscript{15}. Gan \textit{et al}. used and oesophageal Doppler monitor in major surgery to guide fluid management. They demonstrated a significantly higher CO in the study group and a shorter hospital length of stay\textsuperscript{16}. Fenwick \textit{et al}. confirmed that the use of CO monitoring to optimise patients undergoing major surgery was cost-effective\textsuperscript{17}. In general these trials in pre and post-optimisation are examples of goal directed therapy. The CO monitor has no direct therapeutic value, but guides the controlled use of fluid and pharmacology. Early goal directed intervention has been discussed at length in the last chapter and its relevance to ward patients questioned, but the use of this type of monitoring as an aid to fluid administration is slightly different from the more aggressive goal-directed approach. In either case it is intuitive to intervene as soon as possible. Gattinoni showed that increasing DO$_2$ after 12-36 hours after the onset of shock conferred no benefit in patients admitted to the ICU\textsuperscript{1}. This is different from early fluid management, but nevertheless if CO monitoring is to have an impact in guiding therapy, then early deployment is likely to be necessary.
8.1.4 *Stroke Volume Variation*

The studies outlined in the previous section describe the use of CO monitors to guide the optimisation of DO$_2$. This involves the use of fluid, blood and inotropic agents usually in high dependency areas. In the ward simple fluid management still remains the simplest and most fundamental cardiovascular intervention at the disposal of the ward physician. The detection of fluid depletion and appropriate fluid use to correct the deficit can be a difficult challenge if excess fluid use is to be avoided. When to conclude fluid resuscitation and move to other modes of circulatory support such as inotropes remains difficult. In low output states, a poor CO response to fluid may be seen and more may given in the belief that the circulation remains empty. This may worsen the situation. Conversely in sepsis, a high CO and the desire to generate a higher mean arterial pressure may lead to an earlier use of inotropes or vasopressors before appropriate amounts of fluid have been given – Rivers *et al.* It is known that central venous pressure (CVP) as a guide to fluid status has poor predictive value, as has pulmonary capillary occlusion pressure (PAOP); and 50% of patients will not respond to a standard fluid challenge in terms of increasing their cardiac output$^{18,19}$. Thus the CO and its response to fluid may not tell the whole tale of fluid status, and other methods of assessing fluid responsiveness may also need to be utilised.

In ICU patients undergoing positive pressure ventilation, an increase in intra-thoracic pressure during the inspiratory cycle leads to an increase in right atrial pressure. If venous pressure is low, this leads to a reduction of right ventricular (RV) filling and output and by virtue of the circulation, left ventricular (LV) filling and output. This cyclical change in LV output is translated to the arterial tree. CO monitors analysing this waveform can thus detect changes in stoke volume – stroke volume variation
(SVV). This has been shown to be highly predictive of fluid responsiveness. For example an SVV of >10% is predictive of a 15% increase in cardiac output on delivery of 500ml of fluid\textsuperscript{20,21}. SVV relies on constancy within the thoracic cavity. Hence changes in beat-to-beat heart rhythm such as atrial fibrillation or varying ventilatory patterns when spontaneously breathing, will affect the sensitivity of this variable to predict fluid status. The value of SVV as a predictor of fluid responsiveness in the non-ventilated has only been described in animals\textsuperscript{22}. It thus remains of interest, but its role in the fluid management of the ward patient needs assessment.

8.1.5 Cardiac Output Monitoring of Ward Patients

There is no data to date that expounds the virtues of CO monitoring in the resuscitation of ward patients. It may be an area where cardiac output monitoring could also have an impact. This may not be solely in terms of mortality, but as with the high-risk surgical patients, a reduction in length of stay or nosocomial complications; possibly a reduction in ICU admission. If time is of the essence, then CO monitoring on the ward even as part of pre-ICU resuscitation could have value. Inadequate or excessive fluid management based on clinical findings or blood gas results may compromise patient outcome. This may be especially true if there is evidence of pulmonary oedema or inflammation\textsuperscript{6}.

We have seen in the previous chapter that in one institution the fluid management of the acutely unwell could be improved upon. This could take several guises, better protocols and guidelines, greater education in to the prompt treatment of shock, increased use of central venous catheters and ScvO\textsubscript{2} or a more direct involvement of
the ICU via the CCOT. If the use of some form of monitoring either for simple fluid management or RGDT is to be advocated it will require cardiac output monitoring. A simple device with few complications would be required for use in a ward based environment.

8.1.6 Pulse Contour Wave Analysis

Table 8.1 demonstrates the available range of techniques. Of those that give continuous data of haemodynamics, many are invasive with incumbent risks. The use of the arterial waveform derived via an arterial catheter is most attractive in terms of simplicity and ongoing care. This is pulse contour wave analysis.

The two most common systems that are in use in the UK are calibrated by thermodilution (PiCCO®) or dye dilution (LiDCO®). Both have been compared to a PAC as a gold standard and found to produce similar data\(^{23,24}\). However both have the disadvantage of requiring regular calibration (approximately eight hourly). The PiCCO requires a specialised arterial catheter, in a large artery, with a thermistor and ideally, central venous cannulation. LiDCO can function with a normal arterial catheter, but has expensive disposables and is not recommended for use with neuromuscular blocking agents. A novel monitor has appeared on the market which is simpler in its operation. The Vigileo Flotrac® (Edwards Lifescience, LLC, Irvine US) is a pulse contour analysis monitor which is uncalibrated. It uses a software algorithm to determine the aortic compliance from the demographic data of the patient (gender, age, height and weight). The algorithm was developed using data collected from a wide variety of clinical situations involving patients and healthy volunteers. It contains a correction factor that alters the value of SV by using a
mathematical model based on the kurtosis of the arterial waveform. This derives a correction factor ($\chi$) which is calculated every 60 seconds to allow for dynamic changes in vascular tone. It is thus simple to use requiring only a standard arterial cannula and no central catheter. It produces calculations of SV based on the arterial waveform; these are transferred in to cardiac output and cardiac index (CI) by multiplication of SV and heart rate to give CO, then division by body surface area derived from the height of the patient. It also assesses the SVV of the derived SV.

The Vigileo Flotrac® (VF) has been compared to PAC, PICCO and transoesophageal echocardiography in previous studies. Many were performed in surgical patients with mixed results. In the ICU population, two studies in haemodynamically unstable patients have been reported. Compton et al. studied 25 patients requiring fluid resuscitation and/or vasopressors. They compared the cardiac index data from the VF to a PICCO. The bias between PICCO and VF was found to be 0.68 l.min$^{-1}$.m$^{-2}$ with a high percentage of error 95% limits of agreement 1.94 l.min$^{-1}$.m$^{-2}$. Sakka et al. found similar results in cardiac output for 24 patients with septic shock, quoting a bias of 0.5 l.min$^{-1}$ when compared to a PiCCO, but again with a wide percentage of error (SD 2.3 l.min$^{-1}$). Despite these concerns, a recent meta-analysis of the VF concluded that the recent improvements in software have developed the VF into a monitor that has good agreement with intermittent thermodilution in stable situations, and that though it may not perform as well in rapidly changing haemodynamics, the authors agree that its use in early goal directed therapy maybe it’s ‘niche’. One thing is true, it’s simplicity of use via a standard arterial catheter make it very attractive for use in lower ‘tech’ environments such as the general ward. If it can be agreed that CO monitoring can form part of the fluid management or goal directed therapy required in acutely unwell ward patients, then the VF seems particularly
attractive. To be of value, it has to reflect the data that is collected by monitors in established use. Much of the work by Pearse et al. in a similar patient group, high-risk surgical patients, was performed using the LiDCO system. It is also the standard CO monitor at the Chelsea and Westminster Hospital. There is no data comparing the performance of the VF to the LiDCO.

8.1.7 Aims
The previous chapter described problems with fluid management on the wards. It is thought that this could be improved upon by the use of a simple CO monitor to guide fluid resuscitation and inotrope management, even in the ward or prior to ICU transfer. On this assumption, this study aims to compare the performance of the novel VF CO monitor to the established LiDCO monitor. If comparable in terms of accuracy and precision, then a case could be made for its inclusion in the initial management of the acutely unwell ward patient with circulatory shock.

8.2 Methodology
8.2.1 Study Design
This was a partially blinded observational study using patients as their own controls. It was performed on the intensive care unit at Chelsea and Westminster Hospital using a heterogenous group of patients admitted with haemodynamic instability in which CO monitoring was initiated during the first 24 hours of admission.
Inclusion Criteria:

- Adults >16 years
- Patients in whom the attending physicians desired cardiac output monitoring as part of the patient’s ICU care.
- Less than 24 hours after admission.

Exclusion criteria:

- Refusal of consent if alert.
- Contraindications to arterial or central venous cannulation.
- Use of neuromuscular blocking agents.
- Severe aortic regurgitation.
- Pregnancy
- Refusal by attending physicians.
- Not expected to survive >24 hours.

All procedures and therapies were performed as part of routine patient care under the instruction of the attending physicians. No interventions were initiated for study purposes. The physicians were able to use the LiDCO monitor freely and all clinical decisions based on haemodynamic data were derived from the LiDCO monitor. The VF was placed at the back of the ICU bed spaced, turned to face the wall, and thus not in the view of either medical or nursing staff.

Radial artery access was achieved using a standard radial artery catheter chosen by the operator (usually a 20G Abbocath®). The catheter was connected to the MHD8 Flotrac sensor which permits continuous monitoring of arterial pressure. This was
linked to the MHM1E Vigileo monitor with the up-to-date 1.07 software, and the arterial pressure transduced separately to the ICU monitor. The pressure transducer was zeroed to the mid-chest level.

The LiDCO was calibrated according to the manufacturer’s instructions. 0.15 – 0.3 mmol of lithium chloride is injected rapidly into a central vein and blood drawn continuously from the arterial catheter across the electrode sensor. This produces the decay curve upon which the pulse contour wave analyser is calibrated. The LiDCO was calibrated 8-12 hourly, in keeping with the manufacturer’s instructions. The arterial pressure waveform is obtained from the monitor and thus there is only need for one arterial catheter to run both CO monitors.

The study was run for the first 24 hours of the patient’s admission. Values for hourly cardiac output, stroke volume variation and arterial blood pressure were obtained from both machines. Patient demographics, fluid and inotrope therapy were recorded and blood gas values for base excess and plasma lactate concentration. A fluid challenge was defined as a bolus of crystalloid or colloid greater than 250mls within an hour.

8.2.2 Statistical Analysis

Statistical analysis was performed using SPSS 18.0 (LEAD Technologies Inc. USA) Microsoft Excel (Microsoft® Inc.USA) and GraphPad Prism 4.0 (GraphPad software inc. USA) software. For the comparison of CO measurements and agreement between the two techniques, the Bland–Altman method was applied. Statistical advice was sought as the use of Bland-Altman plots to assess levels of agreement for cardiac output monitoring has been questioned in the literature by Myles et al.³¹.
Limits of agreement were defined by 95% limits. The agreement would be considered adequate if the 95% limits were within 30%. In order to establish if the VF reflects SVV response as well as the LiDCO, the differences in SVV pre and post fluid bolus were calculated and then expressed as a Bland–Altman plot for the first fluid bolus each patient received. Other data is presented as a mean (SD) for continuous data and median (IQR) for non-parametric data.

8.2.3 Sample Size Calculation

Based on the previous literature comparing CO monitors, an agreement of less than 0.3l.min$^{-1}$ was considered appropriate$^{32,33}$. There is no statistical literature for power calculations of equivalence testing for a repeated measures analysis, only repeated measures power calculations (up to 8 repeats). Thus the sample size calculation was based on this technique. As such for a significance of 0.05 and a power of 80% a sample size of 25 patients was required.

8.3 Results

25 patients were recruited. The patient characteristics are summarised in Tables 8.2 and 8.3. All were emergency admissions except for one elective post-operative patient. All patients had baseline cardiac output data within 6 hours of admission. A total of 572 cardiac output measurements were recorded in the 25 patients. Episodes of no measurement occurred in 4 patients. 2 required transfer to the operating theatre for urgent surgery, 1 patient required transfer to the CT scanner for diagnostic purposes. 1 patient unexpectedly arrested and died within 8 hours of admission.
23 of 25 patients received vasoactive infusions during measurements and the mean doses are displayed in Table 8.2.

As an example, data gathered for cardiac output measurement at 1 hour, 6 hours, 12 hours and 24 hours for each patient is summarised in Table 8.4. Visual assessment suggests that the VF measures a lower value for CO at the same time point when compared to the LiDCO. This appears to be especially true when the cardiac output is high.

Table 8.2 Baseline characteristics of the patients at recruitment

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Value (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr) (+/-SD)</td>
<td>63.9 (15.0)</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>16 (64)</td>
</tr>
<tr>
<td>Mean APACHE II (+/-SD)</td>
<td>23.24 (4.3)</td>
</tr>
<tr>
<td>Mechanical ventilation (%)</td>
<td>24 (96%)</td>
</tr>
<tr>
<td>Mean mean arterial pressure (kPa) +/- SD</td>
<td>62.6 (12.9)</td>
</tr>
<tr>
<td>Vasoactive drugs (median dose μg.kg⁻¹.min⁻¹ (IQR))</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine (0.13 (0.18))</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>Epinephrine (0.44 (0.42))</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Dobutamine (5 N/A)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>None</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

SD, standard deviation; IQR, inter-quartile range
Table 8.3 Clinical diagnosis of participating subjects

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic shock</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Abdominal sepsis</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Aortic stenosis (post-operative)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Major trauma</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Urinary sepsis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Oesophageal variceal bleeding</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>
Table 8.4 Cardiac output measures for LiDCO and Vigileo at 4 time points (l.min⁻¹)

<table>
<thead>
<tr>
<th>Time</th>
<th>1 hour</th>
<th>6 hours</th>
<th>12 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No.</td>
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<td>Vigileo</td>
<td>LiDCO</td>
<td>Vigileo</td>
</tr>
<tr>
<td>1</td>
<td>2.3</td>
<td>2.1</td>
<td>3.6</td>
<td>3.2</td>
</tr>
<tr>
<td>2</td>
<td>6.8</td>
<td>6.5</td>
<td>10.6</td>
<td>9.8</td>
</tr>
<tr>
<td>3</td>
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<td>4.6</td>
<td>4.4</td>
<td>6.4</td>
<td>6.2</td>
</tr>
<tr>
<td>5</td>
<td>6.8</td>
<td>6.0</td>
<td>7.5</td>
<td>7.2</td>
</tr>
<tr>
<td>6</td>
<td>2.4</td>
<td>1.9</td>
<td>4.1</td>
<td>3.3</td>
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<td>7</td>
<td>7.7</td>
<td>6.8</td>
<td>7.9</td>
<td>6.4</td>
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<td>8.3</td>
<td>8.2</td>
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<td>6.8</td>
<td>6.0</td>
<td>5.4</td>
<td>5.1</td>
</tr>
</tbody>
</table>
A Bland-Altman plot is presented as a graphic representation of the level of agreement between the two systems. The control lines are based on the within subject sum of squares, which produces a model which compensates for the effect of repeated measures. The bias is positive in favour of higher readings by the LiDCO and has a value of 0.58 l.min\(^{-1}\). The upper 95% limit is +1.40 l.min\(^{-1}\) and the lower 95% limit, -0.28 l.min\(^{-1}\) (Figure 8.1).

Figure 8.1 Bland-Altman Plot of the difference between Flotrac and LiDCO derived cardiac outputs against the mean cardiac outputs in the 25 patients in the study. The within-subject variance is estimated by a random effects model which includes the mean measurements of the two methods for each measurement occasion. Bias = 0.58 l.min\(^{-1}\), Upper 95% limit = 1.40 l.min\(^{-1}\), Lower 95% limit -0.28.

23 of the 25 patients received at least one fluid bolus. All 23 received a minimum of 500 ml of fluid as their first bolus, and this was sampled generating 46
measurements for Bland-Altman analysis. This is summarised in Table 8.5 and Figure 8.2. The agreement between the change in SVV before and after the fluid bolus ($\Delta$SVV) was high with bias of 0 and 95% limits of agreement of +3.32% and -3.32%.

![Bland-Altman plot for $\Delta$SVV after a fluid challenge.](image)

**Figure 8.2** Bland-Altman plot for $\Delta$SVV after a fluid challenge. (Bias = 0; Upper 95% limit of agreement = 3.32%; Lower limit of agreement = -3.32%. SD Bias = 1.69%)
Table 8.5  $\Delta$ SVV after a fluid bolus for the LiDCO and Vigileo systems

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>LiDCO (%)</th>
<th>Vigileo (%)</th>
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</thead>
<tbody>
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<td>1</td>
<td>4</td>
<td>3</td>
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<tr>
<td>2</td>
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8.4 Discussion

8.4.1 Cardiac Output

In this chapter a pulse contour analysis device was tested against an established system for continuous CO monitoring. LiDCO has previously been validated against thermodilution techniques using a PAC, although the patient group was that of hyperdynamic hepatic transplant candidates. The results of this study show that the performance of the Vigileo Flotrac® system was comparable in the reporting of cardiac output measurements with the LiDCO in a heterogenous group of ICU patients. The bias of 0.58 l.min\(^{-1}\) combined with narrow limits of agreement (-0.28 l.min\(^{-1}\) and +1.40 l.min\(^{-1}\)) could be argued as clinically acceptable as the SD difference from the mean CO is less than the 30% limit suggested by Critchley et al. However the sample size calculation was determined supposing that the systems would record cardiac outputs of less than 0.3 l.min\(^{-1}\) difference. Clearly a difference of 0.58 l.min\(^{-1}\) could be very significant at lower CO states, but interestingly, the plot maintains close association to zero at cardiac outputs below 6 l.min\(^{-1}\) and it is at the higher end of CO that the two systems diverge in terms of agreement. Not surprisingly the VF has good agreement with the ‘gold standard’ LiDCO at normal cardiac output values. The VF value is derived from a mathematical model based on predominantly normal physiology and responses in healthy subjects. When the physiology becomes significantly deranged at high levels, the algorithm appears to be less able to compensate for its lack of calibration with the abnormal circulation and fails to reflect the CO detected by the LiDCO. In practice this may be of little clinical significance. For example, the difference between a LiDCO CO of 12.4 l.min\(^{-1}\) and a VF CO 11.4 l.min\(^{-1}\) is unlikely to be important in clinical management. Conversely differences of 0.5 l.min\(^{-1}\) at the opposite end of the
The findings suggest that the VF system reasonably reflects the CO as measured by LiDCO in critically ill patients.

These findings are different from two previous studies comparing the VF with other techniques of pulse contour wave analysis CO monitoring\textsuperscript{29,33}. Both these studies concluded that the VF system could not replace more invasive CO monitoring systems in ICU patients. Compton \textit{et al} detected a systematic under-reading of cardiac output measurements by the VF when compared to a PiCCO thermodilution technique. Sakka \textit{et al} reports a bias to over-reading the cardiac output, although they omit to quote a bias. Both studies demonstrated the deterioration in agreement when the values of cardiac output are high similar to this study. The Compton data is also magnified by the use of CI rather than CO bias 0.68 l.min\textsuperscript{-1}.m\textsuperscript{-2} to 0.76 l.min\textsuperscript{-1}.m\textsuperscript{-2}. We chose to use CO as a closer reflection of the true measurement of the system without a further conversion.

Explaining the differences between this and the other two studies in critical illness is difficult. The patient groups appear comparable from their demographics excepting that the patients in other studies had higher abnormal physiological scores, were on higher doses of vasoactive medication and had higher mean arterial blood pressures. The range of CO/CI measured in the other two studies was also higher. Both studies actively sought haemodynamically unstable patients. The patient’s inclusion in this study was only dependent on the need for CO monitoring as decided by the clinicians, although haemodynamic instability was the most common indication. This study enrolled 2 patients not on inotropes and 3 further subjects on doses of norepinephrine less than 0.10 μg.kg\textsuperscript{-1}.min\textsuperscript{-1}. Other studies of surgical patients with more stable haemodynamics have found good agreement between
PiCCO and VF\textsuperscript{32, 35, 36}. It could be an influence of these less unstable subjects on the results.

Methodologically, the two above trials compared PiCCO to VF. We used LiDCO. Both have been validated against the ‘gold standard’ PAC, however the LiDCO has no data supporting its agreement with PAC or PiCCO in these types of patients. It may be that our chosen comparator does not agree well with PiCCO in ICU subjects and that this is where the difference lies. Thermodilution has significant pitfalls to operator variation, patient pathologies, and the indicator used. Techniques independent of thermal influences such as dye-dilution may represent a better technique for calculating CO in these patients. From a pragmatic point of view the use of LiDCO to measure CO is the standard on the ICU at Chelsea and Westminster Hospital. Medical decisions are based upon its information. Thus if a new monitor is to be considered for use in this single institution, it needs to reflect current practice. LiDCO uses dye-dilution calibration which makes it likely that it is a good reflection of changes in CO, if not the absolute value.

The arterial access used in Sakka et al was femoral for both the systems, utilising the same PiCCO catheter. The VF recommendations are for radial artery access, and the difference in waveform between femoral and radial artery may have influenced the results. Compton et al. used two arterial catheters PiCCO in the femoral and VF in the radial. Whilst appropriate to manufacturer’s instructions the actual waveform being analysed is different and possibly subject to differences with use of vasopressors. Indeed they admit that the peripherally derived radial arterial pressure significantly underestimated the central arterial pressure and that a pressure difference of >5mmHg was associated with significant increases in bias. In
the observations reported here, the same arterial waveform was used for both monitors permitting the same arterial waveform to be analysed.

Finally, the use of all time samples for all patients being analysed in the same graph is statistically unsound, and both of the previous studies were guilty of this analysis. When repeated measures data are available, it is desirable to use all the data to compare the two methods. However, the original Bland–Altman method was developed for two sets of measurements done on one occasion and so this approach is not suitable for repeated measures. To compensate, Compton analyses one measurement series, and finds a similar large bias with wide limits of agreement. We used a modification of the statistical model developed by Myles et al.\textsuperscript{31}. This adjusts for the mean CO value for the individual over time and the mean measurement between the two methods. It provides a statistically more sound representation of the level of agreement between the two systems.

8.4.2 Stroke Volume Variation

With regards to the agreement of the two systems to detect changes in SVV to a fluid challenge, there was excellent agreement, bias 0, with narrow limits of agreement (+/- 3.32%). No previous studies have compared these two monitors for agreement in SVV as a measure of response to fluid challenge. However both have been validated as predicting fluid responsiveness based on the SVV\textsuperscript{22, 37}. It is therefore exciting that even if the CO values may differ (particularly at the upper end of the spectrum) between LiDCO and VF, the ability for them to agree that a patient is likely or unlikely to respond to fluid may be very useful in maintaining a disciplined fluid resuscitation strategy. This result is useful only in the ventilated ICU patients
and is included here for completeness. The role in the ward environment in spontaneously breathing patients needs clarifying.

The results found here are encouraging, but cannot be immediately extrapolated into the ward environment. Despite good agreement with LiDCO, the ICU patient group does not reflect the ward patient. Further work is now needed to assess haemodynamic parameters seen in acutely unwell ward patients and to assess the impact of spontaneous breathing on the accuracy, but possibly more importantly, the precision of the two systems. Secondly, the introduction to this chapter outlined a desire that a simple CO monitor could aid in guiding fluid therapy on the ward. These observations provide a suggestion that this monitor in particular, may be helpful in the ward, but needs assessment in the target population. The close agreement of SVV is in ventilated patients alone.

The pragmatic aspect of the clinician controlled fluid management used in this study, means that analysis of the response to fluid administration is observational. The criterion of a fluid bolus defined as a volume of >250 ml within an hour takes no account of the patient size or clinical state but is the standard ICU practice. It was chosen as a pragmatic volume that reflects interventional fluid administration above that expected as maintenance fluid. It equates to approximately 3.5 ml.kg\(^{-1}\) for a 70 kg patient and most trials which examine fluid responsiveness, use a 250 ml to 500 ml boluses or up to 15 ml.kg\(^{-1}\) as the volume delivered although often in a shorter time period.\(^{38-40}\) The Surviving Sepsis protocol suggests 1000 ml of crystalloid or 300 ml - 500 ml of colloid over 30 minutes.\(^{41}\) Thus our definition was quite conservative as a threshold.
There is a clear need for a trial looking at the response of the CO or even SVV in ward-based fluid resuscitation. Indeed the use of the VF versus more established monitors of fluid balance both clinical (heart rate, blood pressure, urine output, skin temperature, passive leg raising, mental state etc.) or technical (CVP, ScvO$_2$, Base deficit etc.) would be very valuable.

The VF requires arterial access. This is currently not common practice on the wards, but environments such as the emergency department, CCU and medical admission units (and even labour ward) are increasingly ‘high tech’ level 1/2 bedded areas. It is not unreasonable to expect the growth of arterial catheter use as a standard of care for the acutely unwell in these places. It is a part of the role of the CCOT to transfer skills form the ICU environment to the ward. Care and monitoring of an arterial catheter would seem a reasonable skill to develop in the ward. This would be useful for fluid administration, but the more complex issue is whether ward patients receive inotropes? However if it can be established that ward-based CO parameters and ensuing treatments improve outcome, reduce ICU admission and reduce length of stay, then it may be something that evolves, again with the aid of CCOT.

8.4.3 Conclusions

An assumption was made that some form of cardiac monitoring may assist in the fluid administration in the ward environment, but most systems are considered unsuitable for ward use. The Vigileo Flotrac$^®$ is potentially usable in that environment if it were shown to be accurate and consistent. The observations reported here suggest that this monitor compares favourably with the LiDCO system in the ICU and can be considered as a useful tool in assessing cardiac output and SVV over a wide
range of cardiac output values. Its relative failings at the higher values of cardiac output may only be of academic rather than clinical relevance, but even at low output states it appears to agree with the LiDCO system. It does require arterial access, but is an easier technology to use than the LiDCO system and would have the potential for ward use if arterial catheters could be used there. Further work is needed to validate its use in patients breathing spontaneously. If this were to confirm its efficacy, then it can be considered for ward use. It has pragmatic advantages over other available monitors.
8.5 References


Chapter 9

Thesis Conclusions

9.1 Review of Thesis

This thesis sought to investigate the methods used and effectiveness of, ward based interventions for the care of the critically ill. The advent of critical care outreach teams (CCOT) has brought enhanced care into the wards but with limited means of treatment available. It is important to know the efficacy of these treatments. While there are an increasing number of studies evaluating the overall effect of the teams and their treatments, there is almost no information on the efficacy of the individual treatments commonly employed. The two most common interventions employed in the ward by CCOT are oxygen delivery and fluid administration and it is these two areas that have been addressed in this thesis.

9.1.1 Performance of Oxygen Masks

Oxygen therapy remains a key part of acute intervention. Despite their widespread use, the interface between patient and mask system is not well documented in the presence of abnormal breathing patterns. The model designed to mimic such conditions demonstrated a significant fall off in performance of several of the commonly used systems when respiratory rate and thus minute ventilation increases.

This finding has significant clinical implications as outlined in Chapter 3, but is worth re-iterating. At present in many situations the condition of the patient in terms of
oxygen saturation is at the bedside seen on the context of the set oxygen delivery. Yet it is shown here that the set oxygen delivery and the actual delivery may be very different. This may mean that the condition of the patient may be misinterpreted and their oxygenation perceived to be far worse than it is in reality. Furthermore if the respiratory pattern influences the efficacy of an oxygen delivery system then knowledge of the effect could be important and useful in deciding which delivery system to use in a patient with a high respiratory rate or at least to understand that the actual oxygen delivery may fall short of that expected under those circumstances. Elucidating the physics of the delivery systems potentially permits some stratification of their application to patients with differing disease severity. A poor response to increasing oxygen flow via some of the more predictable mask systems may indicate that less oxygen is being delivered due to the respiratory pattern and may be an indication to change system. It may even suggest the need for a change to a more effective intervention such as CPAP or non invasive ventilation. The chapter also demonstrated that some systems performed more consistently than others.

The relatively predictable performance of the Vapotherm® (high-flow nasal cannulae) encourages the realistic prospect that oxygen delivery can be improved without the need for a sealed mask. Further research in this area could be directed towards more ‘comfortable’ yet efficacious systems. New designs of oxygen delivery systems or rediscovery of old ones, that have suitable ‘reservoirs’ removing the need for tight fitting masks and loud high flow systems could be developed and tested. Hoods helmets and tents should (and are) being evaluated.
9.1.2  *Peak inspiratory flow rates in respiratory distress*

Chapter 4 used a simple hand-held device to measure peak inspiratory flow rates (PIFRs) in patients with evidence of respiratory distress and compared their values to those of a control group of hospital in-patients. The major finding was a significant difference in PIFR between the groups with the patient group exhibiting much higher values. Essentially in patients with respiratory distress the peak inspiratory flow is often greatly increased and taken in the context of the previous chapter’s findings, suggest that this could significantly influence the potential for air entrainment. This would result with deteriorating oxygen delivery as the pattern changes and peak flow rises. The implication is that sick patients paradoxically will have more air entrainment and lower oxygen delivery. This very simple assessment contributes to the findings detected in Chapter 3 and gives a clue that the findings in the model may be transferable to the clinical environment. As a study it can be criticised regarding the comparability of the two groups and how closely they were matched, but it is reasonable to regard the data as demonstrating a phenomenon that is highly likely to influence the performance of mask systems, especially with regards to mixing of delivered oxygen and environmental air. As with the model in Chapter 3, the data obtained in this study could be integrated into further research in to oxygen delivery systems. Analysis of the true nature of the respiratory patterns seen in a variety of ventilatory disorders would be valuable in determining features of novel systems such as reservoir volume, oxygen flow rate etc. These two chapters provide some basic information about a factor affecting mask performance and also the variability of commonly used masks at least in this Institution. It provides some quantification of the performance of oxygen delivery systems. When masks fail CCOT escalate to CPAP and this was investigated in the next section.
9.1.3 Continuous Positive Airway Pressure

The use of CPAP for the ward treatment of acute hypoxia has become ubiquitous, but has several documented problems. It is the method often used when ordinary masks fail and is the next escalation in oxygen delivery. Chapters 5 and 6 investigated the likely mechanisms for its perceived superiority over open mask systems as an intervention for improving oxygenation. We demonstrated that in a model of ventilation, the high flow CPAP system predictably delivers the desired concentration of oxygen regardless of the pattern of ventilation. This was in stark contrast to the performance of some of the open oxygen masks in the Chapter 3. In considering the reasons for this obvious difference the hypothesis was generated that the mode of delivery of oxygen when using CPAP prevents entrainment of air and, to some extent, this is the way in which it works. From this the consideration was raised as to the relative contributions of the application of positive airway pressure (PAP). Using the standard protocol for initiating CPAP in the ward it was shown that in a moderately sized group of heterogenous patients with respiratory failure, the greatest, and probably only, large increment in oxygenation occurs on changing from mask oxygen to a T-piece (CPAP without a valve) to CPAP. Though this was a relatively short period of observation of up to two hours, there is the inescapable observation that at least in this setting, the addition of PAP contributes little more in terms of oxygenation, than the CPAP system, without pressure.

This finding is likely to be contentious. There are certainly several considerations. Was enough PAP used to justify the above conclusions? Only 5 cmH$_2$O and 10 cmH$_2$O were used and this may have been inadequate but in practice in this and many other Institutions those are the values commonly employed by CCOT and so they are relevant values.
Was the length of time of observation long enough? It was impressive that the changes seen were immediate and sustained, yet the addition of PAP did not contribute further in the time period. Certainly over a longer period the contributory effects of PAP may have appeared but firstly this was not seen in the time period and also this is the time period of early active intervention when oxygenation improvements are being sought. A study for a much longer period would be useful and needs to be done.

Was the patient group a fair reflection of those that were likely to benefit from the application of PAP? They may not have been as they were a heterogenous population including only a few patients with conditions where the PAP component is ‘known’ to be effective. In some respects the observations here are therefore a self-fulfilling prophecy, as applying PAP to patients in whom there is no literature to support its use is likely to show no benefit. This was found, but the application of CPAP without pressure did improve oxygenation across the entire population. More importantly the population represented that in which this intervention is commonly used in many Institutions. Thus the criticisms may be valid in terms of study design, but not in terms of current practice in a hospital that is reflective of many in the UK. Further research should be devoted to answering the critique above more fully.

Larger numbers in specific diagnostic categories would elucidate any particular conditions that would show true benefit from PAP, rather than improved oxygen delivery. Acute cardiogenic pulmonary oedema is the condition said to benefit from CPAP. Such a study might finally define the benefit of PAP in acute cardiogenic pulmonary oedema above and separate from other causes of acute respiratory failure.
One consideration derived from these findings is that if the PAP element of CPAP is relatively unimportant then designing oxygen delivery systems that not only deliver the oxygen required but are comfortable and user friendly may be feasible released from the constraints of pressurised systems. It is an important area that needs to be clarified.

Combining the findings of the four chapters examining oxygen delivery as a ward-based intervention it is clear that the higher flow systems (CPAP and Vapotherm®) improve oxygenation across a range respiratory patterns. They appear superior to their ‘older’ and less sophisticated counterparts. It would be very interesting to conduct a randomised control trial of the two methods in specified groups of respiratory failure patients. Outcomes would need to exceed improvement in oxygenation and include morbidity, mortality, endotracheal intonation rates as well as patient acceptability. Other designs for either high-flow, or large reservoir oxygen systems could also be included in such a study. The main aim of such studies would be to demonstrate that oxygenation could be achieved safely with similar outcomes as CPAP, without the disadvantages of a closed mask system.

9.1.4 The Efficacy of CCOT in Delivering Fluid Resuscitation on the Wards

The other area that is key to the activities of CCOT is the use of fluids for cardiovascular intervention. This is a crucial part of the CCOT armamentarium for dealing with hypotension in a wide range of circumstances. Again there is little or no evaluation of either its use or its efficacy in the literature, yet it is widely used.

Chapter 7 did not directly follow on from the studies conducted previously. It audited the use of intravenous fluid resuscitation as an intervention to treat evidence of
circulatory deficiency. It was an interesting and useful exercise. As an audit, probably its greatest achievement was demonstrating how difficult it is to examine such a strategy in the ward environment. As such its inclusion in this thesis could be questioned. However, this thesis set out to assess the interventions performed as part of the care of the acutely unwell ward patient and like oxygen therapy, fluid treatment is ubiquitous. Prompt and disciplined fluid management has been shown to improve outcomes in other environments of clinical medicine and is being championed as a gold standard of care in the ward environment\textsuperscript{1-3}. Whilst this audit was not controlled in order to apply similar conclusions to its findings, it was designed to demonstrate a 'state-of-play' in a UK general hospital.

To try to provide a measurement stick for comparison, as there were no direct comparators, the guidelines for goal directed resuscitation in the emergency department were used. This was in retrospect far less ‘fit for purpose’ than was realised at the outset. Yet there were some interesting findings: There were important delays in initiating fluid therapy following the appearance of a problem. This was followed by delay in the referral to a CCOT for expert advice and support. Both of these delays were exaggerated by comparison with an emergency department because of the unpredictable and sporadic appearance of problems in a ward environment. Nevertheless the difficulties of picking up problems and then dealing with them were clearly shown.

When implemented, fluid management was liberal and often associated with evidence of significant morbidity, such as fluid overload. This was in part because of the lack of means of assessment and of monitoring of what was being administered. Monitoring of fluid therapy in a group of sick individuals was poor or non-existent and raised the question what modalities of monitoring could or should be applied in the
ward environment and by whom? In contrast to these findings the apparent success rate was high in that 35/54 patients neither died nor went on to require critical care. As a measure of success where intervention was needed this would suggest benefit although clearly there could be no comparison with no treatment.

There is a considerable amount of further research that should be done as a response to the findings of Chapter 7. Why is the response to signs of circulatory failure so slow, especially when an early warning scoring system is in place? A study could be designed to evaluate this. More interestingly perhaps would be examining the implementation of a ‘Rivers-esque’ protocol for care of ward patients with evidence of septic shock. Could the application of aggressive management with ScvO₂, Dobutamine, lactate measurements etc. substantially improve the management of ward patients and convey the same level of benefit as alleged for those in an emergency department? As discussed in Chapter 1, the context of the established ward patient is very different from the A&E admission and application of the same technique of resuscitation, though intuitive, may not be correct. Indeed this may lead on to further examination of the part of the ‘Do not actively resuscitate’ order in the management of the ward patient who demonstrates circulatory insufficiency, an aspect of COOT that has not been examined in this thesis. This section obviously raised more questions than answers but it has highlighted an important and large area of practice in many Institutions that to date has not been investigated and where it is suggested there could be improvement.
9.1.5 *The Comparison of a Novel Cardiac Output Monitor with a Standard*

In seeking to improve care for ward patients, one of the principles of CCOT is to export critical care skills and technologies. This study looked at the ability of a simple-to-use cardiac output monitor (Vigileo Flotrac®) to reproduce the results of the standard ICU monitor (LiDCO) in use at Chelsea and Westminster Hospital. The results confirmed an acceptable degree of agreement between the two systems in terms of tracking changes in cardiac output. However, the absolute values differed, but within acceptable limits. Agreement between the two monitors regarding the stroke volume variation (SVV) was also studied and was found to be highly concordant.

This study and the audit of Chapter 7 suggest that further research into this field. AS outlined above, there is no data that defines the need for more invasive monitoring in the acutely unwell ward patient group. Thus a study suggested above incorporating a strict resuscitation protocol with criteria for necessary monitoring, timing of insertion and result-response algorithms, targeted at ward patients would be valuable. This could include, or be followed by study of the value of a CO monitors in general, or specifically the Vigileo Flotrac® in the management of such subjects. It remains questionable whether CO monitors will make the leap from ICU to the wards, but in the author’s own working lifetime nurse administered intravenous antibiotics, continuous CVP monitor transduction, CPAP, BiPAP and low dose inotropes have all transferred across to the ward environment. With appropriate training and safeguards, should the arterial catheter and an associated simple CO device not make a similar crossing? The studies so far have been in the critically ill and its clinical use in ward scenarios and it actual benefits in that environment need to be elucidated first.
9.2 Limitations of the Thesis

The major limitations of each study are discussed in their relevant chapters. However the environment and numbers require special mention. The work done on this thesis was single centre, single observer and whilst all the studies in which a sample size calculation was performed, reached the defined numbers, there are several aspects of the studies that could be improved by increasing the numbers recruited.

The CPAP system study is probably the first to look at the actual oxygenation effects of CPAP at these values including zero, and clearly needs significantly greater numbers to confirm these findings and to resolve two further issues. Firstly, the study was too small to detect changes between the T-piece system and the CPAP system. At present there appears to be no difference between the two. A much larger study (probably multi-centre) would be required to have sufficient power to detect a difference. Secondly, the heterogeneity of the study population was such that deciding if particular patient groups may benefit from CPAP was not possible by subgroup analysis. Differences in response to CPAP by varying causes of respiratory failure would require a much larger study population, or ideally separate studies for separate conditions. Similarly the study looking at peak inspiratory flow could be given more credence if greater numbers could be recruited and again, subgroup analysis may further expand the physiological knowledge base of oxygen delivery in different patient populations. For commonly used techniques such as these it is important the fundamental aspects of delivery are properly elucidated.
9.3 Recommendations for Clinical Practice

9.3.1 Oxygen Therapy

If the delivery of oxygen is one of the most important aspects of care for the acutely hypoxic patient this thesis has shown that the delivery systems commonly used have deficiencies of consistency of delivery that are predictable. The target the clinician wishes to set for his patient may therefore not be achieved using standard systems and more complex variants such as CPAP may be employed. The thesis raises the question that a significant component of the efficacy and consistency of oxygen delivery is dependent on the airtight design of the system rather than the PAP. If this is correct it may allow a new approach to the design of delivery systems unconstrained by the technical requirement for pressurisation. In this author’s opinion it is oxygen in the blood that matters and while an effective delivery system is required it should also conform to the tenet *prima non nocere* and in this regard there are aspects of CPAP that fail. It can be harmful, it is uncomfortable and its use in the treatment of respiratory failure has moved from a specific indication, cardiogenic pulmonary oedema, to any cause of respiratory embarrassment. It often takes time to initiate when specialist teams are involved. The advent of CCOT is likely to mean its use will continue to proliferate and reliance on its efficacy may paradoxically lead to potentially hazardous delays in necessary mechanical ventilation. This would be akin to that expressed by Keenan *et al.* in their recommendations on not persisting with non-invasive ventilation following failed extubation\(^4\). It is of interest that since the CPAP study was presented, the Chelsea & Westminster CCOT have independently reduced their use of CPAP in favour of the Vapotherm\(^\circledR\) system which as a high flow system performs well in terms of oxygen delivery and patients prefer it. This also
needs further investigation. Delivery of oxygen needs to be effective, be it by designing better comfortable mask systems or by mechanical ventilation.

9.3.2 Critical Care Outreach

At the start of this project it was hoped to demonstrate the efficacy of CCO in delivering care to the ward-based critically ill patients. This was overoptimistic and the scale and difficulty of the task was underestimated. It has identified that there is an enormous amount of work still to be done. Chapter 7 would suggest that despite CCOT, there are still significant problems with the ward care of patients with signs of circulatory shock. This is disappointing in that most of the problems directly linked to CCOT stem from logistics rather than capability. A 24 hour service needs to be mandatory to help prevent delay. The Chelsea and Westminster CCOT is nurse led and operates relatively independently of the ICU medical staff. As such they have limited power in prescribing new therapy, deploying monitors such as central catheters, ordering sophisticated interventions and generally carrying enough clinical weight to mobilise the system rapidly for the patient’s benefit. This was highlighted in the audit by the uncontrolled and possibly excessive use of fluid. This is not a criticism of the clinical skills of a group of highly motivated, highly trained individuals, more an assessment of the limitations put upon their skills by national and local rules. I believe that a CCOT should have a medical presence, suitably trained to assess, investigate and deliver critical care. I would hope that this could reduce delays, promote rapid institution of ward interventions, and a smoother transfer to ICU if required. Evidence for this does not lie in this thesis, but further work could be done to investigate this additional input. It will of course cost more.
Even though the use of the Surviving Sepsis Campaign protocol is problematic when considering the resuscitation of patients from all causes of circulatory failure, it is being championed for ward based sepsis. Direct implementation of it as a tool for all other causes is almost foolhardy, but it does have some virtues which need to be identified and the protocol modified accordingly. The impetus placed on timeliness and monitoring is laudable and a focus on reassessment rather than a ‘fire-and-forget’ approach is important. Development of guidelines both local and national should be undertaken to improve the prompt controlled delivery of initial treatments. A study as outlined above could really add weight to such an argument.

9.3.3 Cardiac Output Monitors

The use of pulse contour analysis cardiac output monitors to guide the resuscitation of the circulation has yet to be proved in general critical care patients. However in surgical patients they do convey some benefit and have been shown to be superior to central venous catheters, in assessing fluid status and responsiveness\textsuperscript{1,5,6}. It would be pointless trying to introduce a complex, hi-tech system into the ward environment and any device has to be simple, safe, easy to use, reliable, ‘plug-in and go’ and provide easy-to-understand usable information or it will not be deployed. With appropriate support and staffing, a system like the Vigileo Flotrac\textsuperscript{®} could be used on a ward to aid in the assessment and delivery of resuscitation. Much work is required in this field.
9.4 Recommendations for Future Research

Potential research projects have been outlined in each of the chapter summaries. This thesis set out to appraise the interventions delivered to acutely unwell ward patients. What appeared initially simple grew into something very complex. Whilst it appears the number of ‘interventions at the disposal of the ward-based clinician seem few, the evidence for their use, their method of delivery, their clinical benefit and actual current delivery have all yet to be elucidated. Attempting to assess such a broad church may have been folly, and if starting again it may have been more prudent to focus on just one intervention. The oxygen delivery systems could have been taken further forward with attempts to perform the Vapotherm® vs CPAP study and this stands out as a significant follow-up piece of research that could be done. In addition, developing novel system designs and subjecting them to model and then clinical trial might have produced a more succinct and directed thesis.

If I was to start over then this would probably have been a better tactic. However the desire to detect and observe the other aspects of the immediate care received by critically ill patients is strong. Does what we do to ward patients have a bearing on their outcome? Is the CCOT in its current guise useful? Which patients benefit from aggressive intervention and which may not? Can we improve on the monitoring and management of such patients? This thesis only scratches at the surface of these questions. Thus further work could include:

- The demography. CCOT works in a very varied and busy environment. What is the true nature of the work in terms of how many patients are treated and for which conditions? This probably cannot be defined, but some population statistics would be helpful.
CCOT carries an instruction to educate and disseminate skills and information and the effectiveness of this deserves study. How effective are training courses such as ALERT on preparing staff for their interaction with critical illness? What impact does ward based teaching have on the critical care skills of the tutee? Six months later do trainees use what they were taught and do they turn reactive to proactive?

One very important element that came out of the audit and has been reported previously, is the ability of CCOT/MET to make decisions which may mitigate against aggressive therapy and provide a framework for the limitation of treatment. It would be interesting to look at the incidence of this phenomenon and how it affects both the patient group and ward staff.

Non-specific interventions which include aspects of infection control, rehabilitation, management of post ICU patients both in the hospital and in the community, all need to be addressed.

9.5 Final Conclusions

While there is still significant focus on what happens once a patient arrives in an ITU there remains very little information on what happens before, yet we know how important that is. In starting with the basics of demonstrating the mechanisms of action of a commonly available ward based intervention, this thesis established that not all CCO interventions are as well understood as first thought and that there is scope for major improvement. Evidence that 3 years after the introduction of a CCOT, the appropriate tracking, triggering and timely intervening on the general wards is still poor, could question the constrained efficacy of CCOT in its current
guise. It is important to temper negativity with the observation that the majority of patients do not go to ITU or die and that there is clear benefit in terms of ward management although hard to quantify. Critical care outreach is here to stay and it needs to remain. It may be difficult to show benefit in trials, but it is the author’s contention that removal of CCOT would clearly and rapidly demonstrate significant detriment. It will evolve and change as with all medical specialities, but in doing this needs to become standardised and critically assessed to ensure that it can deliver that which was desired at its inception. Goldhill et al. started by evaluating scoring systems. This thesis makes the next step which is evaluating commonly employed methods. These are two steps of a long and difficult road.

‘The first step towards amendment is the recognition of error’. Seneca (5-65 A.D.)
9.6 References


Appendix 1

Mathematical Derivation of the Possible Contribution of Dead Space Gases to the EOIC

A.1 Introduction

The mechanical model permits the application of simple physical principles to allow the estimation of the possible further detriment the inclusion of dead space gases and vapours might have to the EIOC obtained from measurement. For this mathematical formula we have selected the Hudson mask as the example, although the calculations could be used with data from any of the oxygen delivery systems tested.

Derivation of Formula for $EIOC_{corr}$

Tidal volume ($V_t$) in an average 70kg male $500 \text{ ml}^1$

Dead space (both anatomical and physiological) ($V_D$) $30\%$ of $V_t^1$

Oxygen Consumption $250 \text{ ml.min}^{-1[1]}$

Respiratory Quotient (R) $0.8^1$

The data that we have derived from the model requires correction factors for the effect of dead space to be added in.
A.1.1 Carbon Dioxide

For each breath, at the end of expiration we can assume that $V_D$ contains gas from the alveolus ($V_A$). The oxygen concentration of $V_A$ at end expiration ($V_A[O2]$) is the original oxygen concentration at end inspiration ($V_i[O2]$) minus the proportion of oxygen consumed and is reflected in the value of EtO$_2$. If $R$ is assumed to be 0.8, then it can be assumed that the 80% of the difference between $V_i[O2]$ and $V_D[O2]$ is made up of CO$_2$. Resting oxygen consumption is approximately 250 ml.min$^{-1}$, thus CO$_2$ production is:

$$0.8 \times 250 = 200 \text{ ml.min}^{-1}.$$

At a respiratory rate of 10 breaths.min$^{-1}$, the contribution of CO$_2$ per breath would be:

$$200 \div 10 = 20 \text{ ml}.$$

This CO$_2$ would be distributed in a $V_A$ of:

$$V_A = V_t - V_D$$

$$= 500 - 150 = 350.$$

The CO$_2$ would contribute $(20 \div 350) \times 100 = 5.7\%$ of the value of $V_D$ gas at end-expiration.

The value contribution of CO$_2$ at a respiratory rate of 30 would have a value of approximately 2% assuming a constant O$_2$ consumption, Respiratory quotient, $V_t$ and $V_D$:$V_A$ ratio. These assumptions may not be applicable in pathology that results in such a high respiratory rate.
A.1.2 Water Vapour

Fully saturated air contains water vapour at a partial pressure of $47 \text{ mmHg}$. If atmospheric pressure is assumed to be $760 \text{ mmHg}$, then water vapour will contribute:

$\left( \frac{47}{760} \right) \times 100 = 6.18\%$

So this could be added as a correction factor to the EIOC as the model results for the non-humidified systems (all except the Vapotherm®)

If it is assumed that both inhaled and exhaled gases are fully saturated and that the water vapour is distributed evenly through all gases, then the correction required for the oxygen concentrations as a percent is:

$= 0.0618 \times \text{EIOC}$

e.g. for an EIOC of 40% we must subtract:

$= 0.0618 \times 40$

$= 2.47\%$

The additional contribution of CO$_2$ between approximately 2% and 5.7% would mean between approximately 8% and 13% of the V$_D$ would contain water vapour and CO$_2$.

A.1.3 Dead Space

If we assume that V$_D$ contributes 30% to the value of V$_t$, and that the EtO$_2$ reflects the concentration of oxygen in the dead space then it can be said that the contribution of this gas to V[$O_2$] is:
= 0.3 x EtO₂

i.e. 30% of the gas inhaled has an oxygen concentration of the EtO₂

This is added to the concentration of oxygen delivered by the oxygen system in the rest of Vt (70%).

= 0.7 x EIOC

= (0.3 x EtO₂) + (0.7 x EIOC)

Now add in the contribution of water vapour for a final formula that approximates the FiO₂ for VD of 30%

EIOC_{corr} = [(0.3 x EtO₂) + (0.7 x EIOC)] – (0.0618 x EIOC)

### A.2 Examples

From the data for a Hudson Mask:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vt</td>
<td>500 ml</td>
</tr>
<tr>
<td>RR</td>
<td>10 breaths.min⁻¹</td>
</tr>
<tr>
<td>Oxygen flow rate</td>
<td>2 l.min⁻¹</td>
</tr>
</tbody>
</table>

Assuming the EtO₂ is 30% and a VD of 30%

EIOC_{corr} = [(0.3 x 30) + (0.7 x 42)] – (0.0618 x 42)

= 35.80%
The estimation of the EtO₂ and proportions of V_D and V_A, make this method only an approximation of the contribution of dead space to the EIOC derived from the model, but it does allow the plotting of families of curves for both increasing V_D at the same tidal volume, as well as variation in the EtO₂ (see below).

A.2.1 Example 1: Hudson Mask 500 ml. Effect of Varying Proportion of Vt that is V_D

Table A.1 shows the EIOC measured for the Hudson mask across the range of respiratory rates when the Vt was set at 500 ml. We can calculate the EIOC_corr for a V_D:V_A ratio of 30:70 by putting the values of EIOC into the formula and assume that the EtO₂ remains fixed at 30%:

$$ EIOC_{corr} = [(0.3 \times EtO_2) + (0.7 \times EIOC)] - (0.0618 \times EIOC). $$

This results in Table A.2.

Table A.1 Effective inspired oxygen concentration (EIOC) values for a Hudson mask at a tidal volume of 500 ml.

<table>
<thead>
<tr>
<th>Oxygen Flow Rate (L.min⁻¹)</th>
<th>Respiratory rate (breaths.min⁻¹)</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td>42.00</td>
<td>35.00</td>
<td>33.00</td>
<td>30.00</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>59.33</td>
<td>50.67</td>
<td>44.67</td>
<td>40.33</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>65.33</td>
<td>56.67</td>
<td>50.33</td>
<td>44.67</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>74.33</td>
<td>65.00</td>
<td>58.00</td>
<td>51.33</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>82.00</td>
<td>71.33</td>
<td>63.67</td>
<td>55.67</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>88.33</td>
<td>79.67</td>
<td>72.67</td>
<td>63.33</td>
</tr>
</tbody>
</table>
Table A.2 EIOCcorr for a Hudson mask at 500 ml assuming an EtO2 of 0.3 and a VD:VA ratio of 30:70.

<table>
<thead>
<tr>
<th>Oxygen Flow Rate (l.min⁻¹)</th>
<th>Respiratory rate (breaths.min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>35.80</td>
</tr>
<tr>
<td>4</td>
<td>46.87</td>
</tr>
<tr>
<td>6</td>
<td>50.70</td>
</tr>
<tr>
<td>8</td>
<td>56.44</td>
</tr>
<tr>
<td>10</td>
<td>61.33</td>
</tr>
<tr>
<td>15</td>
<td>65.37</td>
</tr>
</tbody>
</table>

There is increasing reduction in EIOCcorr as the oxygen flow rate and respiratory rate increases. This is in part to the assumption that the EtO2 is fixed at 30% and therefore has a greater influence on the EIOCcorr at higher EIOC’s. Estimation of EtO2 is difficult in vivo as it is dependent on oxygen uptake which can vary significantly, particularly in respiratory pathology.

If we consider only the EIOCcorr for the Hudson mask at Vt 500 ml and oxygen flow rate of 4 l.min⁻¹. We can use the derived formula to approximate the effect of altering the ratio of V_D and V_A assuming that EtO2 is maintained at 30%. This is summarised in Table A.3 and shown graphically in Figure A.1.
Figure A.1 The effect of varying the VD:VA ratio on the EIOCcorr for a Hudson mask delivering oxygen at 4 l.min⁻¹ to a Vt of 500 ml with an assumed EtO₂ of 30%. 60:40 (×), 50:50 (□), 40:60 (◇), 30:70 (△), 20:80 (○) and no correction (●).
Table A.3 The Hudson mask with oxygen flow rate of 4 l.min\(^{-1}\) and a Vt of 500 ml. The effect on EIOC\(_{corr}\) of altering the V\(_D\):V\(_A\) ratio assuming a constant EtO\(_2\) of 30%.

<table>
<thead>
<tr>
<th>V(_D) : V(_A) Ratio</th>
<th>Respiratory rate (breaths.min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>No Correction</td>
<td>59.33</td>
</tr>
<tr>
<td>20:80</td>
<td>49.80</td>
</tr>
<tr>
<td>30:70</td>
<td>46.87</td>
</tr>
<tr>
<td>40:60</td>
<td>43.93</td>
</tr>
<tr>
<td>50:50</td>
<td>41.00</td>
</tr>
<tr>
<td>60:40</td>
<td>38.07</td>
</tr>
</tbody>
</table>

The calculations results confirms that introduction of a correction factor further reduces the EIOC that the mask delivers. Also increasing the contribution of the dead space gases and vapours by increasing the proportion of Vt that is V\(_D\) reduces the EIOC still further. This simplistic view of mixing of gases in the model relies on significant assumptions and the values derived for EIOC\(_{corr}\) can only be viewed as a guide for the real mask performance \textit{in vivo}.

\textbf{A.2.2 Example 2: Hudson Mask Vt 500 ml. Effect of varying the value of EtO\(_2\)}

The derived formula for calculating EIOC\(_{corr}\) to allow for the effect of dead space gases and vapours relies on an approximation of EtO\(_2\) as a reflection of oxygen consumption and carbon dioxide production. The value of EtO\(_2\) is predominantly dependent upon the FiO\(_2\) and oxygen consumption. Oxygen consumption can vary widely in pathology and so for the purpose of this example we present calculations.
based on a spectrum of possible EtO$_2$ values. This represents the best and worse case scenarios depending upon the value of EtO$_2$ as a representation of oxygen consumption, and its contribution to the concentration of oxygen in the dead space gases.

Using the Hudson mask again at 500 ml and 4 l.min$^{-1}$ oxygen flow rate. The EIOC$_{corr}$ values obtained with the EtO$_2$ varying between 40% and 15% are represented in Table A.4 and Figure A.2.

Table A.4 Hudson mask at 500 ml delivering 4 l.min$^{-1}$ oxygen flow rate. Effect of varying the EtO$_2$ on the EIOC$_{corr}$ if the VD:VA ratio is constant at 30:70

<table>
<thead>
<tr>
<th>EtO$_2$ (%)</th>
<th>Respiratory rate (breaths.min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>No Correction</td>
<td>59.33</td>
</tr>
<tr>
<td>15</td>
<td>42.37</td>
</tr>
<tr>
<td>20</td>
<td>43.87</td>
</tr>
<tr>
<td>25</td>
<td>45.37</td>
</tr>
<tr>
<td>30</td>
<td>46.87</td>
</tr>
<tr>
<td>35</td>
<td>48.37</td>
</tr>
<tr>
<td>40</td>
<td>49.87</td>
</tr>
</tbody>
</table>
Figure A.2 The effect of varying the EtO2 on the EIOCcorr for a Hudson mask delivering oxygen at 4 l.min⁻¹ to a Vt of 500 ml with an fixed VD:VA ratio of 30:70. 0.15 (+), 0.2 (×), 0.25 (○), 0.3 (◇), 0.35 (△), 0.4 (○) and no correction (●).
The table and figure also confirm that assuming a lower oxygen concentration in the expired gas will produce a further reduction in delivery by the oxygen systems, and that the greater the difference between the oxygen concentration delivered and the EtO₂ results in a lower corrected EIOC. Once again we caution that the above calculations represent true values in vivo, as their derivation depends upon assumptions about EtO₂ and Vₐ:V₃ ratio, both of which are potentially extremely variable in the patient population. However, the above tables and figures do demonstrate the possible effects of the dead space on the delivery of oxygen to the alveoli and how that would further undermine the performance of the mask in reality as opposed to this bench model.
A.3 References

1. West JB. Respiratory Physiology - The Essentials. 6 ed: Lippincott Williams & Wilkins; 2000.
Appendix 2

Manufacturer’s Data for Equipment Tested
**HUDSON RCI® OXYGEN THERAPY PRODUCTS**

Teleflex Medical and Hudson RCI’s oxygen therapy products are identified by a unique colour-coded system to enable you to select the right product first time.

### Non-Rebreathing Mask

<table>
<thead>
<tr>
<th></th>
<th>Adult</th>
<th>Child</th>
<th>Estimated Oxygen Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen Flow (l/min)</td>
<td></td>
<td></td>
<td>Oxygen Concentration*</td>
</tr>
<tr>
<td>10 - 12</td>
<td>80 - 100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* May require higher flows. The flow should be adjusted so the reservoir bag does not deflate more than one third during inspiration.

### Medium Concentration Mask

<table>
<thead>
<tr>
<th></th>
<th>Adult</th>
<th>Child</th>
<th>Estimated Oxygen Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen Flow (l/min)</td>
<td></td>
<td></td>
<td>Oxygen Concentration*</td>
</tr>
<tr>
<td>5 - 6</td>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 - 8</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 - 10</td>
<td>60%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Nasal Cannula

<table>
<thead>
<tr>
<th></th>
<th>Adult</th>
<th>Child</th>
<th>Estimated Oxygen Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen Flow (l/min)</td>
<td></td>
<td></td>
<td>Oxygen Concentration*</td>
</tr>
<tr>
<td>1</td>
<td>24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>28%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>32%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>36%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>44%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Nebuliser Kit

<table>
<thead>
<tr>
<th></th>
<th>Adult</th>
<th>Child</th>
<th>Recommended Flow Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>6-8 lpm</td>
</tr>
</tbody>
</table>

*Oxygen concentrations are estimates only and may vary significantly, depending on the patient’s respiratory rate, tidal volume, the oxygen flow into the system, the amount of room air entrained, and the mask fit.
Moisture Output
25mg H_2O @ 15 breath/min

Tidal volume 500ml

Resistance to Flow
0.3 hPa (cmH_2O) at gas flow rate 0.5l/sec
0.7 hPa (cmH_2O) at gas flow rate 1.0l/sec
1.2 hPa (cmH_2O) at gas flow rate 1.5l/sec

Integrated oxygen port that can provide up to 60% oxygen concentrations to the patient via the simplest of connections.

O_2 %
27 33 37 42 45 47 53 54 57 60

Dead Space
11ml

Inspired Oxygen Concentration (%)
15 breath/min
Tidal volume 500ml

Smooth, rounded edges aid patient comfort.

Clear housing gives an aesthetic appearance and allows visualisation of contamination.

Simple opening port allows quick and easy access for a suction catheter to aid the removal of secretions.

THE NEW PORTEX THERMOVENT® T2 HME

Original Portex Thermowvent T paper media provides high level performance heat and moisture exchange to patient.

Ordering information

<table>
<thead>
<tr>
<th>Description</th>
<th>Product Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portex Thermowvent® T2 Heat &amp; Moisture Exchanger</td>
<td>108/79/022</td>
</tr>
</tbody>
</table>

The New Portex Thermowvent® T2 HME

providing a clear choice
The New Portex Thermovent® T2 HME
providing a clear choice

Description
• Sterile, single use heat and moisture exchanger.
• Provides effective humidification for spontaneously breathing patients whose upper airways are bypassed by a tracheostomy tube.
• Device can be used for a maximum period of 24 hours.

Indications for use
• For use on adult and paediatric patients with a tidal volume more than 70ml.
• Reduction of heat loss through the broncho pulmonary tree.
• Helping to prevent thickened secretions and changes in lung function.
• Supplying additional oxygen when required.
• Facilitating the removal of secretions.
• Preserving humidity and minimising damage to tracheal epithelial cells.

For more detailed information, please refer to the instructions for use.
Objective of Oxygen Therapy

Surprisingly, it is in this area that we can make an increase in results. O2 therapy is comparatively well understood, but often patients feel that they are breathing air, whereas the reality is that they are not. The O2 therapy is to increase inspired oxygen tension to that of about 100 mmHg. Ideally, the inspired O2 is the O2 tension in the air in the alveoli. Patients naturally maintain an arterial blood O2 tension of about 60 mmHg.

1. Irrespective of the cause, hypoxia should be treated using a Ventimask which gives an appropriate oxygen concentration, to bring oxygenation and ventilation to near normal.

2. When an enteral ventilation system, is used, by O2, entonox (O2+N2), is usually indicated if there is a cor pulmonale (left heart pressure). Oxygen therapy will then return respiratory parameters and patient’s condition.

3. When nasal cannulae and Ventimask technique are used, in excess of the above stated tension and pressure, hypoxia is usually treated with O2 therapy, and the inspired O2 and 28% Ventimask are appropriate under these circumstances, and will produce the optimum performance with minimum of complications.

Rationale for controlled oxygen therapy

Hypoxia can be treated with some sort of a mask, and it is important to consider the patients who are treated with a mask. The patients who are treated with a mask are treated to achieve a satisfactory blood oxygen level, to avoid hypoxia. In these patients, oxygen should be administered, to achieve a satisfactory blood oxygen level, to avoid hypoxia.

The resulting oxygen concentration varies not only on a breath by breath basis, but also from patient to patient. The resulting oxygen concentration is dependent on the patient’s condition and the mask’s performance. The mask’s performance is dependent on the mask’s design, size and placement of the mask, and the tidal volume. The mask’s performance is dependent on the mask’s design, size and placement of the mask, and the tidal volume.

Variable Performance Devices:

The change in the condition of the lungs under treatment.

1. Variable Performance

These devices allow a controlled delivery of nasal, endotracheal and endobronchial oxygen. They are very simple to use and require little maintenance. They are easy to change the conditions of the lungs under treatment.

2. Fixed Performance

Fixed Performance Masks:

These devices allow a controlled delivery of nasal, endotracheal and endobronchial oxygen. They are very simple to use and require little maintenance. They are easy to change the conditions of the lungs under treatment.

The advantage of using a variable performance device on a fixed gas delivery system is that it is easy to change the conditions of the lungs under treatment.

Fixed Performance Masks:

The advantage of using a variable performance device on a fixed gas delivery system is that it is easy to change the conditions of the lungs under treatment.

How a Fixed Performance Mask Works

A fixed performance mask achieves the required oxygen concentration by controlling the delivery of the inspired gas mixture. The inspired gas mixture is controlled to achieve the desired O2 concentration. The inspired gas mixture is controlled to achieve the desired O2 concentration.

1. Determining the amount of inspired oxygen at the end of expiration

Knowing the amount of inspired oxygen at the end of expiration is essential to achieve the desired O2 concentration.

2. Determining the amount of inspired oxygen at the end of expiration

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5. Determining the amount of inspired oxygen at the end of expiration

Knowing the amount of inspired oxygen at the end of expiration is essential to achieve the desired O2 concentration.

Oxyhaemoglobin Dissociation Curve

The oxyhaemoglobin dissociation curve is the relationship between the oxygen saturation of the hemoglobin and the oxygen tension of the hemoglobin.

This curve is used to determine the oxygen saturation of the hemoglobin and the oxygen tension of the hemoglobin.

A) Principles of operation

A fixed performance mask achieves the required oxygen concentration by controlling the delivery of the inspired gas mixture. The inspired gas mixture is controlled to achieve the desired O2 concentration. The inspired gas mixture is controlled to achieve the desired O2 concentration.

B) Calculating total gas mixture flow rates

The total gas mixture flow rate is calculated to achieve the desired O2 concentration. The total gas mixture flow rate is calculated to achieve the desired O2 concentration.

C) Calculating partial gas mixture flow rates

The partial gas mixture flow rates are calculated to achieve the desired O2 concentration. The partial gas mixture flow rates are calculated to achieve the desired O2 concentration.

D) Calculating total gas mixture flow rates

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E) Calculating partial gas mixture flow rates

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F) Calculating total gas mixture flow rates

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G) Calculating partial gas mixture flow rates

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H) Calculating total gas mixture flow rates

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I) Calculating partial gas mixture flow rates

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J) Calculating total gas mixture flow rates

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K) Calculating partial gas mixture flow rates

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L) Calculating total gas mixture flow rates

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M) Calculating partial gas mixture flow rates

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N) Calculating total gas mixture flow rates

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X) Calculating total gas mixture flow rates

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Y) Calculating partial gas mixture flow rates

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Z) Calculating total gas mixture flow rates

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Section 1 Indications and Contraindications

Primary Indications:
Used to warm and humidify breathing gases, generally prescribed during oxygen therapy where concentrations of oxygen greater than ambient air are utilized to treat symptoms and manifestations of hypoxia including:
• Documented hypoxemia: decreased PaO₂ in blood below normal range
• Acute care in which hypoxemia is suspected
• Severe trauma
• Acute myocardial infarction

Secondary Indications:
• Managing hypothermia
• Treating bronchospasm caused by cold air

Contraindications:
General:
• Any situations in which humidification is contra-indicated (see AARC Clinical Practice Guidelines)

Specific to Nasal Cannula:
• Patients with occluded or defective nares should not use the system.

Section 2 Definitions, Warnings and Cautions

2.1 Definitions
A WARNING indicates that a potentially harmful situation may occur.
A CAUTION indicates a condition that may lead to equipment damage, malfunction, or inaccurate operation.
A NOTE indicates a point of emphasis to make operation more efficient or convenient.

ASEPTIC TECHNIQUE is practices and procedures performed under carefully controlled conditions with the goal of minimizing contamination by pathogens. Specifically with respiratory equipment, especially with reference to the Vapotherm 2000i, this includes proper hand washing and avoiding direct hand contact with connection points.

Please take the time to familiarize yourself with the definitions, warnings, cautions and notes listed in this manual. They cover safety considerations, special requirements, and regulations.

The user of this product assumes sole responsibility for any malfunction due to operation or maintenance performed by anyone not trained by Vapotherm™ staff or official training documentation.

When handling any part of the Vapotherm 2000i, always follow hospital infection control guidelines and Standard Precautions. Vapotherm recommends that users follow the disinfection procedure found in this manual. Vapotherm also recommends that users follow the Centers for Disease Control (CDC) publications: Guidelines for Maintenance of In-Use Respiratory Therapy Equipment and Guidelines for Prevention of Nosocomial Pneumonia.

2.2 General Warnings
• Federal Law (U.S.) restricts the sale of this device to, or by the order of any physician.
• This is a humidification device generally used for providing continuous flows of breathing gas. The Vapotherm 2000i is not a ventilatory device and should not be used as life support.
• This device will not operate without flow.
Section 2 Warnings and Cautions

General Warnings (cont.)

- The Vapotherm® 2000i must be disinfected between each patient use and after 30 days of use on the same patient.
- Gas flow delivered by this device is limited to 40 liters per minute. Maximum operational flow rate should not be exceeded.
- Prior to use machine should be positioned and secured to a sturdy IV pole.
- The system includes several disposable elements that are labeled as single patient use only: do not attempt to sterilize or reuse. Follow all local and federal regulations for disposal.
- Oxygen supports combustion; this device should not be used near or around open flames, oil, grease or any flammables or anesthetics.
- Performance verification must be performed prior to use.
- Service on the device should be performed by qualified, certified service technicians ONLY.
- To prevent injury do not attempt to perform any service to the Vapotherm 2000i while a patient is connected to the device.
- If the device is damaged or not working properly do not use. Contact Vapotherm or your authorized Vapotherm representative.
- Do not operate if power cord is damaged.
- The device should not be turned on and left unattended.
- Do not use the Vapotherm 2000i in or around water other than the water bag that feeds the system.
- Failure to utilize sterile water supply or clean gas supply may increase risk of bacterial contamination.
- The Vapotherm 2000i utilizes warmed water and can pose a risk for colonization of bacteria and patient infection if disinfection procedures are not followed.
- Gas flow is external to the Vapotherm, but the care giver should confirm the integrity of all respiratory gases utilized to ensure they are free of contamination.
- Gas supply must be made of clean dry medical grade gas to prevent harm to the patient and prevent damage to the Vapotherm 2000i.
- An oxygen analyzer with alarms must be used when the delivered concentration level is critical. The Vapotherm 2000i does not provide oxygen concentration analysis capability.
- To reduce any potential transmission of contaminated water from the system, all assembly and/or disassembly of the unit should take place outside the primary care areas.
- The 2000i is not a Continuous Positive Airway Device (CPAP). There are no controls to deliver or monitor airway pressure. The 2000i humidifies breathing gases that are delivered externally through standard air/oxygen blender and flowmeter. The 2000i should not be used to deliver pressure in a closed system.

2.3 Cautions

- Verify that the power source is compatible with the electrical specifications shown on each component. For proper grounding reliability, connect the 2000i power cord only to a properly marked hospital grade receptacle. DO NOT USE EXTENSION CORDS. If any doubt exists as to the grounding connection, DO NOT operate the device.
- Do not immerse the Vapotherm 2000i in water. Do not steam or gas sterilize the Vapotherm 2000i.
- Read and understand this manual prior to operating the system.
- The Vapotherm 2000i must be disinfected if the water circuit is opened up by removing or replacing a component.
- Aseptic techniques (including proper hand washing and avoiding direct hand contact with connection points) and Standard Precautions should always be followed when handling medical equipment.
- Standard Precautions should always be followed when coming in contact with patients.

Section 2 Warnings and Cautions

2.4 General Inspection

When unpacking the Vapotherm 2000i system, ensure that the unit is inspected for damage before use. Report any damage or missing parts immediately to your authorized Vapotherm distributor.

When renting a Vapotherm 2000i, customers should require the rental service to provide a certification that the machine has been disinfected before accepting delivery.

Section 3 About the Vapotherm 2000i and 2000h

The Vapotherm™ 2000h for home use consists of the combination of a 2000i unit and the “Home Care Compressor Kit (Part number HCK200-M)”. The HCK-200 Kit consists of an HS-100 Stand, a 5060A Room Air Compressor and Flowmeter assembly.

1. A Vapotherm authorized Durable Medical Equipment (DME) Supplier is responsible for the following:
   - Assembling the 2000i unit and the kit components
   - Instructing the user in their responsibilities for operating the system
   - Providing 1000 ml sterile water bags as needed
   - Routine servicing of the system
   - Removing, replacing, and disposing of the disposable components (Vapor Transfer Cartridge, Vapotherm Spike Set -1 & Delivery Tube) every 30 days
   - Disinfecting of the 2000i unit every thirty days following the procedure found in Section 8.1 – 8.6 of the 2000i Operating Instruction Manual

2. The user/home care provider is responsible for the following:
   - Change nasal cannulas when soiled or excessively wet from secretions. Dispose of properly.
   - Installing and replacing the sterile water bag
   - Avoid liquid spills on the components
   - Do not attempt any repairs. If you have any problems with your Vapotherm 2000i device notify the DME provider immediately
Section 3 About the Vapotherm 2000i

The Vapotherm 2000i warms and humidifies flows of air, oxygen or medical gas blends for delivery to a patient, by nasal cannula or Vapotherm approved interface. Warming and humidification of breathing gas occurs in a Vapor Transfer Cartridge, where air and water are separated by a membrane permeable to water vapor. The membrane consists of microtubules constructed of polysulfone material. The membrane meets HIMA (Health Industry Manufacturers Association) standards on filters for sterilizing liquids and has been shown to effectively exclude bacteria from crossing from the water circulation to the gas flow.

The warmed humidified gas stream reaches the patient via a patented triple lumen Patient Delivery Tube. Humidified gas flow is delivered through the center lumen. The outer lumens contain water which is warmed via an internal heater and propelled through the system via an internal pump (See schematic, fig. 1). This maintains breathing gas temperature and minimizes condensation. The final patient interface is a Vapotherm nasal cannula or approved interface configured to minimize resistance and heat loss.

NOTE: The water circuit and gas circuit of the Vapotherm 2000i do not come in contact with each other.

Respiratory gases are supplied to the Vapotherm™ 2000i from an external gas supply, typically through a standard wall-mounted flow meter connected to the hospital medical gas supply. Gas flow rate is controlled by the external flow meter or medical gas blender. There are no flow controls on the Vapotherm™ 2000i. Connections for gas flow and water are made via the rear panel. All Vapotherm 2000i controls are on the front panel of the device.

WARNING: Use of patient interfaces not recommended by Vapotherm may cause safety concerns or affect the performance of the device.

Section 4 Set-up

4.1 The 2000i Unit

1. The back of the 2000i has an IV pole clamp that enables IV pole attachment.
2. The unit should be mounted on a sturdy IV pole approximately two feet from the top of the pole to facilitate ease of access and proper flow from sterile water system.
3. If using an oxygen blender, mount the blender above the Vapotherm 2000i on the IV pole.
4. Connect blender hoses into both air and oxygen wall connections.
5. Plug Vapotherm power cord into a hospital wall power outlet.

WARNINGS:

Aseptic technique (including proper hand washing and avoiding direct hand contact with connection points) should always be followed when setting up and operating the Vapotherm 2000i.

The medical gas source is external to the Vapotherm 2000i. Always verify the integrity of the medical gas source and utilize bacterial filters if necessary.

Closed system components (VSS-1, Vapor Transfer Cartridge and Patient Delivery Tube) should not be opened in patient care area.

4.2 Selecting the Vapor Transfer Cartridge

Vapotherm provides both a high flow cartridge (VT01-AS) and a low flow cartridge (VT01-BS).

- The high flow cartridge (VT01-AS) should be used with the pediatric cannula with an operational flow range of 5–20 liters per minute (lpm) or with adult sized cannula with an operational flow range of 8–40 lpm.
- The low flow cartridge (VT01-BS) should be used with the neonatal, premature, infant, or intermediate sized cannula with an operational flow range of 1–8 lpm.

WARNINGS:

Do not exceed maximum operational flow rates of 40 lpm for the high flow cartridge (VT01-AS) and 8 lpm for the low flow cartridge (VT01-BS). Ensure that the correct cartridge is inserted before operating.
Section 4 Set-up

4.3 Inserting the Vapor Transfer Cartridge

1. The Vapor Transfer Cartridge (VT01-AS or VT01-BS) attaches to the unit by two water and two air connections.
2. When facing the unit, access is via a hinged cover on right side. The cartridge may be fitted in either direction.
3. Date the cartridge.
4. Remove protective caps from luer side ports of cartridge (Fig. 1).
5. Attach lower air tube from Vapotherm 2000i to lower end of cartridge.
6. Insert projecting side ports into matching connections in unit. Press cartridge firmly into place (Fig. 2).
7. Attach upper air tube from Vapotherm 2000i to top of cartridge (Fig. 3). Make sure tubing is not kinked.
8. Close hinged cover. If it does not close easily, check that cartridge is pressed fully into place and that air tubes are not interfering with cover.

WARNINGS:
The cartridge must be changed between patients and discarded after each use.
If the cartridge is removed, the unit should be disinfected.
If the cartridge is dropped, it should be discarded.
NOTE: Do not remove cartridge from the Vapotherm 2000i without first draining the machine.

4.4 Inserting the Patient Delivery Tube

1. Insert Patient Delivery Tube into lower portion of the unit by aligning blue tabs on tube with notches on bottom of unit.
2. Firmly press into place (Fig. 4, see next page). Blue lip on tube must be flush with the bottom of unit.
3. Rotate 1/4 turn clockwise and pull slightly downwards to lock into place (Fig. 4, see next page).

WARNING: The Patient Delivery Tube is a single patient use item and should be changed with each patient.
If the Patient Delivery Tube is removed from the device for any reason the Vapotherm 2000i should be disinfected following the routine disinfection procedure before returning to service.

CAUTION: Unit will not operate correctly if the Patient Delivery Tube is inserted improperly or not locked into place.

Section 4 Set-up

4.5 Vapotherm Spike Set (VSS-1): for connecting Sterile Water Bag

1. Hang a sterile water bag from IV Pole.
2. Connect VSS-1 to the water inlet port on back of unit and make sure it locks into place (Fig. 5).
3. Ensure the VSS-1 is clamped then remove spike cap. Wipe spike with disinfectant wipes, 70-90% isopropyl alcohol.
4. Firmly insert spike into sterile water bag while avoiding direct hand contact with the spike tip and water bag septum.
5. Leave VSS-1 spike set clamped until ready to fill unit.

WARNINGS:
The VSS-1 is a single patient use item and should be changed with each patient.
If the VSS-1 is removed from the Vapotherm device for any reason the Vapotherm 2000i should be disinfected following the routine disinfection procedure before being returned to service.

CAUTION: Never leave the VSS-1 unclamped when the system is not running.
NOTE: Removing an empty sterile water container does not constitute opening the closed system. New sterile water containers can be spiked using the same VSS-1 without removing the device from service following the procedure above.

4.6 Connect To A Gas Source

1. Connect a source of air, oxygen or medical gas blender to the gas inlet port of Vapotherm 2000i (Fig. 6). Gas inlet connection is a hose barb that accepts female fitting on a standard 1/4” (6.35mm) oxygen tube.

NOTE: Vapotherm will not operate unless there is gas pressure at gas inlet. With no flow/pressure sensed, a “System Failure” alarm will sound.
Section 5 Operation of The Vapotherm- 2000i

5.1 Prepare for Activating the Unit
1. Ensure that the Vapotherm 2000i power cord is plugged into a hospital electrical wall outlet.
2. Unclamp the Vapotherm Spike Set (VSS-1) (Fig. 1).

5.2 Turn on Flow
1. If using the high flow cartridge (VT01-AS) flow should be started at least 8 lpm for warm-up.
2. If using the low flow cartridge (VT01-BS) flow should be set to at least 5 lpm for warm-up.
3. Turn on flow.

5.3 Priming the Unit
1. Unit should be started in CLEANING MODE “CL” to prime a new Patient Delivery Tube.
2. To place unit in CLEANING MODE, press both the power on and the ALARM SILENCE/MUTE buttons simultaneously (Fig. 2).
3. The display will show “CL” and LED next to cleaning icon will illuminate.
4. Water will begin to circulate and fill the Patient Delivery Tube.
5. Operate in CLEANING MODE until Patient Delivery Tube has been purged of air bubbles.
6. When air has been purged, press POWER to stop system
7. Wait until display blanks.

NOTES:
Pressing both the power and alarm mute buttons will set unit in CLEANING MODE, pressing only the power button sets unit in NORMAL mode.
Water is not being heated in CLEANING MODE: the purpose of this mode is to fill the outer lumens of the Patient Delivery Tube with water.
Gas flow is highly recommended (but not mandatory) during priming.

5.4 Activate the Unit
1. Press the Power button only, to start in NORMAL MODE (Fig. 3).
2. If not using the Patient Delivery Tube with integrated cannula, do not place cannula on the end of tube until warm up is complete.

5.5 Setting the Temperature and Warm-Up
1. The Vapotherm 2000i displays the actual temperature of the circulating water. Press and release the up or down arrow on the front of the unit to display temperature setting for 3 seconds.
2. To adjust the temperature setting of the Vapotherm 2000i, press and hold the up or down arrow until the desired temperature is displayed in the LED.

NOTES:
The Vapotherm 2000i always defaults to previous set temperature at power up.
The temperature can be set between 33 and 43˚C.

5.6 Connecting to Patient
1. Wait for desired operating temperature to be reached BEFORE placing the cannula on the end of the Patient Delivoy Tube.
2. Check water level, temperature display and gas flow rate.
3. Size cannula to patient by ensuring that nasal prongs do not fit tightly into nares.
4. Attach properly sized cannula that is designed to function with the cartridge installed in the machine onto the delivery tube. Adjust the flow to the desired rate and place the cannula on the patient.
5. Some condensation of moisture around nose is possible. In addition, high moisture level may mobilize mucus from nose and sinuses. Make sure patient has a supply of tissues.

Some carbohydrate types operational flow rates
<table>
<thead>
<tr>
<th>Cartridge Type</th>
<th>Operational Flow Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Flow (VT01-AS) Adult</td>
<td>8 – 40 lpm</td>
</tr>
<tr>
<td>High Flow (VT01-AS) Pediatric</td>
<td>5 – 20 lpm</td>
</tr>
<tr>
<td>Low Flow (VT01-BS) Premature, neonatal, infant, intermediate</td>
<td>1 – 8 lpm</td>
</tr>
</tbody>
</table>

WARNING:
Always follow aseptic technique (including proper hand washing and avoiding direct hand contact with connection points) when setting up the Vapotherm 2000i and Standard Precautions when placing on a patient.
Cannula should not obstruct the nares of the patient.
Change nasal cannulas when soiled.
After start-up, during the normal purging of the Patient Delivery Tube, air will release and appear as bubbles in the bubble trap of the VSS-1. If the Patient Delivery Tube is filled and a stream of continuous bubbles appear in the bubble trap, it may indicate a problem with the cartridge or Patient Delivery Tube and both should be checked or changed.
NOTE:
If using a low flow cartridge (VT01-BS) the flow cannot be decreased below 5 lpm until an appropriate cannula has been attached to the delivery tube.
Droplets of condensation may appear at the end of Patient Delivery Tube while unit is warming up. This is normal and will stop within a few minutes when temperature is reached. If this condition continues refer to trouble shooting section. If the system operates while not connected to a patient, condensation is likely to develop.
Section 5 Operation of The Vapotherm- 2000i

5.7 Operations – General Guidelines

1. Check that water is properly circulating through the machine by making sure the Patient Delivery Tube is warm across the entire length.
2. If good circulation cannot be confirmed, check that the water flow is not obstructed by air bubbles.
3. Take precautions to minimize cooling of the unheated cannula by trying to maintain contact with the patient’s skin and insulating the exposed portion of the cannula with bedding.
4. Cartridge door should be closed during operation.

NOTE: Condensation in the cannula may occur at low flow rates. To minimize condensation, these general guidelines should be followed:
   - If using flow rates less than 5 lpm, do not set the temperature higher than 34°C.
   - The Vapotherm unit should not be in a position where it is cooled (e.g., by an air conditioning outlet).

CAUTION: DO NOT EXCEED flows of 8 lpm for VT01-BS and 40 lpm for VT01-AS cartridge. DO NOT SET flows below 1 lpm for VT01-BS.

WARNING: Never occlude the nares with cannula.

NOTES:

- It may become necessary to disconnect the cannula from the Patient Delivery Tube for short periods, such as when moving a patient out of a radiant warmer. At flow rates less than 5 lpm, cannula disconnection will activate a system failure alarm, requiring a reset. To avoid this alarm, briefly turn off unit by pressing the power key once. The display will show two bars. Disconnect the cannula from Patient Delivery Tube and move the patient, reconnect the cannula, then press the power key once more to restart the unit.
- A SYSTEM FAIL (88) alarm will activate if there is insufficient gas pressure in the manifold. If no cannula is fitted, flow rate at startup should be at least 5 lpm. The minimum flow rate for operation is 1 lpm if a neonate, infant or premature-sized cannula is fitted, 5 lpm with a pediatric cannula, and 8 lpm with an adult cannula. Cannulas are single use patient items, dispose of as necessary or according to your institution’s guidelines or when visibly soiled or excessively wet from secretions. Weekly change out is recommended to avoid any hardening of nasal prongs.
- An air lock can develop at the pump, preventing normal water flow. Try restarting the unit in cleaning mode.

Section 6 Alarms, Trouble Shooting and Component Change-Outs

6.1 General

1. Periodically check for alarm conditions.
2. Unit will shut down if there is no gas flow. However, flow will not be interrupted if unit shuts down or malfunctions for any other reason.
3. Unit will shut down if temperature safety limits are exceeded, or if water level is low for more than 4 mins. However, unheated gas flow will continue.

NOTE: Should a malfunction occur, indicators on the front panel will light and an alarm will sound. If the actions listed here do not correct the problem causing the alarm, the unit should be returned to an approved facility for service.

6.2 Alarms and Troubleshooting

<table>
<thead>
<tr>
<th>Alarm indication</th>
<th>Cause</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water low</td>
<td>Water is not filling system properly</td>
<td>Make sure VSS-1 spike set is open, and the tube is not kinked or blocked by air bubbles.</td>
</tr>
<tr>
<td></td>
<td>Low Water Pressure</td>
<td>Make sure gas and water connections are open, gas can flow to unit, and air has purged from water system. If not, run ‘CLEANING MODE’.</td>
</tr>
<tr>
<td></td>
<td>Malfunctioning Water or Gas Pressure Sensor</td>
<td>Send in for service.</td>
</tr>
<tr>
<td>System Failure</td>
<td>Insufficient gas or water pressure.</td>
<td>Make sure the gas and water circuits are open and functional and air has purged from the water circuit if the unit is in normal operating mode. Run in “CLEANING MODE”. Make sure there is correct flow for cartridge flow rates. If using &lt;5lpm with a low flow cartridge, a nasal cannula must be attached. If a component failure return the unit for service.</td>
</tr>
<tr>
<td></td>
<td>Malfunctioning Water or Gas Pressure Sensor</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: To restart after a system failure, the unit must be reset by a momentary pressure on the Power button. Do not hold the Power button. The alarm will shut off after a delay of about a second, and the unit can then be restarted normally.

| Cartridge | Water drops in the circuit will cause a cartridge alarm; this does not necessarily mean the cartridge needs to be replaced. | |
**Section 6 Alarms, Trouble Shooting and Component Change-Outs**

<table>
<thead>
<tr>
<th>Alarm indication</th>
<th>Cause</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartridge</td>
<td>If the Cartridge Alarm is continuous and air bubbles are rising into the VSS-1 bubble trap or if a flow or water is visible in the tube below the cartridge, then the cartridge has failed. If cartridge alarm is intermittent and there are no bubbles in the VSS-1 bubble trap or no obvious water flow below the cartridge there may be condensation in the system.</td>
<td>First disconnect the patient from the unit, shut down unit, drain unit, disinfect unit, replace cartridge, VSS-1 and delivery tube, and follow set up instructions. Occasional brief alarms due to condensation are not a cause for concern. Try briefly pinching and releasing tube under cartridge to dislodge the drops and/or decrease set temperature.</td>
</tr>
<tr>
<td>High Temperature Alarm</td>
<td>Malfunction of Temperature Control System.</td>
<td>Shut down system and return for service. <strong>NOTE:</strong> A momentary High Temperature alarm may occur when the unit has been switched off and on again. If the temperature then stabilizes, no action is needed.</td>
</tr>
<tr>
<td>Blocked Tube Alarm</td>
<td>High water or air pressure due to high resistance in water circulation or air outlet; or malfunctioning pressure sensor. Blocked tube alarm due to high WATER pressure will cause a continuous or intermittent tone and alarm light. The flow of breathing gas continues, but is no longer heated.</td>
<td>Check that delivery tube is correctly positioned, rotated clockwise, and pulled into locked position. Check that water is circulating within delivery tube. If alarm persists replace delivery tube and/or cartridge. Disinfect unit prior to replacing components. Find and correct the cause of obstruction. The most common cause is a kink in the nasal cannula or in the prong. Attempting to run the Vapotherm 2000i at very high flow through a patient interface not approved by Vapotherm may also raise the internal pressure sufficiently to trigger a Blocked Tube Alarm.</td>
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</tbody>
</table>

*If further assistance is needed please call your clinical product specialist or local distributor representative.*

**Section 6 Alarms, Trouble Shooting and Component Change-Outs**

**6.3 Component Change Outs**

**WARNINGS:**
The vapor transfer cartridge, patient delivery tube, and VSS-1 spike set are all single use only and should be discarded after removal from the Vapotherm 2000i.
The Patient Delivery Tube, VSS-1 and Vapor Transfer Cartridge should not be changed or replaced in the patient care area.
The system must be disinfected any time the Vapor Transfer Cartridge, VSS-1 or Patient Delivery Tube are removed.

**NOTE:** The cannula and sterile water source can be replaced without disinfecting the system. As with all respiratory equipment, proper hand washing techniques should be followed before contacting or replacing any patient interfaces.

**6.3.1 Replacing Vapor Transfer Cartridge**

1. Power off unit. Disconnect gas flow.
2. Close clip on VSS-1. (Fig. 1)
3. Open hinged cover.
4. Disconnect air tubes from cartridge ends by pressing tubing away from cartridge. (Fig. 2)
5. Remove cartridge by pulling straight outwards. (Fig. 2)
6. Proceed to Section 8.0 and disinfect the Vapotherm® 2000i device before returning the device to service.
7. For set-up please refer to Section 4.3 of the manual.

**CAUTION:** Do not grip cartridge tubing with sharp instruments.

**6.3.2 Replacing the Patient Delivery Tube**

1. Power unit off. Disconnect gas flow.
2. To remove tube, push base of tube upwards, rotate 1/4 turn counter clockwise and pull downward. (Fig. 3)
3. Proceed to Section 8.0 and disinfect the Vapotherm® 2000i device before returning the device to service.
4. For set-up please refer to Section 4.4 of the manual.

**6.3.3 Replacing the VSS-1 Spike Set**

1. Power off unit. Disconnect gas flow.
2. Clamp VSS-1 and remove VSS-1 Spike Set from the water inlet port on the back of the Vapotherm 2000i by releasing the quick connect on the water inlet port.
3. Proceed to Section 8.0 and disinfect the Vapotherm® 2000i device before returning the device to service.
4. For set-up please refer to Section 4.5 of the manual.
Section 7 Removing From Patient and System Shut Down

1. Remove cannula or other interface from patient.
2. Press and release power switch (Fig. 1). Display will show “--”
3. Close clip on VSS-1 (Fig. 2).
4. After 1 minute, water pump shuts off and numeric display is blank. Unit may now be disconnected from power outlet.
5. CAUTIONS: Avoid disconnecting from power or gas sources while machine is operating.
   Do not unplug from power source until display is blank.

Section 8 Routine Disinfecting Protocol

8.1 Disinfection Supplies

1. DK-301 (a-e included in kit)  
   a. Disinfection Bag A  
   b. Disinfection Bag B  
   c. Disinfection Tube  
   d. Cartridge Bypass Tubes

2. Gloves
3. Safety Glasses
4. Disinfectant wipes, 70-90% isopropyl alcohol
5. Approved Disinfectant
6. 1000ml Sterile Water Bag
7. Medical Grade Air Source
8. Standard adult flow meter with oxygen 7ft tubing attached

WARNINGS:
Vapotherm should be disinfected after each patient or every 30 days on a single patient. Do not disinfect in an open patient care area.
The DK-301 disinfection kit is a single use item. Operators should open a new disinfection kit for each disinfection procedure and discard the components at the end of the procedure.
Disinfection Procedure should be performed in a well ventilated area. Use Standard Precautions and aseptic techniques during this procedure.
The Vapor Transfer Cartridge SHOULD NOT be in place when disinfecting the unit.
The Vapor Transfer Cartridge is a single use disposable and must be discarded after each patient use.
DK-301 IS NOT designed to disinfect Vapor Transfer Cartridges.

8.2 Pre-Cleaning Process

1. After patient use, it is recommended that the Vapotherm 2000i System remain attached to the IV pole with all the component parts intact.
2. Move the Vapotherm 2000i System to a hospital approved reprocessing area outside the patient care area.
   CAUTIONS: Avoid disconnecting from power or gas sources while machine is operating.
   WARNING: The water circuit of the Vapotherm 2000i System is not sterile and can potentially have bacterial contamination. The water circuit of the device should never be opened in a patient care area.
   Transport the Vapotherm 2000i System to an appropriate area for draining, cleaning and disinfection.
3. Wash hands and put on gloves.
4. Drain the Vapotherm 2000i System in a receptacle by cutting the delivery tube. (Fig. 1)
5. Remove and dispose of the delivery tube, cannula, VSS-1 spike set, and sterile water source.
6. CAUTIONS: Avoid disconnecting from power or gas sources while machine is operating.
   WARNING: The water circuit of the Vapotherm 2000i system has the potential for bacterial growth so standard precautions should be used to open the water circuit. Disposable components should be disposed of in accordance with hospital guidelines and operators should wash their hands after breaking down the device.
Section 8 Routine Disinfecting Protocol

8.3 Pre-Disinfection Cleaning and Decontamination

1. Wash hands and put on new gloves.
   **WARNING:** Always use standard precautions when cleaning and disinfecting the Vapotherm 2000i system.
   Always use individually wrapped 70-90% isopropyl alcohol disinfectant wipes when wiping down the Vapotherm 2000i and disinfection kit components.
   Always use a new disinfectant wipe taken directly from the package or container and ensure that the disinfectant wipe has not dried out before using it on the Vapotherm 2000i device.

2. Wipe exterior casing including inside hinged cover with an approved disinfectant wipe. (Fig. 2)

3. Wipe inside and outside of the following connections with an approved disinfectant wipe:
   a. Four cartridge connection ports inside hinged cover (Upper and lower cartridge air tubes and the water connection ports)
   b. Water inlet and air inlet connectors on rear of unit
   c. Delivery tube port on the bottom of unit.

8.4 Set-up (cont.)

1. Take the 4 inch bypass tube with 90° barb fittings (Bypass Tube A) and wipe the ends with an approved disinfectant wipe. Press firmly into the inner cartridge connection ports (water circuit). (Fig. 3)

2. Take the 6 inch bypass tube with straight barb fittings (Bypass Tube B) and wipe the ends with an approved disinfectant wipe. Insert firmly into outer upper and lower cartridge ports (air circuit). (Fig. 4)
   **WARNING:** The By-pass Tubing has been designed to optimize the flow of solutions through the Vapotherm 2000i system. Failure to use the By-Pass Tubing supplied by Vapotherm®, Inc. could lead to improper disinfection and or drying.

3. Close hinged cover.

4. Prepare 200ml of approved disinfectant solution and add it to Bag A with slide clamp closed (see Appendix A – “Disinfection Solutions” for approved disinfection solutions, appropriate concentrations, and required hold times).

**WARNINGS:** Disinfection solutions, concentrations and hold times in Appendix A have been verified by independent laboratory testing to adequately disinfect the Vapotherm® 2000i machine when following these instructions. Modifying this procedure or using an alternative disinfection solution, concentration, or hold time could result in inadequate disinfection thereby increasing the risk of contamination.

Always wear gloves when handling disinfectant solutions, work in a well ventilated area, and use an accurate measuring device to ensure the proper concentration of disinfection solution and water.
Section 8 Routine Disinfecting Protocol

8.5 Disinfect Gas and Water Circuits

1. Open clamp on Bag A. Disinfectant will start to drain from Bag A through the unit and into Bag B. (Fig. 9)
2. When disinfectant has stopped draining into Bag B, clamp Bag A.

NOTE: Not all contents from Bag A will drain into Bag B.

CAUTION: Running the system dry can damage the water pump.

3. Start the Vapotherm 2000i system in cleaning mode by pressing the Mute and Power buttons at the same time (Fig. 10). Disinfectant will circulate through gas and water circuits. Run unit in cleaning mode for the required hold time given in Appendix A for the disinfection solution used.

WARNING: Operating the Vapotherm 2000i system in cleaning mode for less than the required hold time may not adequately disinfect the machine and could lead to contamination of the air and water circuits thereby increasing the risk of infection.

4. After circulating disinfection solution through the machine for the appropriate hold time, turn the Vapotherm 2000i off by pressing the power button.

5. Unclamp and lower Bag A and hang onto Vapotherm i.v. pole clamp knob. (Fig. 11)

6. The disinfectant that was contained in reservoir Bag B, has circulated through the unit, and the circulated disinfectant solution drains into Bag A for collection and disposal.

7. Hang 1000 ml of pre-packaged sterile water on i.v. pole.

8. Loosen cap on Bag A to allow air to vent out of the bag as sterile water fills the bag.

WARNING: The disinfection procedure has been specifically designed to use 200 ml of disinfection solution and 1000 ml of sterile water. Bag A is designed to hold 1200 ml of solution. Using larger than the recommended volumes during disinfection or rinsing could cause a spill of diluted disinfection solution.

9. Close the clamp on Bag B, remove the spike, and discard the Bag B in accordance with all applicable regulations and institutional guidelines.

10. Wipe spike with an approved disinfectant wipe and firmly insert into the spike port of a prepackaged sterile water bag. Confirm that water is flowing.

11. Immediately start the Vapotherm 2000i in cleaning mode by pressing the Mute and Power buttons at the same time. (Fig. 10)

12. Run the cleaning mode to circulate the sterile water through the Vapotherm 2000i system until all the water has drained from the sterile water bag. Immediately turn off the system.

CAUTION: Running the system dry can damage the water pump.

13. Clamp tubing and close cap on Bag A and disconnect the bag from the disinfectant tube.

WARNING: Failure to clamp off or close the cap of Bag A firmly before disconnecting it from the disinfection tube could cause diluted disinfection solution to spill.

8.6 Drying

1. Ensure that the Disinfectant Tube, Cartridge Bypass Tubes and the Y-Spike Assembly are all in place.

CAUTION: In order to dry the Vapotherm 2000i system, the Disinfectant Tube, Bypass Tubes and the Y-Spike Assembly must all be connected to the Vapotherm 2000i system.

2. Remove the spike from the empty sterile water bag and wipe with an approved disinfectant wipe.

3. Insert spike from Y-Spike Assembly into standard oxygen tubing.

4. Set flowmeter to 15 lpm.

5. Take the Vapotherm 2000i system and position the system flat on its side opposite the cartridge door for 2 minutes. (Fig 12)

6. After 2 minutes attach the Vapotherm® 2000i device back on the IV Pole and continue to dry at 15 lpm for 25 minutes.

7. After a minimum of 25 minutes, disconnect the disinfection tube, the cartridge By-Pass tubing and Y-spike assembly and close the door to the cartridge area for storage. Discard all components of the DK-301 kit in accordance with all applicable regulations and institutional guidelines.

8. Wipe down exterior casing with disinfectant wipe.

9. Place a sticker over the cartridge access door to certify that the device has been disinfected.

10. Log the disinfection procedure on a Vapotherm 2000i Disinfection Log Sheet or in a similar log approved by your institution. Appendix B has a Sample Disinfection Log. The Disinfection Log can be accessed and printed out at www.vatherm.com.

11. Place the system in a clean plastic cover and seal the end by tying a knot or a clip.

12. The system is now ready for use or storage.

CAUTION: Do not set the flowmeter above 35 lpm or start the drying process without the disinfecting tube in place. This can cause damage to the pressure transducers in the Vapotherm 2000i system.

WARNING:
Gram (-) bacteria can grow in moist environments. The Vapotherm 2000i system should not be stored with visible water remaining in the device.

Vapotherm should be disinfected after each patient or every 30 days on a single patient.
Do not disinfect in an open patient care area.

The DK-301 disinfection kit is a single use item and must be discarded after the disinfection procedure.
Section 9 General Information

9.1 Specifications

<table>
<thead>
<tr>
<th>Specification</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimensions</td>
<td>Height 11&quot; (280 mm), width 5.5&quot; (140 mm), depth 4.5&quot; (114 mm) excluding IV pole clamp.</td>
</tr>
<tr>
<td>Weight</td>
<td>Less than 6 lbs (2.7 kg) without water reservoir.</td>
</tr>
<tr>
<td>Vapotherm spike set</td>
<td>Works with sterile water bags up to 2000 ml bag.</td>
</tr>
<tr>
<td>Circulating water volume</td>
<td>&lt;100 ml (excluding Patient Delivery Tube).</td>
</tr>
<tr>
<td>Mounting</td>
<td>Rear mounted clamp fits standard IV pole or hanger.</td>
</tr>
<tr>
<td>Power</td>
<td>(US) 115 V, 60 Hz, 250 VA (warm up), approximately 80 VA (continuous).</td>
</tr>
<tr>
<td></td>
<td>(Other versions) 220–240 V, 50–60 Hz, 250 VA (warm up), approximately 80 VA (continuous).</td>
</tr>
<tr>
<td>Gas source pressure</td>
<td>4–50 psi. At high pressures (e.g., hospital wall system) the Vapotherm 2000i must be connected to the gas outlet via a standard medical flowmeter and flow regulator with approved fittings.</td>
</tr>
<tr>
<td>Gas flow</td>
<td>Controlled by external flowmeter. Operating range 1–40 lpm, dependent on cartridge type and patient interface used.</td>
</tr>
<tr>
<td>Output gas temperature</td>
<td>(US) 33–43°C at outlet of the delivery tube, adjustable by front panel settings. (Other versions) 33–41°C.</td>
</tr>
<tr>
<td>Humidification</td>
<td>Vapor phase, by transpiration through microporous membrane. Output is at least 95% relative humidity at nasal cannula at a flow rate up to 20 lpm, at least 90% at flow rates from 20–40 lpm, over the full range of operating conditions.</td>
</tr>
</tbody>
</table>

9.2 Definitions and symbols

- Type BF Class 1
- Attention Consult Manual
- Silence Alarms
- Power On/Off
- Alternating Current
- Single Patient Use

Section 10 Warranty

Vapotherm, Inc warrants that the Vapotherm™ 2000i shall be free of defects of workmanship and materials and will perform in accordance with the product specifications for a period of one year from the date of sale by Vapotherm, Inc. If the product fails to perform in accordance with the product specifications, Vapotherm, Inc. will repair, or replace, at its option, the defective materials or part. This warranty does not cover damage caused by accident, misuse, abuse, alteration and other defects not related to material or workmanship.

VAPOTHERM, INC. DISCLAIMS ALL LIABILITY FOR ECONOMIC LOSS, LOSS OR PROFITS, OVERHEAD OR CONSEQUENTIAL DAMAGES WHICH MAY BE CLAIMED TO ARISE FROM ANY SALE OR USE OF THIS PRODUCT. THIS WARRANTY IS GIVEN IN LIEU OF ALL OTHER EXPRESS WARRANTIES.
Appendix A – Disinfection Solutions

This appendix lists approved disinfectant solutions and the required hold times necessary to disinfect the Vapotherm 2000i machine using the routine disinfection procedure outlined in the Vapotherm 2000i Manual Rev B, Section 8. The following disinfectants have been independently tested by an ISO compliant FDA registered lab using “good laboratory practices” (GLP):

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Active Ingredients</th>
<th>Trade Name</th>
<th>Concentration</th>
<th>Hold Time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minntech Corporation</td>
<td>Hydrogen Peroxide 22% and Peracetic Acid 4.5%</td>
<td>Minncare™</td>
<td>1%</td>
<td>10 minutes at 20˚C</td>
</tr>
<tr>
<td>Maril Products Inc.</td>
<td>Dimethyl Benzyl Ammonium Chloride 10% and Dimethyl Ethyl Benzyl Ammonium 10%</td>
<td>Control 3™</td>
<td>1%</td>
<td>10 minutes at 20˚C</td>
</tr>
</tbody>
</table>

*Section 8 Step 4 of the Vapotherm 2000i Operating Manual requires approved disinfection solutions to be circulated through the device for an appropriate hold time as outlined in this column of Disinfection Appendix A.

WARNINGS:
These disinfectant solutions are designed to be used to disinfect the Vapotherm 2000i machine without the cartridge in place. These disinfectant solutions ARE NOT approved to disinfect the cartridge.

Failure to properly prepare the disinfection solution or circulate the disinfection solution throughout the machine for the appropriate hold time could result in inadequate disinfection.

Disinfectants must be used at proper concentrations. User must confirm solution has been mixed according to disinfectant manufacturers instructions, or used in pre-diluted form.

Solutions must not be used past their expiration dates. See disinfectant manufacturer's product labeling for instructions.
Appendix A – Disinfection Solutions (cont.)

Dilution Instructions for preparing a 1% solution of Minncare®- and Control III

Supplies Needed:

- A beaker, graduated cylinder, or container suitable for measuring and mixing 200ml of disinfectant solution

**WARNING:** Components or instruments that are not part of the DK-301 Kit and are used to mix or pour disinfectant solutions should be either single use components or glassware that has been sterilized, high level disinfected, or pasteurized before use in accordance with your institution’s specific disinfection and sterilization procedures.

- 10ml syringe, or pipette, graduated in 1ml increments
- Concentrate Disinfectant
- Minncare® Cold Sterilant EPA Reg No. 52252-4 (22.00% Hydrogen Peroxide, 4.50% Peroxyacetic Acid, 73.50% Inert Ingredients)
- Control III® Disinfectant P/N 10006 (10% n-alkyl dimethyl benzyl ammonium chloride, 10% n-alkyl ethyl benzyl ammonium chloride, 80% inert ingredients)
- 200 ml of sterile water

**WARNINGS:**
Always follow manufactures recommendations for handling disinfectant solutions.
Always wear Personal Protective Equipment when handing disinfectant solution.

**Procedure:**

1. Don appropriate Personal Protective Equipment: Safety goggles, gloves, splash apron.
2. Using an appropriate syringe or pipette, draw up 2ml of undiluted Minncare- (EPA Reg No. 52252-4) or Control III- (P/N 10006) and expel it in a device appropriate for measuring 200ml of solution.
3. Make up 200ml of solution by adding sterile water to the measuring device.
4. Close the slide clamp on Disinfection Bag A and pour disinfectant solution into the bag.
5. Close the cap of Bag A firmly, to avoid spills and continue with Step 6 in Section 8.4 of the disinfection procedure (Page 18).
6. Attach to IV Pole and Vapotherm 2000i according to Disinfection procedure and continue to follow Disinfection Protocol.

---

Appendix B – Sample Disinfection Log

<table>
<thead>
<tr>
<th>Vapotherm 2000i Machine Serial No.</th>
<th>Hospital ID (if Applicable)</th>
<th>Disinfection Date</th>
<th>Disinfectant Solution &amp; Hold Time</th>
<th>Operator</th>
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</thead>
<tbody>
<tr>
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ROLE OF PRESSURE IN HIGH FLOW THERAPY

Thomas L. Miller, PhD, MEd
Director, Clinical Research and Education
Vapotherm, Inc.
Research Assistant Professor of Pediatrics
Jefferson Medical College
This information is provided in response to requests from users to elaborate on the role of pressure in a high flow nasal cannula system. This educational paper provides summary material related to flow and pressure from the respiratory and neonatal literature. Material contained herein is not designed to provide clinical practice guidelines and is consistent with official instructions for use for Vapotherm, Inc.

**Indications for Use for Vapotherm® High Flow Devices:**

Vapotherm, Inc. manufactures high flow humidification devices and patient circuits for use in respiratory support for neonatal, pediatric and adult patients. These products are not intended for use as continuous positive airway pressure (CPAP) devices, but rather as high flow systems to deliver conditioned breathing gases. Vapotherm recommends that users always maintain an open system, including applying a cannula that does not occlude more than 50% of the patient’s nares.

**Precision Flow™**

The Precision Flow™ is intended to be used for adding warm moisture to breathing gases from an external source for administration to a neonate/infant, pediatric and adult patient in hospitals, sub-acute institutions, and home settings. It adds heat and moisture to a blended medical air/oxygen mixture and assures the integrity of the precise air/oxygen mixture via an integral oxygen analyzer. The flow rates may be from 1 to 40 liters per minute via nasal cannula.

**Vapotherm 2000i®**

The Vapotherm 2000i is designed to add moisture to and to warm breathing gases for administration to patients, including neonates/infants, pediatrics, and adults. The flow rates may be from 1 to 40 liters per minute via nasal cannula. Environments for use include home, hospital, and sub-acute institutions.

**BACKGROUND ON MECHANISMS OF ACTION IN HIGH FLOW THERAPY**

Recent developments in gas conditioning technology introduced by Vapotherm have facilitated the expansion in the use of a nasal cannula. No longer restricted to conventional flow limitations (≤ 6 L/min in adults; ≤ 2 L/min in infants), nasal cannulae are now being used for High Flow Therapy (HFT™). HFT™ refers to the use of nasal cannula gas flows that exceed patient inspiratory flow rates such as to: 1) insure that the patient will inspire the intended gas composition without entrainment of room air, and 2) provide for other physiologic impacts including purging of end-expiratory gas from the nasopharynx during expiration and development of mild distending pressure.

In a recent paper by Dysart and colleagues, five potential underlying mechanisms of action for HFT™ are identified:\(^\text{1}\):
1) Washout of the nasopharyngeal dead space
2) Reduction in inspiratory resistance associated with gas flow through the nasopharynx
3) Improvement in respiratory mechanical parameters associated with gas temperature and state of humidification
4) Reduction in metabolic work associated with gas conditioning
5) Provision of mild distending pressure

This paper discusses topics related to the fifth identified mechanism, distending pressure, with respect to nasopharyngeal pressure development and including expected pressure ranges and safety. Specifically, the scope of this paper will define the relationship between pressure in the patient circuit and the nasopharynx, and identify the factors that contribute to inadvertent pressure development.

**KEY DEFINITIONS**

**High Flow Therapy (HFT™):** Respiratory gas therapy where the flow from the external gas source exceeds a patient’s inspiratory flow rates, eliminating entrainment of room air during inspiration.

**Patient Circuit:** Tubing connecting the gas source to the cannula.

**Nasopharynx:** The body cavity being purged during HFT™.

**Pressure:** The distending force created when a gas stream comes in contact with resistance.

**Flow:** The stream or current of respiratory gas through the device and respiratory systems, typically quantified in liters per minute (L/min).

**Resistance:** A force that tends to oppose flow, resulting in back pressure.

**Resistor:** A specific point or region in the flow path that has been identified as having relatively high resistance, resulting in significant backpressure (i.e., a bottleneck).

**FLOW AND PRESSURE FUNDAMENTALS**

HFT™ is intended to be an open system, with flow delivered to a patient via nasal cannula, where the cannula prongs do not occlude the nares and where the patient’s mouth is not held closed. In this open system, the pressure in each compartment is a function of the resistor(s) that lie in series downstream from that compartment. In this regard, circuit pressures will always be substantially greater than pressure in the nasopharynx*. To explain why circuit pressures will always be substantially greater than nasopharyngeal pressure, consider Figure 1.
(*NOTE: the exception to this rule would be in the event of a complete or nearly complete blockage of flow exiting the patient’s nasal and oral orifices. The Vapotherm® Precision Flow™ is designed with the ability to recognize an occlusion and alarm, and halt flow until the occlusion has been resolved.)

FIGURE 1. SCHEMATIC OF A HIGH FLOW THERAPY CIRCUIT / PATIENT INTERFACE

\[ R = \text{resistive element; } P = \text{pressure compartment impacted by downstream resistance} \]

Figure 1 demonstrates that there are two principle resistors and thus two pressure compartments in the circuit / patient interface. Resistor #1 (R₁) represents the nasal cannula and therefore pressure compartment #1 (P₁) represents the patient circuit. Resistor #2 (R₂) represents the components resistive to gas exhausting from the patient’s nose (around the cannula) and mouth and therefore pressure compartment #2 (P₂) represents pressure generated in the nasopharynx. For each pressure compartment, the established pressure is a result of the total downstream resistance (Rₜ; Equation 1); therefore, P₁ is always a function of both R₁ and R₂, while P₂ is only ever a function of R₂. Furthermore, because under normal conditions R₁ is dramatically greater than R₂, we can expect P₁ to be much greater than P₂.

EQUATION 1: DEFINITION OF TOTAL RESISTANCE FOR SERIES RESISTORS

\[ Rₜ = R₁ + R₂ \]

Where \( Rₜ \) is total resistance and \( R₁ \) and \( R₂ \) are individual resistors in series

PRESSURE IN THE DEVICE CIRCUIT

The aforementioned principles translate to practical application of HFT™ therapy in the following manner. Because a nasal cannula offers such a high resistance to flow, any device intended to drive high flow rates through a cannula (defined in respiratory care terms as > 6 L/min) must be designed to contain and function under these normally high operating patient circuit pressures. Any attempt to relieve circuit pressures via a pressure relief valve to protect device components, would naturally result in a reduction of actual flow through the cannula thus lessening the intended flow (see Figure 2)². However, the
high circuit pressures do not translate to the patient because they are a function of the cannula resistance which is upstream to the nasopharynx.

FIGURE 2. IMPACT OF A PRESSURE RELIEF VALVE IN A HFT™ SYSTEM

This figure is reproduced from data presented in Lampland et al² using a Fisher and Paykel® system with and without a pressure relief valve (PRV) set to 45 cmH₂O.

With the pressure relief valve in place, the system does not permit more than 2 L/min to pass through the cannula regardless of the flow entering the humidifier.

PRESSURE IN THE NASOPHARYNX

Nasopharyngeal pressure (positive airway pressure) is determined by three principle factors³:
1) the flow setting,
2) the patient’s unique anatomical dimensions, and
3) the leak out of the nose around the prongs and out of the mouth.

In HFT™, the basic flow setting is meant fundamentally to exceed normal inspiratory flow rates so as to eliminate entrainment of room air. Inspiratory flow rates can be easily calculated for a patient based on actual or predicted values (Equation 2). For example, if an adult patient exhibits textbook values for respiration (tidal volume = 500ml, breathing frequency = 12 br/min, inspiratory time fraction is 0.3), then inspiratory flow rate is approximately 20 L/min. In this case, a HFT™ flow setting of 25 L/min would ensure meeting the definition of HFT™. At these relatively moderate flow rates only moderate nasopharyngeal pressure can be expected, and flow rates can be titrated upward to enhance nasopharyngeal washout effects without generating substantial increases in pharyngeal pressure. However, Vapotherm emphasizes that during HFT™ pressure is not the principle mechanism of action and caregivers should not utilize excessive flows in an attempt to generate substantial distending pressures.
EQUATION 2: CALCULATION OF HFT™ FLOW RATES FOR PATIENT PREDICTED VALUES

\[ V_I = \frac{(V_T \times f)}{F_{ti}} \]

Where \( V_I \) is inspiratory flow in L/min, \( V_T \) is tidal volume in L, \( f \) is breathing frequency in breaths/min and \( F_{ti} \) is fraction of inspiratory time (typically 0.3)

Anatomical size of the patient at the nares and internally are factors in determining distending pressure\(^3,4\) because anatomy largely defines the resistance to flow passing through and out of the nasopharynx. However, if flow ranges are determined based on predicted normal inspiratory flow rates, then anatomical features are accounted for as these computations account for a patient’s size. The relationship between anatomy and flow resistance is more clinically relevant with infants as opposed to adults, where in some cases just two or three liters per minute of flow may constitute HFT™.

The most critical factor in determining nasopharyngeal pressure development when initiating HFT™ is the relationship between internal diameter of the nares and the size of the nasal cannula used\(^3,5,6\). Going back to the original report of pressure development with a nasal cannula, esophageal pressure was not recordable when a very small cannula was used, but mild pressure was produced when a larger cannula, relative to the patient size, was used at the same flow rate\(^5\). In a bench model, Kahn and colleagues demonstrate that nasopharyngeal pressure development is predominantly a function of the leak around the prongs\(^3\), thus making the selection of which nasal prong size to use an important part of applying the therapy.

Vapotherm recommends selecting nasal prongs that have an outside diameter no more than 50% of the inside diameter of the patient’s nares. With this fitting mild distending pressure will develop, which will support the other mechanisms of action; however, there is still adequate room for leak around the prongs. The leak is necessary to allow for a reasonable amount of flush in the nasal cavity to accomplish the actions of dead space washout.

EXPECTED NASOPHARYNGEAL PRESSURE RANGES

In the adult patient population, caregivers have not often raised concerns about pressure development. This is presumed to be because the large anatomical size in the adult is not considered conducive to excessive pressure development relative to the airway pressures provided by pressure support therapies. However, Bamford and colleagues presented in abstract form a study demonstrating oropharyngeal pressures in adults\(^7\). These data are presented in Figure 3.
Reproduced from Bamford et al 2004; Data are means ± SEM for minimum, peak and mean oropharyngeal pressures.

In the neonatal community, a significant body of literature has been amassed to describe the resultant airway pressures during the application of HFT™. Table 1 reports the findings from these studies, which are consistent in agreement that maximum pressures are typically not different from a CPAP setting of 6 cmH₂O. Note that in a number of these studies, the protocols called for a closed mouth and occluded nares in an effort to establish greater pressures.

**CONCLUSION**

Pressure in the patient circuit is necessary to drive high flows though a nasal cannula, but this circuit pressure is isolated from the patient’s nasopharynx. In individual patients, nasopharyngeal pressure during HFT™ is dependent on factors which include flow rate, patient’s size and the relationship between cannula prong size and the internal diameter of the nares. However, pressure generation has been evaluated in a number of recent papers and shown to be moderate.
<table>
<thead>
<tr>
<th><strong>Study</strong></th>
<th><strong>Journal</strong></th>
<th><strong>Year</strong></th>
<th><strong># of Infants</strong></th>
<th><strong>Wt Range (gm)</strong></th>
<th><strong>Flow Range (L/min)</strong></th>
<th><strong>Conclusions of Airway Pressure</strong></th>
<th><strong>Relevant Circumstances</strong></th>
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<tr>
<td>Saslow⁸</td>
<td>J Perinatol</td>
<td>2006</td>
<td>18</td>
<td>580 – 1990</td>
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<td>Not more that CPAP of 6 cmH₂O</td>
<td>Esophageal manometry referenced to CPAP 6 cmH₂O</td>
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<td>Pyon⁹</td>
<td>PAS (abstract)</td>
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<td>8</td>
<td>&lt; 2000</td>
<td>6 - 8</td>
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<td>Spence¹⁰</td>
<td>J Perinatol</td>
<td>2007</td>
<td>14</td>
<td></td>
<td>Up to 5</td>
<td>Intrapharyngeal pressure was 4.8 ± 0.5 cmH₂O at 5 L/min</td>
<td>Mouth closed and nasal catheter</td>
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<td>Wilkinson⁴</td>
<td>J Perinatol</td>
<td>2008</td>
<td>18</td>
<td>534 - 1868</td>
<td>2 - 8</td>
<td>Mean pharyngeal pressure of 5.3 cmH₂O at 5 L/min</td>
<td>Nasal catheter</td>
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<td>Kubicka¹¹</td>
<td>Pediatrics</td>
<td>2008</td>
<td>27</td>
<td>200 - 3500</td>
<td>1 - 5</td>
<td>Highest oral cavity pressure recorded was 4.8 cmH₂O</td>
<td>Mouth closed with snug prongs</td>
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<tr>
<td>Lampland²</td>
<td>J Pediatr</td>
<td>2009</td>
<td>15</td>
<td>1324 ± 424</td>
<td>1 - 6</td>
<td>Similar to CPAP of 6 cmH₂O</td>
<td>Esophageal manometry referenced to CPAP 6 cmH₂O</td>
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REFERENCES:
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Made in USA
# Table of Contents

- Introduction ................................................. 1
- How it works .................................................. 2
- Setting up the WhisperFlow System ......................... 2
- Notes to Figures 2 through 5 ............................... 9
- Operating the WhisperFlow System ....................... 10
- Monitoring the patient ..................................... 12
- Maintenance ............................................... 12
- Environmental specifications ............................. 13
- Accessories ............................................... 16
- Customer Service and Product Support ................. 16
- Manufacturer ............................................ 17
- Approvals ............................................... 17
- Year of manufacture .................................... 17
- Parts list ............................................... 18
Introduction

The WhisperFlow CPAP System delivers continuous positive airway pressure (CPAP) throughout the breathing cycle. It provides CPAP at preset levels throughout inspiration and exhalation, independent of the patient's flow rate. The WhisperFlow System is intended for use on spontaneously breathing patients.

The variable generator WhisperFlow System allows you to vary fractional inspired oxygen (FIO$_2$) from 28% to 100%. The fixed generator WhisperFlow System delivers FIO$_2$ from 28% to 33%, depending on the flow and PEEP valve used.

![Figure 1. WhisperFlow CPAP System: variable and fixed generators](image)
The WhisperFlow System may be contraindicated for patients with any of these conditions:

- Fluid retention
- Pneumothorax
- Decreased cardiac output and gastric distention
- Severe facial injury (noninvasive use)
- Hypotension secondary to hypovolemia.

**How it works**

The WhisperFlow CPAP System is a precision venturi device that uses an oxygen supply in conjunction with entrained air to generate an output flow. The WhisperFlow System uses a 60 psi (412 kPa) oxygen supply, and can generate flows over 150 L/min. down to 28% fractional inspired oxygen (FIO₂). The WhisperFlow CPAP valves, which are placed within the circuit, are used to maintain preset positive pressure at flow rates from 10 to 150 L/min.

**Setting up the WhisperFlow System**

**WARNING**: Do not use the WhisperFlow System without an oxygen analyzer to alert you to a loss of oxygen wall pressure or other system faults.

**WARNING**: Always ensure that the PEEP valve is correctly connected to the patient circuit, and that the exhaust port of the PEEP valve is not attached to the circuit.

**WARNING**: The ON/OFF knob controls a continuous valve. Be sure to turn the knob FULLY counterclockwise, one half turn, for the fully ON position.

**WARNING**: Place a pressure gauge or pressure monitor in-line, between the generator outlet and the patient interface by use of an in-line tee. Alternatively, pressure can be monitored by attaching pressure monitoring tubing to the mask port.
**CAUTION:** To avoid damage to the WhisperFlow System by entraining particles into the device, always install a filter on the fresh gas intake port.

**CAUTION:** The WhisperFlow System, as with similar systems from other manufacturers, does not include a non-rebreathing valve for use with tracheal tubes. If the oxygen supply fails while the patient’s tracheal tube is connected to the system, the patient will rebreathe the gas in the supply tubing and may be asphyxiated.

1. Select a sealing face mask or endotracheal (ET) tube as the patient connection. Ensure that the mask fits comfortably, seals the bridge of the nose, and fully covers the nose and mouth.

2. Choose the PEEP valve. (See the parts list for a complete list of available PEEP valve sizes and part numbers.)

3. Assemble the circuit according to Figures 2 through 6, depending on the mask, oxygen analyzer, pressure gauge or monitor, and humidifier you are using. As you assemble the circuit, please note:
   - Use a pressure relief valve to protect the patient's lungs from trauma in the event that the PEEP valve becomes occluded. Select a PEEP valve at least 5 cmH₂O higher than the expiratory PEEP valve.
   - To ensure accurate measurement of the FIO₂ delivered to the patient, use an inline oxygen analyzer upstream of the patient connection and humidification device (if used).
   - To assist in detecting adequate flow from the generator, place a pressure gauge, 0-30cmH₂O, or pressure monitor, in-line between the generator outlet and the patient interface, or attach a pressure monitor line to the patient mask. Should the registered pressure decrease significantly during patient inhalation, then the flow to the patient needs to be increased.
• The WhisperFlow System can deliver a minimum FIO2 of 28-29% to the patient. However, the longer the tube lengths used, the higher the minimum FIO2. (Longer tubing increases the resistance of the patient circuit, allowing the generator to entrain less air.)

• The WhisperFlow System's location upstream of the patient and the high flows it produces make contamination and resulting cross-infection highly unlikely. However, if cross contamination is a concern, attach a 22-mm OD/ID filter to the output port of the generator.
Figure 2. Dual-port mask, oxygen probe with integrated tee piece
Figure 3. Dual-port mask, 15-mm oxygen probe
Figure 4. ET tube connection, 15-mm oxygen probe

CAUTION: The WhisperFlow System, as with similar systems from other manufacturers, does not include a non-rebreathing valve for use with tracheal tubes. If the oxygen supply fails while the patient’s tracheal tube is connected to the system, the patient will rebreathe the gas in the supply tubing and may be asphyxiated.
CAUTION: The WhisperFlow System, as with similar systems from other manufacturers, does not include a non-rebreathing valve for use with tracheal tubes. If the oxygen supply fails while the patient’s tracheal tube is connected to the system, the patient will rebreathe the gas in the supply tubing and may be asphyxiated.
Notes to Figures 2 through 5

The notes below apply to Figures 2 through 5 above:

- Figures 2 through 5 show how to assemble the WhisperFlow system and WhisperFlow accessories. The WhisperFlow unit should only be used with the accessories supplied by the manufacturer, Respironics, or its authorized agent. In particular, the face mask has an integral one-way valve, which prevents exhalation into the delivery tubing in the event of no fresh gas flow. When used with a tee-piece however, exhalation into the delivery tubing will result in CO2 rebreathing, and may result in asphyxiation.

- If the fresh gas flow fails, the one-way valve will minimize the risk of asphyxiation when there is no oxygen pressure. However, if there is no fresh gas flow, the patient will have to inhale at ambient pressure, though will still continue to exhale at the PEEP pressure (see Table 1); this will result in an increased work of breathing and may not be well tolerated by some patients. Therefore, when there is no oxygen flow from the WhisperFlow System, the mask should not be worn, and nor should the device be connected to a tracheal tube.

- External monitoring should be used to ensure that the WhisperFlow generator setting is suitable for the patient. An in-line pressure gauge or pressure monitor will show a constant pressure approximately the same as the PEEP valve specification. If the delivered flow is too low, the pressure exhibited will indicate a significant drop when the patient inhales. This inadequate flow can be corrected by increasing the flow from the WhisperFlow generator.

- The oxygen monitor with alarms is used in setting and monitoring the FIO2 delivered by the unit. It may alert the user to the loss of oxygen flow if the patient continues to draw fresh gas without oxygen through the air inlet of the WhisperFlow generator.

- The safety PEEP valve is placed in the circuit line in the event that the PEEP valve attached to the face mask or endotracheal tube becomes occluded. Thus any excess circuit pressure above the prescribed PEEP pressure will be relieved.
Operating the WhisperFlow System

1. Turn all control valves off by turning fully clockwise (finger-tight only).

2. Connect the oxygen supply, then listen for leaks:
   - Variable generator: Connect directly to the oxygen supply or connect an oxygen hose between the WhisperFlow System oxygen fitting and the oxygen supply.
   - Fixed generator: Connect directly to flowmeter capable of delivering at least 13 L/min. at 60 psi (412 kPa).

**WARNING:** Do not connect any gas supply other than oxygen to the WhisperFlow System.
NOTE: The WhisperFlow should not be connected directly to oxygen tanks with pressures over 230 bar (3336 PSI). Frost may form on the regulator and the device when FIO₂ settings are higher than 30%.

3. Turn the ON/OFF valve fully on (one-half turn). Turn the flow adjustment valve fully on and check that the output flow from the patient outlet varies accordingly.

WARNING: The ON/OFF knob controls a continuous valve. Be sure to turn the knob fully counterclockwise, one half-turn, for the full ON position.

4. For higher concentrations (variable generator only), turn the oxygen adjustment valve counter-clockwise until the oxygen analyzer displays the appropriate FIO₂ for 30 seconds.

5. Leave the oxygen and flow controls as you have just set them, then turn the ON/OFF valve fully off (clockwise). Attach the circuit to the patient, and then turn the ON/OFF valve fully on (counter-clockwise).

6. Watch the PEEP valve to ensure that it remains open during inspiration. Gradually reduce the circuit flow by turning the flow adjustment valve down to point when you can still feel a slight flow at the CPAP valve when the patient inspires. Monitor the FIO₂ as you reduce the circuit flow: as the circuit flow decreases, the FIO₂ rises slightly. You can reduce the FIO₂ by closing the oxygen adjustment valve.

7. Monitor the in-line pressure gauge or monitor. If the pressure drops significantly then the flow is inadequate.
Monitoring the patient

During operation, be sure to check the following on regular basis:

- Ensure that there are no leaks at the patient connection.
- Ensure that there is flow from the PEEP valve during inspiration (which means that the generator is supplying adequate flow to meet patient demand).
- Monitor the in-line pressure gauge or monitor during inspiration. If the pressure drops significantly, then the flow is inadequate.
- Monitor the patient's arterial blood oxygen saturation (SaO₂).
- Monitor the patient for signs of dehydration and discomfort in the upper airways.
- Monitor the patient's delivered FIO₂.

Maintenance

Under normal conditions, the WhisperFlow System does not require any special maintenance or sterilization. However, the WhisperFlow System generator can be gas-sterilized using ethylene oxide (EtO). Following sterilization, open all the valves fully, connect to an oxygen supply for five minutes, and verify performance before reuse.

**CAUTION:** Do not autoclave or immerse the WhisperFlow System or any of its components in any solution. The circuit, including the inlet filter, is for single patient use.

Follow these steps to test the WhisperFlow System's minimum FIO₂ annually:

1. Variable generator only: set the flow adjustment to its maximum, and the oxygen adjustment valve to its minimum.

2. Attach a 10-cmH₂O PEEP valve to the generator using a patient circuit.

3. Ensure that the FIO₂ at a circuit pressure of 10 cmH₂O does not exceed 30%.
Environmental specifications

Temperature

- Operating: 5 to 45 °C at 15 to 95% relative humidity
- Storage: -40 to 60 °C at 95% relative humidity

Oxygen supply

- 40 to 80 psi (275 to 550 kPa)
- For flow requirements see Figure 10.

**NOTE:** The WhisperFlow should not be connected directly to oxygen tanks with pressures over 230 bar (3336 PSI). Frost may form on the regulator and the device when FIO₂ settings are higher than 30%.

![Graph](Figure 7. Maximum flow and minimum oxygen versus pressure)
**Figure 8.** Minimum oxygen achievable at different flow settings for different PEEP values

**Figure 9.** Circuit pressure loss per meter of tubing
Figure 10. Oxygen supply consumption at several flow and oxygen settings

Table 1: Pressure required to breathe through a system comprising a face mask, 1.8m tubing, and a CPAP generator in the instance where oxygen supply is lost.

<table>
<thead>
<tr>
<th>Inspiratory Flow (L/min.)</th>
<th>Approximate Pressure Drop (cmH₂O)</th>
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</thead>
<tbody>
<tr>
<td>20</td>
<td>-1.0</td>
</tr>
<tr>
<td>40</td>
<td>-2.7</td>
</tr>
<tr>
<td>60</td>
<td>-3.9</td>
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<tr>
<td>80</td>
<td>-4.9</td>
</tr>
<tr>
<td>100</td>
<td>-5.1</td>
</tr>
</tbody>
</table>

Table 1: Pressure required to breathe through a system comprising a face mask, 1.8m tubing, and a CPAP generator in the instance where oxygen supply is lost.
Accessories

The following accessories are compatible with the WhisperFlow CPAP System:

- Mounting pole: Any pole with a clamp range of 10 to 40 mm.
- Humidifier: Fisher and Paykel MR730 and MR480. The MR410 Humidifier can also be used when inspiratory flow rates are set to less than 50 L/min.
- Oxygen monitor: You can use any in-line oxygen monitor with the WhisperFlow System. Some WhisperFlow procedure packs include a connector for attaching the oxygen monitors using a silicone tee or 15-mm probe.

Please contact your local dealer before using other accessories with the WhisperFlow System.

Customer Service and Product Support

Full service and repair is available from the manufacturer.

USA and Canada
Phone 1-800-345-6443 or 724-387-4000
Customer Service Fax 1-800-886-0245
Product Support Fax 1-724-387-5236
International Customer Service Phone 724-387-4000
International Customer Support Fax 724-387-5012

Europe/Africa/Middle East +33-1-47-52-30-00
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Wallingford, CT 06492 Asia Pacific +852-3194-2280
USA www.respironics.com

Approvals
The WhisperFlow System complies with the requirements of directive
93/42/EEC concerning medical devices and therefore bears the CE mark.

Authorized Representative:
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Gewerbestrasse 17
82211 Herrsching
Deutschland
Telephone: +49 8-152930640

Year of manufacture
The fifth and sixth digits of the serial number indicate the WhisperFlow System's
year of manufacture.
### Parts list

<table>
<thead>
<tr>
<th>Description</th>
<th>Part number</th>
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<tbody>
<tr>
<td>WhisperFlow CPAP System, variable generator (where x indicates the gas fitting, hose, and country). Contact your local dealer for further details.</td>
<td>8-20860x-00</td>
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<tr>
<td>WhisperFlow CPAP System, fixed generator</td>
<td>8-208530-00</td>
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<td>CPAP valve, 2.5 cmH₂O</td>
<td>8-208503-00</td>
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<td>CPAP valve, 5 cmH₂O</td>
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<td>Filter, 22 mm</td>
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<td>Tee piece, oxygen analyzer, 22M/22M/(22M/15F) ports</td>
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<td>Connector, 22M/22F with Pressure Port</td>
<td>8-100327-00</td>
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<td>Connector, 22F/22F ports</td>
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<td>Head strap, four-point, nonlatex</td>
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<tr>
<td>WhisperFlow Mounting Kit</td>
<td>8-100068-00</td>
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<tr>
<td>Several CPAP procedure packs are available: please contact your local dealer for further details.</td>
<td></td>
</tr>
</tbody>
</table>
Vital Signs, Inc. introduces the ACCU-PEEP™ threshold resistor. For use in conjunction with CPAP Systems and anesthesia/ventilation, the ACCU-PEEP™ has two main features:

Provides consistent levels of PEEP irrespective of flow

The unique design of the Vital Signs® valve results in minimal deviation in expiratory pressures at all flows. In both CPAP and anesthesia/ventilation applications, the clinician can be assured that the resistance levels will be maintained regardless of flow. The design of the valve makes it particularly well suited for the high flows associated with CPAP.

Allows for exhalation if valve is incorrectly positioned and provides entrainment if flow is insufficient in a CPAP application.

This unique feature of the Vital Signs® PEEP valve reduces the risks associated with flows delivered below the patient’s peak inspiratory demand.

The standard connections of the valve allows for its use in anesthesia and other respiratory applications.

---


---

ORDERING INFORMATION

<table>
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<th>DESCRIPTION</th>
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<td>ACCU-PEEP™ Valve 10.0 cm H2O</td>
<td>10</td>
</tr>
<tr>
<td>9012B</td>
<td>ACCU-PEEP™ Valve 12.5 cm H2O</td>
<td>10</td>
</tr>
<tr>
<td>9015B</td>
<td>ACCU-PEEP™ Valve 15.0 cm H2O</td>
<td>10</td>
</tr>
<tr>
<td>9022B</td>
<td>ACCU-PEEP™ Valve 20.0 cm H2O</td>
<td>10</td>
</tr>
<tr>
<td>9005A</td>
<td>PEEP Valve Adapter</td>
<td>10</td>
</tr>
</tbody>
</table>
Vigileo Monitor

The Vigileo monitor allows for the continuous monitoring of essential hemodynamic information, providing rapid insight on a minimally invasive, easy-to-use platform. The Vigileo monitor works with the FloTrac sensor to measure and display key flow parameters and the PreSep catheter to provide central venous oxygen saturation (ScvO₂).

Act Early

- Provides immediate hemodynamic insight that may be missed using traditional vital signs alone
- The FloTrac sensor quickly connects to an existing arterial line
- The PreSep catheter provides real-time insight into tissue perfusion

Easy to Use and Less Invasive

- Simply requires patient age, gender, height and weight to initiate CCO monitoring
- Provides the same utility as continuous SvO₂ monitoring from a Swan-Ganz catheter but on a central line
- Requires no additional catheters, boluses or chemical indicators
Vigileo Monitor
Product Specifications

Power/Electrical
• AC Mains: 100-240 VAC, 50/60 Hz, 1A maximum consumption

Color Display
• 5.2 in. (132.5 mm) x 3.9 in. (99.4 mm) TFT
• 640 x 480 pixels

Measuring Time
• CCO: display updated every 20 seconds or 5 minutes
• ScvO₂/SvO₂: display updated every 2 seconds

Startup Time
• Initial display in 60 seconds

Trend Range
• 0.1-72 hours

Display Capacity
• 2 trend lines, 2 numerical displays

Size
• Height: 7.3 in. (185.4 mm)
• Width: 10.7 in. (271.8 mm)
• Depth: 8.4 in. (213.4 mm)

Weight
• 6.0 lbs. (2.76 Kg)

Bi-directional Patient Monitor Communications

Analog Input/Output (Selectable Voltage)
• Input: 0 to 1 V, 0 to 5 V, 0 to 10 V
• Output: 0 to 1 V, 0 to 10 V

Digital I/O, Serial Communication Interface (RS232)
• Maximum data rate = 57.6 kilo baud

CVP Slave Compatible for Continuous SVR
• Pressure slave cables available for select physiologic bedside monitors

Printer Communications
• USB Port: V1.1-compatible type A connector

For additional educational information visit: www.Edwards.com/FloTrac

Rx only. See instructions for use for full prescribing information.
LiDCOplus
CONTINUOUS, REAL-TIME CARDIOVASCULAR MONITORING

www.lidco.com
Introducing the LiDCOplus Hemodynamic Monitor

CONTINUOUS, REAL-TIME MONITORING OF CARDIAC OUTPUT

Monitoring of the key cardiovascular parameters of blood pressure, cardiac output and oxygen delivery is essential for many major surgical and acutely ill patients. In addition, there are many other patients that could benefit from real-time cardiovascular monitoring if it were available in a safe and easy to apply manner. This was the philosophy that resulted in the development, design and manufacture of the unique LiDCOplus Hemodynamic Monitor.

The LiDCOplus system is a combination of the two innovative and novel monitors - the LiDCO System indicator dilution cardiac output monitor and the PulseCO System real time, continuous arterial waveform monitor, produced by LiDCO Ltd.

This unique combination provides beat-to-beat measurement of cardiac output with lower risk and high precision.
The LiDCO™ System cardiac output method provides a bolus indicator dilution method of measuring cardiac output. A small dose of lithium chloride is injected via a central or peripheral venous line; the resulting arterial lithium concentration-time curve is recorded by withdrawing blood past a lithium sensor attached to the patient’s existing arterial line. In terms of accuracy, clinical studies have demonstrated that over a wide range of cardiac outputs the LiDCO method is at least as accurate as thermodilution and even in patients with varying cardiac outputs7-12. In one study LiDCO and thermodilution cardiac output were compared with an electromagnetic flow probe. The results of this study indicated that LiDCO had a higher precision compared with conventional bolus thermodilution cardiac output12. The dose of lithium needed (0.15 - 0.3 mmol for an average adult) is very small and has no known pharmacological effects74.

The PulseCO™ System software (incorporated in the LiDCO™ Monitor) calculates continuous beat-to-beat cardiac output by analysis of the arterial blood pressure trace following calibration with an absolute LiDCO cardiac output value. This method has been shown to be accurate and reliable in various clinical settings. It has also been shown that recalibration is unnecessary for at least eight hours26, 79, 80 and more recently for 24 hours94.

**PULSECO SYSTEM AUTOCORRELATION ALGORITHM**

The analogue arterial blood pressure trace is slaved from the conventional blood pressure monitor and undergoes a three step transformation

- **Step 1** Arterial pressure transformation into a volume-time waveform (incorporating arterial tree compliance)
- **Step 2** Deriving nominal stroke volume and heartbeat duration
- **Step 3** Actual stroke volume via calibration with an absolute cardiac output value
The PulseCO software calculates continuous beat-to-beat cardiac output by analysis of the arterial blood pressure trace following calibration with an absolute cardiac output value. This absolute cardiac output value is accurately and precisely measured using the innovative LiDCO lithium chloride bolus indicator dilution method.

The PulseCO software calculates the pulse power and derived stroke volume from the arterial waveform. This avoids the necessity for detection of any particular waveform features such as the dichrotic notch. Furthermore, arterial wave reflection does not have to be estimated. Due to this innovative and patented method of calculation, the PulseCO remains accurate and reliable over a wide range of hemodynamic states in surgical, post operative and intensive care settings. Studies have demonstrated that re-calibration is unnecessary for at least eight hours and more recently 24 hours.

The LiDCOplus serves as a reliable alternative to continuous cardiac output monitoring with the pulmonary artery catheter and can easily be used intraoperatively, in the ICU/HDU, trauma or burns unit, and cath lab.

LiDCOplus’s accuracy is ensured with the proven LiDCOplus lithium indicator dilution calibration procedure that uses existing venous and arterial access, making it fast, cost effective and minimally invasive.

The LiDCOplus calculates cardiac output continuously by analysis of the arterial blood pressure trace following calibration with the absolute LiDCO cardiac output value. The concept of estimating cardiac output from the arterial pressure waveform has been extensively researched with the first researchers (Erlanger and Hooker) publishing in 1904.
The LiDCO System is an innovative bolus indicator dilution method of measuring cardiac output and Intra-Thoracic Blood Volume (ITBV) - the innovation is the use of lithium chloride as the indicator. A small dose of lithium chloride is injected via a central or peripheral venous line (Fig 1); the resulting arterial lithium concentration-time curve is recorded by withdrawing blood past a lithium sensor attached to the patient’s existing arterial line (Fig 2); the Monitor then calculates the cardiac output from the area of the primary dilution curve (Fig 3). The mean transit time of the lithium is derived for calculation of the ITBV.

The signal to noise ratio and hence accuracy for lithium is better than that seen with thermodilution - due to the fact that the lithium dose can be scaled to the size and cardiac output of the patient. Thermal noise from fluid infusion, respiration and patient warming has little, if any, effect on the lithium curve. The precision of the LiDCO System method means that only one lithium injection is required to accurately determine the cardiac output. In terms of accuracy, clinical studies have demonstrated that the single bolus LiDCO System method is at least as accurate as triplicate bolus thermodilution over a wide range of cardiac outputs and even in patients with varying cardiac outputs.\(^7\)\(^{12}\)

The lithium chloride indicator dilution method of measuring cardiac output and intra-thoracic blood volume (ITBV)
Arterial Pressure

The arterial pressure waveform is slaved from your conventional blood pressure monitor via an analogue cable link. At the touch of a button the arterial pressure waveform is displayed on the LiDCOplus screen. This can be viewed on the screen whenever the Trend, Graph and Chart screens are in use.

This Blood Pressure Waveform window is used to check the patient’s systolic, diastolic and mean pressure. The pressure waveform shape and values should equate to those displayed on the primary blood pressure monitor.

This window also provides you with access to preload response values or volume status indicators of: Systolic Pressure Variation (SPV), Pulse Pressure Variation (PPV%), Stroke Volume Variation (SVV%) as well as Heart Rate Variation (HRV%).

\[
SVV\% = \frac{(SV_{\text{max}} - SV_{\text{min}})}{\left(\frac{SV_{\text{max}} + SV_{\text{min}}}{2}\right)} \times 100
\]

Patient with SVV less than 10% are unlikely to be preload responsive.

**DYNAMIC VOLUME STATUS INDICATORS FOR VENTILATED PATIENTS**

Thoracic pressure changes caused by mechanical ventilation induce cyclic changes in Left Ventricular Stroke Volume. These changes can provide an indication of the patient’s ventricular preload status (see figure of Frank-Starling curve)\(18, 20, 26, 66, 81-83\).

By superimposing the Preload Response Parameters Window onto the Trend, Graph, or Chart screens, a continuous measurement of Stroke Volume, Systolic Pressure and Pulse Pressure Variation is displayed numerically and graphically.

For closed chest ventilated patients these volume status measurements provide a way of predicting fluid volume status and likely response to volume infusions. A fluid imbalance can have an adverse effect on a patient’s cardiac performance and, in turn, oxygen delivery to key organs\(13-35, 50, 58, 66, 67, 81\).
Event Response

PRE-LOAD RESPONSIVENESS VIA THE EVENT RESPONSE DISPLAY

The Event Response display allows the user to view up to 2 hemodynamic variables in a higher resolution during a specific period (e.g. fluid challenge, inotrope change). The LiDCOplus will also display percent change from start for each variable as a numeric value. Trend lines can also be added to the graphical display.

This feature is very useful when evaluating the patient’s response to targeted interventions such as a fluid challenges or changes in inotrope therapy. The advantage this screen brings is in averaging the data display to smooth any noise and magnifying the display of changes so that they are easily viewed at a glance from a distance.

Press to configure Event Response
Press to capture screen image as JPG
Press the event button to reveal the submenu below.
Press to select target variable(s)
Press to select display interval
A new data point is plotted every 10, 20 or 30 seconds.

Press to Restart
Press to Stop
Elapsed time until a new point is plotted

Target Variable data:
Starting baseline
Current value and % Change from baseline

The Trend line is switched on
Baseline value

Press to Exit
Press to minimize

7
Benefits to you and your patient

**BENEFITS OF LIDCOplus CONTINUOUS CARDIAC OUTPUT MONITORING INCLUDE:**

- Provides early warning of patient deterioration
- Optimisation of oxygen delivery
- Optimisation of fluid management
- Rational drug administration (e.g., Inotropes)
- The patient’s condition is clearly communicated to clinical staff
- Reduces the work of health care staff
- Decrease the procedural complications
- Is minimally invasive and therefore widely applicable
- Is accurate
- Can be nurse driven
- Provides real time, beat-to-beat cardiac output and oxygen delivery
- Provides real time preload and afterload values
- Provides indexed values
- Provides easy data interpretation
- Provides bedside information management
- Has easy to use event markers
- Provides information not simply data
- Can be linked to most commonly found BP monitors
- Records historical data

**BENEFITS OF THE LIDCO – LITHIUM CHLORIDE INDICATOR DILUTION CARDIAC OUTPUT METHOD:**

- Provides an absolute cardiac output value via a novel and proven indicator dilution technique
- Provides ITBV
- Requires no additional invasive catheters to insert into the patient
- Is safe – using non-toxic bolus dosages
- Is simple and quick to set up
- Can be used with a range of LiCl dosages
- Is as accurate as meaned triplicate thermodilution
- Is not temperature dependent
- Is less invasive monitoring
- Utilises existing peripheral or central venous and arterial lines
- Can be set up and used by nursing staff
- Is a well studied and validated technique
The Trend Screen

A CLEAR CONTINUOUS DISPLAY

The Trend screen provides a continuous record of the patients' hemodynamics. This large, clear and continuously updating screen displays the actual and indexed values for Cardiac Output, Systemic Vascular Resistance, Mean Arterial Pressure, Heart Rate and Left Ventricle Stroke Volume. Oxygen Delivery and Venous Oxygen Saturation can also be displayed if selected. The clinician can accurately track the patients' trend over several hours or minutes.

This screen facilitates intraoperative patient management allowing assessment of the immediate response to fluid challenge, drugs or other therapeutic interventions.

EVENT MARKER

Mark any number of events, such as initiation of inotropic agent or start of fluid infusion, using the event marker button. There are several standard descriptions that can be selected and additional detail added.

The marked event will appear as a small flag on the Trend and History screens and will be recorded in the LiDCOplus data file as the patient data is downloaded from the history screen. The event history window will allow selection of any events from the past 24 hours and take the user to the area on the hemodynamic history screen where the event was marked.
The Chart Screen

PARAMETER RELATIONSHIPS AT A GLANCE

Showing the relationship between pressure, flow and resistance in an integral bar chart display. This screen simplifies the recognition and diagnosis of hemodynamic imbalance at the bedside. This means that potentially complex hemodynamic data can be easily interpreted and the necessary corrective actions taken quickly.

Pressure = Flow x Resistance

Showing the relationship between pressure, flow and resistance in an integral bar chart display. This screen simplifies the recognition and diagnosis of hemodynamic imbalance at the bedside. This means that potentially complex hemodynamic data can be easily interpreted and the necessary corrective actions taken quickly.

OXYGEN DELIVERY TARGETS AND ScvO2/SvO2 DISPLAY

Oxygen delivery optimisation has been demonstrated to be a key factor in the reduction in both length of stay and complications for post surgical patients in the ICU. Oxygen delivery targets can now be set in the patient limits. These will be used on both the Graph and Chart screens to enhance the display of data. Venous Oxygen Saturation can now be inputted to allow tracking as well as calculation of estimated oxygen consumption.
OXYGEN DELIVERY

The goal of monitoring cardiac output is to maximise the delivery of oxygen to the tissue beds. The LiDCO plus monitor displays the parameter of oxygen delivery (and oxygen delivery index) in real time. The ability to have these two parameters monitored simultaneously on a real-time basis by the LiDCO plus can have a major impact on patient care and outcomes. There is mounting evidence that monitoring oxygen delivery and cardiac output in at-risk patients can significantly reduce mortality and length of hospital stay.

In a recent study utilizing the LiDCO plus, it was shown that optimising oxygen delivery index (DO2I) to a target of 600ml/min/m2 reduced morbidity by 50% and mean length of stay per patient by 12.3 days. Use of the LiDCO plus facilitates the perioperative optimisation of patients.

HEMODYNAMIC PRE-OPTIMISATION IN HIGH-RISK PATIENTS

‘High risk’ surgery patients subjected to a reduction in global oxygen delivery are known to have increased levels of morbidity and mortality. Increasing global oxygen delivery has been reported to result in a dramatic improvement in outcome in these patients. For example, in the USA there are over 30 million operations performed annually, 10-15% of which (approximately 3 million operations) are deemed to be ‘high risk’. These ‘high risk’ patients have an increased risk of death. A recent review of 21 randomised controlled trials with various approaches to treatment revealed statistically significant mortality reductions when patients with acute critical illness were treated early to achieve optimal goals before the development of organ failure. There is convincing evidence that measurement and manipulation of cardiac output, and therefore oxygen delivery, in selected patients reduces the risk of mortality.

MORTALITY OUTCOMES FOLLOWING GOAL DIRECTED STUDIES:

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Study Author (Year)</th>
<th>Mortality of Control Group (%)</th>
<th>Mortality of Goal Directed Treatment Group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Shultz et al (1985)</td>
<td>29.0</td>
<td>2.9</td>
</tr>
<tr>
<td>General</td>
<td>Shoemaker et al (1988)</td>
<td>33.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Vascular</td>
<td>Berlauk et al (1991)</td>
<td>9.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Trauma</td>
<td>Fleming et al (1992)</td>
<td>44.0</td>
<td>24.0</td>
</tr>
<tr>
<td>General &amp; Vascular</td>
<td>Boyd et al (1993)</td>
<td>22.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Trauma</td>
<td>Bishop et al (1995)</td>
<td>37.0</td>
<td>18.0</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>Sinclair et al (1997)</td>
<td>10.0</td>
<td>5.0</td>
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<tr>
<td>Peripheral Vascular</td>
<td>Ziegler et al (1997)</td>
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<td>Elective General</td>
<td>Wilson et al (1999)</td>
<td>17.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Elective Cardiac</td>
<td>Polonen et al (2000)</td>
<td>3.0</td>
<td>1.0</td>
</tr>
<tr>
<td>General &amp; Vascular</td>
<td>Lobo et al (2000)</td>
<td>50.0</td>
<td>15.7</td>
</tr>
</tbody>
</table>
The Graph Screen

**KEEPING PATIENT CARE ON TARGET**

Allows easy assessment of the patient's status at a glance and from a distance from the Monitor - useful in busy ICU's or high dependency units, as an early warning system to avoid adverse events. The graph screen is also ideal for the implementation of goal directed protocols that target oxygen delivery. The graph screen is the ideal "bedside" mode providing clear, easy-to-read feedback on changes to pressure, flow, and resistance. A patient specific "target zone" for Cardiac Output or Oxygen Delivery, Mean Arterial Pressure and thereby Systemic Vascular Resistance is defined specifically for each patient. The continuous display of the patient's last 12 heartbeats provides a ready reference to how well the therapeutic/hemodynamic targets are being maintained. The LiDCOplus Monitor provides point of care information, not just more patient data.

**CONTINUOUS, REAL-TIME MONITORING OF CARDIAC OUTPUT**
The History Screen

The History Screen can be used to look back over the last 24 hours of the patient’s hemodynamic data. The display is similar to the display of the Trend Screen. Touch anywhere on the screen to see the parameter readings, at that time, or track back through the hours of data as required.

This screen is designed to aid in data collection: for clinical studies or simply to have a complete record of the patient’s treatment you can record the patient’s critical parameters at the touch of a button. The beat-to-beat patient data, event markers and calibrations are recorded either as a file for LiDCOview or as an Excel file on a USB memory stick. This powerful tool for data collection provides you with the ability to review, research and train using Historical data. Record several patients or several days of a single patient onto one easy to use USB memory stick.

A picture can be taken of the entire history screen. This can be stored on the hard drive or immediately downloaded to a USB memory stick as a JPEG file.
PulseCO Validation

A number of studies have been completed in various centres in Europe and the USA demonstrating the accuracy and precision of the PulseCO software (hosted within the LiDCOplus Hemodynamic Monitor) when used in cardiothoracic surgery, major surgery and the ICU.\(^{2-6, 79, 80, 94}\)

**INTRA OPERATIVE PERFORMANCE**

One study at the University of Texas evaluated the change/drift in calibration factor across a postoperative period of 8 hours in a group of 20 cardiac surgery patients.\(^{90}\)

The results of the study found:

- that the range of cardiac outputs was 3.33 to 8.47 litres per minute;
- that, once calibrated, the PulseCO tracked the cardiac output continuously through the post surgery period without changes in calibration factor;
- that no significant differences were noted between the LiDCO, the thermodilution control and the PulseCO reading.

<table>
<thead>
<tr>
<th>Differences in CO measurements by technique (Liters/min).</th>
<th>0 hours</th>
<th>2 hours</th>
<th>4 hours</th>
<th>6 hours</th>
<th>8 hours</th>
<th>all times</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLdiff</td>
<td>-0.1±0.1</td>
<td>0.0±0.1</td>
<td>0.1±0.1</td>
<td>0.0±0.2</td>
<td>-0.2±0.2</td>
<td>0.0±0.1</td>
</tr>
<tr>
<td>PLdiff</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
</tr>
<tr>
<td>PTdiff</td>
<td>0.1±0.1</td>
<td>0.0±0.1</td>
<td>0.0±0.1</td>
<td>0.0±0.2</td>
<td>0.2±0.2</td>
<td>0.0±0.1</td>
</tr>
</tbody>
</table>

**Conclusion:**

'This technique appears to offer a safe, reliable and less invasive alternative to the traditional PA catheter for cardiac output monitoring in the immediate post-operative period after surgery.'

A study in intensive care patients\(^{94}\) has shown good correlation of LiDCO and PulseCO without recalibration over 24hrs.
The results of the study found:

- that the range of cardiac output was 3.45 to 10.47 litres per minute;
- that there were acceptable bias and limits of agreement throughout the study with a correlation of $r^2 = 0.89$;
- that 68% of catheters had an undesirable dynamic response but that this did not affect the agreement between the measurements of cardiac output obtained by the PulseCO software and the Lithium dilution ($p = 0.976$).

A further study was undertaken at Duke University to examine the effects of arterial damping in a group of 22 patients in a surgical intensive care unit. The study was designed to evaluate the change/drift in calibration factor across a 24 hour period and in addition to examine whether the dynamic response (damping) of the arterial pressure monitoring system has an effect on the accuracy of the PulseCO software.

Conclusion:

‘Technical limitations of arterial catheter monitoring systems, such as low natural frequency or under or over damping, do not appear to influence the accuracy of the PulseCO measurement.’

‘The pulse contour algorithm appears accurate despite a wide variety of arterial pressure waveform contours that are seen in clinical practice.’

‘Recalibration of the PulseCO software is recommended every four hours, but we have extended the period between calibrations to eight hours and demonstrated that the PulseCO software is still accurate after this time.’
The LiDCOplus - Lithium Indicator Dilution

The LiDCOplus bolus lithium indicator dilution method is used to provide an accurate actual cardiac output value for the patient. The lithium indicator dilution method is a very accurate and minimally invasive indicator dilution cardiac output measurement method. This is used to calibrate the PulseCO arterial waveform stroke volume value. It can also be used to calculate intra thoracic blood volume (ITBV).

THE PRINCIPLE

The bolus indicator dilution method of measuring cardiac output was first described by Henriques and developed by Hamilton et al in 1932. This became widely adopted - the original technique using indocyanine green (ICG) as the marker. However, as this technique required frequent blood sampling and manual analysis of the dilution curve, it proved to be technically difficult and time consuming. The use of Lithium as an indicator of cardiac output was first described in 1993 and has since been extensively validated. Lithium like ICG, is a non-diffusible indicator. The method of using bolus indicator dilution to measure volume was described by Stewart and the method of ITBV calculation is simply ITBV=C0xMTt. MTt is the mean transit time of the lithium indicator from injection to detection.

The LiDCOplus Monitor provides a lithium bolus indicator dilution method of measuring cardiac output. A small dose of lithium chloride is injected via a central or peripheral venous line; the resulting arterial lithium concentration-time curve is recorded by withdrawing blood past a lithium sensor.

4] This value is then used to calibrate the LiDCOplus to give continuous cardiac output and derived variables from arterial waveform analysis.

3] The Lithium indicator dilution “wash-out” curve on the LiDCOplus provides an accurate absolute cardiac output value.

1] A bolus of Lithium is flushed through a central or venous line.

2] A Lithium sensitive sensor, attached to a peripheral arterial line, detects the concentration of Lithium ions in the arterial blood.

4] This value is then used to calibrate the LiDCOplus to give continuous cardiac output and derived variables from arterial waveform analysis.

3] The Lithium indicator dilution “wash-out” curve on the LiDCOplus provides an accurate absolute cardiac output value.
ADVANTAGES OF THE LiDCO plus LITHIUM INDICATOR DILUTION METHOD

The advantages of the LiDCO plus method are that it is safe, accurate and simple to use:

- **Safe** - Central/peripheral venous and arterial catheters are usually already in place in patients needing cardiac output measurements. No further catheter is needed, so the method avoids the risks associated with pulmonary artery catheterisation. The method requires withdrawal of approximately 5 ml blood per determination; for an adult this is an insignificant amount. The injectate is a solution of lithium chloride. The dose needed (0.15 - 0.30 mmol for an average adult) is very small and has no known pharmacological effect. The dosage regimen recommended is very conservative, making worst case assumptions on volume of distribution of lithium, patient weight (assumes 40kg) and absence of renal function.

- **Accurate** - Clinical trials have been completed that demonstrate that the LiD CO System is at least as accurate as thermodilution.

- **Simple to use** - The method is simple and quick to use. It has the advantage that there is no unpleasant procedure for a conscious patient to undergo (such as insertion of a pulmonary artery catheter) and the time taken to set up and apply is between 5 and 10 minutes.

THE SENSOR

The sensor consists of a lithium-selective electrode in a flow-through cell. It is disposable, sterilised by gamma irradiation and foil packed. The sensor is connected to a three-way tap on the arterial line and a small peristaltic pump restricts the flow through it to 4.5 ml/min. The flow-through cell is made of polycarbonate and designed with an eccentric inlet so that the blood swirls past the tip of the electrode. The lithium-selective electrode is made of polyurethane with a central lumen. Silver chloride paint coats the inside and the outside. A wick, which is soaked in saline when the cell is first primed, makes the electrical connection between the blood in the cell in the vicinity of the tip of the electrode and the remote reference. This arrangement ensures adequate constancy of the voltage of the reference which is far enough from the blood to avoid a significant temperature effect. The electrode is filled with a reference material which provides a constant ionic environment and supports the membrane which is dip cast. The membrane is made of polyvinyl chloride and contains a lithium ionophore to make it selectively permeable to lithium ions.

The LiD CO lithium-selective electrode in a flow through cell.
Indicator Dilution Screen

GREATER PRECISION THAN A SINGLE BOLUS THERMODILUTION

DERIVATION OF ABSOLUTE CARDIAC OUTPUT VALUE

The voltage across the sensor membrane is related via the Nernst equation to the plasma [Li⁺]. A correction is applied for plasma sodium concentration because in the absence of lithium the baseline voltage is determined by the sodium concentration. The voltage is measured using an amplifier optically isolated from the patient, then digitised on-line and analysed by the LiDCO plus Monitor software.

Indicator dilution curves recorded in arterial blood consist of primary and secondary curves due to the initial circulation and then re-circulation of the indicator. Cardiac output is calculated as:

\[
\text{Cardiac Output} = \frac{(\text{Lithium Dose} \times 60)}{\text{Area} \times (1-\text{PCV})}
\]

Where lithium dose is in mmol; Area is the integral of the primary curve (mM.s); PCV is packed cell volume which may be calculated as hemoglobin concentration (g/dl) / 34; this correction is needed because lithium is distributed in the plasma and not into the red or white cells on the first pass to the arterial circulation.
VALIDATION

Validation comparing the LiDCO System with bolus pulmonary artery catheter thermodilution technique (Figure 8) demonstrated a good overall agreement between the two methods (see Figure 8 \( r^2 = 0.94 \)) \(^{11} \). The conclusions were that a single bolus of lithium was at least as accurate as meaned triplicate bolus thermodilution. In another study where thermodilution and lithium dilution were compared to an aortic electromagnetic flow probe the LiDCO results showed less variability and therefore the LiDCO System was found to have a greater precision than single bolus thermodilution \(^{12} \).

Larger animals (horses) and paediatric subjects have also been studied to ensure that the lithium dilution technique remained valid at extremes of flows (Figure 9). The body weight studied ranged from as small as a 2kg baby* up to a 550kg horse\(^ {10} \).

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LITHIUM CHLORIDE: THE FACTS

Multiple dosages of Lithium have been extensively investigated and the safety profile is well established. The pharmacokinetics of intravenous lithium chloride in man (and animals) has been documented \(^ {74} \). Lithium chloride has been used extensively in medicine for prophylactic and therapeutic treatment of unipolar and bipolar manic-depressive disorders \(^ {75}, 76 \). The lithium chloride is distributed throughout the total body water and excreted almost entirely by the kidneys. The half-life of lithium chloride in humans is 19.8 - 41.3 hrs \(^ {77}, 78 \). The recommended maximum total dose for a Lithium indicator dilution would have to be exceeded many times before toxic levels are reached. In fact, a single lithium chloride LiDCO indicator dilution determination at 0.3mmol is the equivalent to a steady state plasma lithium concentration of 1/240th of the therapeutic level. Lithium has been used for the measurement of cardiac output in thousands of patients over many years without a single side effect being reported.

*The use of LiDCOplus is unlicensed in patients <40kg (88lb)
REFERENCES

31. Pereira et al. (1987) Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs.
27. Pizov et al. (1996) Positive end-expiratory pressure-induced hemodynamic changes are reflected in the arterial pressure waveform.

20 LiDCO® plus CONTINUOUS, REAL-TIME CARDIOVASCULAR MONITORING
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Appendix 3

Ethics Committee Communications
Dr Thomas A J Wagstaff
Clinical Research Fellow
Department of Anaesthesia and Intensive Care
Chelsea and Westminster NHS Trust
369, Fulham Road,
London SW10 9NH

12 October 2005

Dear Dr. Wagstaff

Full title of study: Peak Inspiratory Flow Rates in Respiratory Distress
REC reference number: 05/Q0401/129

The Research Ethics Committee reviewed the above application at the meeting held on 03 October 2005.

Ethical Opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form. Confirmation of approval for other sites listed in the application will be issued as soon as local assessors have confirmed they have no objection.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The documents reviewed and approved at the meeting were:

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Research governance approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final research governance approval from the R&D Department for the relevant NHS care organisation.

Membership of the Committee

The members of the Ethic Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

With the Committees best wishes for the success of this project.

Yours sincerely

Dr Steve Yentis
Chair

Email: achakraborty@hhnt.org

Enclosures: List if names and professions of members who were present at the meeting and those who submitted written comments

Standard approval conditions

Site approval form (SF1)

Copy to: Professor Mervyn Maze
Chelsea and Westminster NHS Trust
Room JL18
369 Fulham Road London
SW10 9NH

An advisory committee to North West London Strategic Health Authority
Dr Thomas A J Wagstaff  
Clinical Research Fellow  
Department of Anaesthesia and Intensive Care  
Chelsea and Westminster NHS Trust  
369, Fulham Road,  
London SW10 9NH  

18 January 2006  

Dear Dr. Wagstaff  

Full title of study: Comparison of Two Cardiac Output Monitors  
REC reference number: 06/Q0401/10  

The Research Ethics Committee reviewed the above application at the meeting held on 09 January 2006.  

Ethical Opinion  

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation.  

Ethical review of research sites  

The favourable opinion applies to the research sites listed on the attached form. Confirmation of approval for other sites listed in the application will be issued as soon as local assessors have confirmed they have no objection.  

Conditions of approval  

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.  

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An advisory committee to North West London Strategic Health Authority
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Copy to: Professor Mervyn Maze
Chelsea and Westminster NHS Trust
Room JL18
369 Fulham Road London
SW10 9NH

An advisory committee to North West London Strategic Health Authority
Appendix 4

Publications
APPARATUS

Performance of six types of oxygen delivery devices at varying respiratory rates*

T. A. J. Wagstaff¹ and N. Soni²

1 Clinical Research Fellow, 2 Director Intensive Care, Magill Department of Anaesthesia, Intensive Care and Pain Management, Chelsea and Westminster Hospital, 369, Fulham Road, London SW10 9NH, UK

Summary

The administration of a known concentration of oxygen is an important part of routine care of the sick patient. Many devices are currently available. The actual concentration of oxygen that can be delivered by these devices can be affected by several factors, both from the patient as well as the device itself. Measuring the $F_{\text{IO}_2}$ delivered to the lungs in vivo can be both difficult and potentially uncomfortable for the subjects. We constructed a model using a resuscitation manikin, a ventilator and a set of bellows to simulate ventilation. With this model we tested a series of devices – variable performance, fixed performance and high flow – at two fixed tidal volumes. The respiratory rate was increased and its effect on the oxygen concentration assessed. Variable performance systems such as the Hudson mask deliver a significantly reduced oxygen concentration at high respiratory rates. Fixed performance systems delivering 24–40% oxygen deliver appropriate oxygen concentrations across the range of respiratory rates, whereas those delivering 60% show a reduction in performance. High flow systems show no failure of performance at increased respiratory rates.

Correspondence to: Dr Adrian Wagstaff
E-mail: adrian.wagstaff@imperial.ac.uk

*Parts of this study were presented as an oral presentation at the Doctors Updates meeting in Da Bilha, Portugal, October 2005.
Accepted: 9 January 2007

Modern management of the sick patient involves the administration of oxygen in supposedly known concentrations. There are many delivery systems commercially available whose performances are documented in the literature [1–8]. This is usually reported as the actual delivery from the system [3], the resultant inspired concentration of oxygen [1, 2, 4–9], or the arterial oxygenation achieved [9].

From a physics perspective, the actual concentration of oxygen delivered is determined by the interaction between the delivery system and the patient’s breathing pattern [4]. In contrast, most of the in vivo measurements that have been reported were carried out in normal subjects breathing at rest or trained to vary their tidal volumes [1–5, 7–18]. Several of these studies do point out that there are multiple factors which may compromise the performance of these devices and result in an effective $F_{\text{IO}_2}$ that is less, or occasionally more, than that expected [4,7]. The factors that influence the concentration actually inspired by the patient are summarised in Table 1.

Few studies have tried to evaluate delivery system performance in the adverse circumstances in which the systems are commonly used [19–21]. Practical difficulties include the instantaneous and simultaneous measurement of $F_{\text{IO}_2}$ and gas flow. This is compounded by the problems of identifying and accessing a suitable sampling site [8]. The predominant problem is the relationship of the oxygen flow into the mask, the size of the reservoir effect of the mask and the peak inspiratory flow rate, the combination of which will determine air entrainment and therefore oxygen dilution.

An alternative approach is to devise a model that could mimic spontaneous breathing patterns and to collect the mixed inspired gas from the model lungs. The mixed inspired gas would, to a certain degree, represent the final concentration of inspired oxygen. This could be described as the ‘effective inspired oxygen concentration’.
(EIOC), as it represents the resultant oxygen concentration in the model over the inspiratory phase of ventilation. This avoids many of the measurement problems of the previous methods, but remains only a model. As the oxygen delivery from these systems is largely determined by the physics of the system, the model should lend itself to providing useful information about the relative performance of oxygen delivery systems.

The intention of this study was to devise such a model and to use it to assess the effective inspired oxygen delivery of several commonly used systems with changing respiratory patterns.

**Methods**

The concept behind the model that was devised is that by collecting the ‘exhaled’ gas from the model, the mean oxygen concentration that had arrived in the lung could be measured easily. It is this mean concentration, derived from the entirety of inspiration, that represents the actual or effective oxygen delivery. This system is considerably simpler than trying to measure simultaneously the oxygen concentration and flow.

**The model**

An experimental rig was constructed as shown in Fig. 1. A Laerdal Airway Management Trainer manikin (Laerdal, Orpington, UK), was used to simulate the nasopharynx, larynx and trachea. The manikin’s ‘bronchi’ were attached via a Y-piece to a set of ‘slave’ bellows. These were driven by a second set of ‘driving’ bellows by way of a connecting rod. The driving bellows were connected to a Dräger Evita ventilator (Dräger Medical, Hemel Hempstead, UK), set to deliver a square wave. This would allow changes in respiratory rate, tidal volume, inspired : expired (I : E) ratio and maximum inspiratory flow rate. As the driving bellows expand, a reciprocal negative pressure is produced in the slave bellows. This acts as ‘inspiration’. Gas is thus ‘inhaled’ into the slave bellows. Expiration is passive by way of a return spring. This spring conferred a more sinusoidal profile to the square wave ventilation delivered by the ventilator. Unidirectional valves block gas return to the manikin and conduct expired gas via a T-piece to a 10-l airtight canister to allow adequate mixing of ‘exhaled’ gas. This mixed gas represents the mean inspired concentration in the model and for the purpose of this study is called the EIOC. This gas was then piped past a Datex-Ohmeda 5120 oxygen analyser (GE Healthcare, Chalfont St. Giles, UK), and the oxygen percentages recorded. All connecting tubes were 22-mm Intersurgical Elephant Tubing (Intersurgical Ltd., Wokingham, UK).

![Figure 1](image)

The experimental rig: The two sets of bellows are demonstrated. Diagram A. Positive pressure from the Dräger Evita ventilator (>>) inflates the first set of bellows and via the connecting rod, causes the second set of bellows to open and draw in gas (solid arrows, diagram B). The negative pressure derived from the second set of bellows draws gas from the manikin (dashed arrows, diagram B). During the expiratory cycle of the ventilator the gas within the second set of bellows is expelled by a return spring (solid arrows, diagram C) into a 10-l mixing chamber and then out to the environment past a Datex-Ohmeda 5120 oxygen analyser (dashed arrows, diagram C). Direction of gas movement around the apparatus was controlled by unidirectional flow valves (▲).
Calibration
Control measurements were performed by intubating the manikin with a 7.0-mm cuffed tracheal tube. Ventilating at a tidal volume of 300 and 500 ml, with a respiratory rate of 10 breaths.min⁻¹, an I : E ratio of 1 : 2 and no positive end-expiratory pressure (PEEP), the manikin 'breathed' firstly air and then 100% oxygen via a Mapleson C system. The oxygen analyser was thus calibrated to 21% and 100%, respectively. The time taken to reach concentrations of 100% from 21% was assessed and found to have a mean of 4 min 12.3 s and 3 min 5.8 s for 300 and 500 ml, respectively. Tidal volume measures were achieved using a Wright's respirometer inserted in the expiratory limb of the slave system. Its reflection of inspiratory volume was assessed by attaching a second respirometer to the end of the tracheal tube. There was concordance between the two at tidal volumes of 100, 250, 500, 750 and 1000 ml at respiratory rates of 10, 20 and 30 breaths.min⁻¹.

Devices
The devices selected for study are those commonly used for oxygen delivery in our institution (Table 2).

<table>
<thead>
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<th>Variable performance devices</th>
<th>Fixed performance devices</th>
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<tr>
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<td>Fixed Performance mask with Venturi inserts (Intersurgical)</td>
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<td>Variable Performance Hudson-type mask (Teleflex Medical)</td>
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<td>Variable Performance mask with reservoir bag and safety vent (Teleflex Medical)</td>
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<td>Vapotherm</td>
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<td>Thermovent T2 HME (Smiths Medical)</td>
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(The Thermovent T2 HME (Smiths Medical, Hythe, UK) is designed for use with a tracheostomy. To examine this device, the manikin was intubated orally, as we were not permitted to perform a tracheostomy on the manikin.

Assessment
A standard regimen was executed for each of the above devices. The first sets of measurements were performed at a measured tidal volume that was fixed at 500 ml. The I : E ratio remained constant at 1 : 2. The value of the inspiratory flow rate delivered by the ventilator was set at the minimum required to generate the appropriate tidal volume at each respiratory rate while maintaining the I : E ratio at 1 : 2. For each change in respiratory rate, the manikin was ventilated for 5 min to ensure that equilibrium had been reached at the oxygen analyser. On completion of each cycle, a further period of 5 min 'washout' on air was performed before the next alteration in respiratory rate. The maximum oxygen concentrations were recorded for the devices at 10, 15, 20 and 30 breaths.min⁻¹. The variable performance devices were tested at oxygen flow rates of 2, 4, 6, 8, 10 and 15 l.min⁻¹ as delivered by an AHE ball flow meter. The fixed performance devices were assessed using the oxygen flow rates for the appropriate inserts, as recommended by the manufacturer. The high flow system, the Vapotherm, was analysed at two fresh gas flow rates (15 and 30 l.min⁻¹) and four oxygen concentrations (30, 60, 80 and 100%).

The measurements were then repeated in the same manner, but with a measured tidal volume fixed at 300 ml. Each assessment was repeated three times to ensure reproducibility. Ventilator adjustments, application of the oxygen system to the mannequin, and measurements were done by the same investigator, and repeated on different days using the same equipment.

Results
Variable performance systems
The variable performance systems that were analysed were the Hudson mask with and without the non-rebreathing reservoir bag attachment, nasal cannulae, and the Thermovent HME.

Hudson mask
The Hudson mask showed evidence of deterioration of performance as the respiratory rate increased both at tidal volumes of 300 ml and 500 ml. At a respiratory rate of 10 breaths.min⁻¹, the mask delivered a mean EIOC of 94.67% and 88.33% at 15 l.min⁻¹ oxygen flow rate for tidal volumes of 300 and 500 ml, respectively. This was reduced to a mean of 75.67% and 63.33% when the respiratory rate was raised to 30 breaths.min⁻¹. The reduction in performance was greater at 500 ml tidal volume (38.30%) than at 300 ml (20.07%) (Fig. 2).
mask. The mean EIOC delivered by the non-rebreathing system at 15 l.min⁻¹ oxygen flow rate and 10 breaths.min⁻¹ respiratory rate was 85.67% and 79.33% for 300 ml and 500 ml tidal volume, respectively. In fact, for all oxygen flow rates, the non-rebreathing system failed to perform as well as the standard Hudson mask, across all respiratory rates and at both tidal volumes. It also showed deterioration in performance as the respiratory rate increased. For example, at an oxygen flow rate of 15 l min⁻¹, the mean EIOC fell from 85.67% to 68.33% (20.2%) and 79.33% to 59.67% (24.78%) at 300 ml and 500 ml tidal volume, respectively (Fig. 3).

Nasal cannulae
Of interest, the nasal cannulae achieved the highest EIOC of all the variable performance systems. This was maintained across all oxygen flow rates and both tidal volumes. In particular, at 15 l.min⁻¹, a respiratory rate of 10 breaths.min⁻¹ and a tidal volume of 300 ml, the mean EIOC was 97.33%, approaching the holy grail of 100% in a self-ventilating patient. However, the cannulae also demonstrated deterioration in performance as the respiratory rate increased at both tidal volumes. At an oxygen flow rate of 6 l.min⁻¹, oxygen concentrations fell from 87.67% to 69.33% (20.92%) and from 81.33% to 54.67% (14.75%) at 300 ml and 500 ml, respectively (Fig. 4).

Thermovent H2 HME
As with the above oxygen delivery systems, the Thermovent system in the intubated manikin showed deterioration in performance at higher respiratory rates. Unlike the previous systems, at lower oxygen flow rates the performance was more consistent (2 l.min⁻¹ oxygen flow rate, Vₜ 500 ml: 10 breaths.min⁻¹ oxygen = 31.67%, 30 breaths.min⁻¹; oxygen = 25.67%), and also the change in tidal volume had less of an influence on the EIOC (at 4 l min⁻¹ oxygen flow rate and 30 breaths.min⁻¹: with Vₜ 300 ml, oxygen = 32%; Vₜ 500 ml oxygen = 31.33%) (Fig. 5).

Fixed performance system
The fixed performance system that was tested was the Venturi mask and inserts supplied by Intersurgical.

Venturi system
The Venturi system showed consistent performance at the lower oxygen concentration inserts at both tidal volumes examined. The mean EIOC measured was close to that expected by the insert. For example, at 30 breaths.min⁻¹ with a tidal volume of 500 ml, the 24% and 28% inserts delivered a mean EIOC of 23.67% and 26%, respectively. There was, however, some reduction in the EIOC at the higher oxygen concentration inserts, particularly at

**Hudson non-rebreathing mask**

The addition of a reservoir bag and flap valves over the orifices does not improve the performance of the Hudson
500 ml tidal volume. (Vt 300 ml, 60% insert, 10 breaths.min⁻¹ oxygen = 59.67%; 30 breaths.min⁻¹ oxygen = 53.33%. Vt 500 ml, 60% insert, 10 breaths.min⁻¹ oxygen = 57.33%, 30 breaths.min⁻¹ oxygen = 50.33%) (Fig. 6).

**Figure 3** Effective inspired oxygen concentration (EIOC) achieved by a Hudson non-rebreathing mask at four oxygen flow rates: 2 L.min⁻¹ (□), 6 L.min⁻¹ (○), 10 L.min⁻¹ (△) and 15 L.min⁻¹ (○), across a range of respiratory rates at tidal volumes of 300 ml (A) and 500 ml (B).

**Figure 4** Effective inspired oxygen concentration (EIOC) achieved by nasal cannulae at four oxygen flow rates: 2 L.min⁻¹ (□), 6 L.min⁻¹ (○), 10 L.min⁻¹ (△) and 15 L.min⁻¹ (○), across a range of respiratory rates at tidal volumes of 300 ml (A) and 500 ml (B).

**High flow, high concentration system**
The high flow, high concentration system that was tested was the Vapotherm system.
The Vapotherm system was additionally analysed at two gas flow rates, 15 and 30 l.min\(^{-1}\). The oxygen concentration was selected on the dial on the system. In terms of consistent performance, this system showed very little reduction in EIOC as the respiratory rate changed. At tidal volumes of 300 ml, there was no change in EIOC at 20, 40, 60, 80, and 100%. At tidal volumes of 500 ml, the EIOC was consistent across a range of respiratory rates.

**Figure 5** Effective inspired oxygen concentration (EIOC) achieved by a Thermovent T2 HME at four oxygen flow rates: 2 l.min\(^{-1}\) (□), 6 l.min\(^{-1}\) (○), 10 l.min\(^{-1}\) (△) and 15 l.min\(^{-1}\) (○), across a range of respiratory rates at tidal volumes of 300 ml (A) and 500 ml (B).

**Figure 6** Effective inspired oxygen concentration (EIOC) achieved by a each Venturi Mask insert: 24% (○), 28% (□), 35% (○), 40% (△) and 60% (○), across a range of respiratory rates at tidal volumes of 300 ml (A) and 500 ml (B).

**Vapotherm**

The Vapotherm system was additionally analysed at two gas flow rates, 15 and 30 l.min\(^{-1}\). The oxygen concentration was selected on the dial on the system. In terms of consistent performance, this system showed very little reduction in EIOC as the respiratory rate changed. At tidal volumes of 300 ml, there was no change in EIOC at...
all oxygen concentrations as the respiratory rate increased. Doubling of the gas flow rate also had little influence on the EIOC. With the tidal volume set at 500 ml, however, there was a slight reduction in EIOC at 15 l.min\(^{-1}\) gas flow (\(F_{iO_2} 100\%, \ 10 \text{ breaths.min}^{-1} \ 71.67, \ 30 \text{ breaths.}\ \text{min}^{-1} \ \text{oxygen} = 67.67\%\)). This, however, was abolished when the gas flow rate was increased to 30 l.min\(^{-1}\). Of greatest interest was that in this model the Vapotherm is not able to deliver the dialled \(F_{iO_2}\). For example, at both 300 ml and 500 ml tidal volume, the maximum EIOC achieved for ‘100%’ \(F_{iO_2}\) was 78.67% and 76.67%, respectively. Increasing the gas flow rate did improve delivery, particularly in the 500 ml assessment, but only by a maximum of 7% (30 breaths.min\(^{-1}\) 100% \(F_{iO_2}\) \(V_t\) 500 ml) (Fig. 7).

**Discussion**

The model clearly demonstrates a reduction in the effective inspired oxygen concentration (the mixed oxygen concentration from the entire inspiratory phase) with the variable performance masks as the respiratory rate increases while at a fixed tidal volume. This varied between delivery systems. With nasal cannulae and an oxygen flow rate of 4 l.min\(^{-1}\), EIOC falls from 69.67% to 48% when the respiratory rate increases from 10 to 30 breaths.min\(^{-1}\) and the tidal volume is 500 ml.

With the fixed performance systems, the impact of altered ventilation is substantially diminished. The 24% Venturi mask shows no reduction in performance, whereas the 60% mask deteriorates from 57.33% oxygen at 10 breaths per minute and a tidal volume of 500 ml, to 50.33% oxygen at 30 breaths per minute.

The Vapotherm, which is a high flow rate system, shows minimal change across the range of respiratory rates. Interestingly, changing the gas flow rate from 15 to 30 l.min\(^{-1}\) has only a minimal effect on EIOC and neither produces the value that is selected on the oxygen : air mix dial, particularly at the higher \(F_{iO_2}\). The system is known to achieve 99% humidity and this would compromise the EIOC; however, this could only account for a drop of approximately 5% with fully saturated air.

Table 3 summarises the manufacturers’ recommendations for oxygen flow rates for their variable performance devices tested, and the resultant oxygen concentration to be expected. The studies we have performed indicate that with many of the currently used oxygen delivery systems this predicted performance is unpredictable. To compound the potential problem, the delivery deteriorates with the increased rate of breathing, and presumably increasing peak inspiratory flow rate (PIFR), which is characteristic of sick patients. The actual \(F_{iO_2}\) that is inspired by the patient and reaches the distal airways is difficult to predict for several reasons (see Table 1). The entrainment of environmental air will be influenced by the relationship between oxygen gas flow through the

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Figure 7  Effective inspired oxygen concentration (EIOC) achieved by the Vapotherm for four different oxygen concentrations at 30 l.min\(^{-1}\) gas flow: 30% (□), 60% (○), 80% (△) and 100% (○) across a range of respiratory rates at tidal volumes of 300 ml (A) and 500 ml (B).
system, the inspiratory pattern of the patient and to some degree the dead space of the mask and pharynx. The single most important factor is probably the relationship between the tidal volume and the PIFR, and at what point this exceeds the available volume of undiluted oxygen within the mask and pharynx. In sick patients, the respiratory pattern is often altered and tends towards relatively lower tidal volumes at an increased respiratory rate and hence a high PIFR. Respiratory rates in excess of 30 breaths min\(^{-1}\) are not uncommon and may be associated with PIFRs of greater than 30 l min\(^{-1}\) and loss or diminution of the respiratory pause. This will increase entrainment of environmental air which, combined with rebreathing of dead space gases, will dilute the inspired oxygen concentration.

Attempts to measure this in the past have focused upon trying to measure instantaneously \(F_{iO_2}\) and gas flow. This has been hampered by the sampling site, flow and oxygen concentration measurement, and aligning these electronically. Sampling in patients needs to be as far down the airway as possible, which again poses a difficulty. The accuracy of the pneumotachograph is problematic and its presence will invariably alter the mechanics of the delivery system itself. Rapid, real time oxygen concentration analysis has been difficult, and even now, when available, would have to synchronise with flow measurement to provide the amount of oxygen delivered.

An alternative approach is this model that mimics spontaneous breathing patterns. It may produce a more realistic indication of how these delivery systems function in adverse circumstances. This contrasts with most previous models which have evaluated the concentration of the oxygen flowing through the delivery system without looking at the interplay between delivery and respiratory pattern [3].

There are problems with the model. Firstly, there is the absence of the contribution that carbon dioxide and water vapour (with the exception of the Vapotherm) make to the concentration of oxygen in the exhaled gas. The rebreathing of any exhaled gas is prevented by the effects of the unidirectional valves passing ‘inhaled’ gas to the oxygen analyser. The contribution of the dead space gases to \(F_{iO_2}\) can, however, be estimated by making assumptions about the proportion that dead space contributes to tidal volume, oxygen uptake and carbon dioxide production. A relatively simple formula can be derived to predict further reduction in the measured EIOC values caused by the presence of dead space gases (see Appendix). These are, however, only estimates and can not accurately predict \(F_{iO_2}\) based on this model’s data because of the complexity of pulmonary physiology. The variation in anatomical and physiological dead space and changes in oxygen consumption and carbon dioxide production, particularly in acute illness, make the derived values in the Appendix only approximations.

Secondly, the action of the valves also prevents ongoing entrainment of delivered oxygen during the end of the expiratory phase and respiratory pause. If the results are to be extrapolated to the clinical setting, the limitations noted above would be more likely to cause the device to perform even less well than we have demonstrated, owing to the presence of gases and vapours other than oxygen and air and the rebreathing of a proportion of dead space derived from both the device and upper airway.

In only one of the delivery systems did the model produce an unexpected result. When the nasal cannulae were used, the effective inspired oxygen was higher than with the Hudson mask, which was not an intuitively sound result. In the model, the oxygen is delivered into the nose of the manikin, and even though the mouth was open, it is possible that it effectively produces a pharynx full of oxygen resulting in a high inspired oxygen value. It is impossible to say if this represents the clinical situation.

**Conclusion**

Using this model, an indication of the performance of different oxygen delivery systems has been achieved. The variable performance systems, including those with a rebreathing bag, appear to function poorly under adverse conditions. The fixed performance systems are predictably better, but only up to 60% oxygen, which may be inadequate. The high flow systems perform well across the circumstances tested. Anxieties about comfort and airway drying may be misplaced [22]. This model could

**Table 3** Manufacturers’ recommendations for oxygen flow rates and resultant oxygen concentrations for the variable performance device (Teleflex Medical. Hudson RCI Therapy Products. Personal communication 2006). The fixed performance devices Venturi and Vapotherm have been omitted as their correct use

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*May require higher flows. The flow should be adjusted so that the reservoir bag does not deflate more than one third during inspiration.
be used to produce realistic tables of oxygen delivery system performance.

References

5 Ling E, McDonald L, Dinesen TR, DuVall D. The OxyArm—a new minimal contact oxygen delivery system for mouth or nose breathing. Canadian Journal of Anaesthesia 2002; 49: 297–301.

Appendix: Mathematical derivation of the possible contribution of dead space gases to the EIOC

This is a mechanical model and as such permits the application of simple physical principles to allow the estimation of the possible further detrimental effect that the inclusion of dead space gases and vapours might have on the EIOC obtained from measurement. For this mathematical formula, we have selected the Hudson mask as the example, although the calculations could be used with data from any of the oxygen delivery systems tested.

A. Derivation of formula for EIOC corrected (EIOC<sub>core</sub>)

Tidal volume (V<sub>T</sub>) in an average 70 kg male: 500 ml [23]

Dead space; both anatomical and physiological (V<sub>D</sub>): 30% of V<sub>T</sub> [23].

Oxygen consumption: 250 ml min<sup>−1</sup> [23]

Respiratory quotient (R): 0.8 [23]

The data that we have derived from the model requires correction factors for the effect of dead space to be added in.

Carbon dioxide

For each breath, at the end of expiration we can assume that V<sub>E</sub> contains gas from the alveolus (V<sub>A</sub>). The oxygen concentration of V<sub>A</sub> at end expiration (V<sub>A</sub>[O<sub>2</sub>]) is the original oxygen concentration at end inspiration (V<sub>I</sub>[O<sub>2</sub>]) minus the proportion of oxygen consumed and is reflected in the value of V<sub>E</sub>[O<sub>2</sub]]. If R is assumed to be 0.8, then it can be assumed that the 80% of the difference between V<sub>I</sub>[O<sub>2</sub>] and V<sub>E</sub>[O<sub>2</sub>] is made up of carbon dioxide. Resting oxygen consumption is approxima-
tely 250 ml.min\(^{-1}\), thus carbon dioxide production is 0.8 \times 250 = 200 ml.min\(^{-1}\).

At a respiratory rate of 10 breaths.min\(^{-1}\), the contribution of carbon dioxide per breath would be 200 + 10 = 20 ml.

This carbon dioxide would be distributed in a \(V_A\) of \(V_A = V_t - V_D\) (500 - 150 = 350).

The carbon dioxide would contribute \((20 \times 350) \times 100 = 5.7\%\) of the value of \(V_D\) gas at end-expiration.

The value contribution of carbon dioxide at a respiratory rate of 30 would have a value of approximately 2% assuming a constant oxygen consumption. Respiratory quotient, \(V_t\) and \(V_D : V_A\) ratio. These assumptions may not be applicable in pathology that results in such a high respiratory rate.

**Water vapour**

Fully saturated air contains water vapour at a partial pressure of 47 mmHg [23]. If atmospheric pressure is assumed to be 760 mmHg, then water vapour will contribute \((47 + 760) \times 100 = 6.18\%\).

So this could be added as a correction factor to the EIOC as the model results for the non-humidified systems (all except the Vapotherm\(^3\)).

If it is assumed that both inhaled and exhaled gases are fully saturated and that the water vapour is distributed evenly through all gases, then the correction required for the oxygen concentrations as a percentage is \(= 0.0618 \times \text{EIOC}\). For example, for an EIOC of 40% we must subtract \(= 0.0618 \times 40 = (2.47\%)\).

The additional contribution of carbon dioxide of between approximately 2% and 5.7% would mean between approximately 8% and 13% of the \(V_D\) would contain water vapour and carbon dioxide.

**Dead space**

If we assume that \(V_D\) contributes 30% to the value of \(V_t\), and that the \(E_tO_2\) reflects the concentration of oxygen in the dead space, then it can be said that the contribution of this gas to \(V_t[O_2]\) is \(= 0.3 \times E_tO_2\), i.e. 30% of the gas inhaled has an oxygen concentration of the \(E_tO_2\).

This is added to the concentration of oxygen delivered by the oxygen system in the rest of \(V_t\) (70%): \(0.7 \times \text{EIOC} = (0.3 \times E_tO_2) + (0.7 \times \text{EIOC})\).

Now add in the contribution of water vapour for a final formula that approximates the \(F_tO_2\) for \(V_D\) of 30%:

\[
\text{EIOC}_{corr} = [(0.3 \times E_tO_2) + (0.7 \times \text{EIOC})] - (0.0618 \times \text{EIOC}).
\]

**Example**

From the data for a Hudson Mask:

\(V_t\) : 500 ml

Respiratory rate: 10 breaths.min\(^{-1}\)

Oxygen flow rate: 2 l.min\(^{-1}\)

Assuming the \(E_tO_2\) is 30% and a \(V_D\) of 30%, \(EIOC_{corr} = [(0.3 \times 30) + (0.7 \times 42)] - (0.0618 \times 42) = 35.80\%\).

The estimation of the \(E_tO_2\) and proportions of \(V_D\) and \(V_A\), make this method only an approximation of the contribution of dead space to the EIOC derived from the model, but it does allow the plotting of families of curves for both increasing \(V_D\) at the same tidal volume, as well as variation in the \(E_tO_2\) (see below).

**B. Example 1: Hudson mask \(V_t\) 500 ml. Effect of varying the proportion of \(V_t\) that is \(V_D\)**

Table A1 shows the EIOC measured for the Hudson mask across the range of respiratory rates when the \(V_t\) was set at 500 ml. We can calculate the \(EIOC_{corr}\) for a \(V_D : V_A\) ratio of 30 : 70 by putting the values of EIOC into the formula and assume that the \(E_tO_2\) remains fixed at 30%: \(EIOC_{corr} = [(0.3 \times E_tO_2) + (0.7 \times \text{EIOC})] - (0.0618 \times \text{EIOC})\).

This results in Table A2.

There is increasing reduction in \(EIOC_{corr}\) as the oxygen flow rate and respiratory rate increases. This is, in part, due to the assumption that the \(E_tO_2\) is fixed at 30% and therefore has a greater influence on the \(EIOC_{corr}\) at higher EIOCs. Estimation of \(E_tO_2\) is difficult in vivo as it is dependent on oxygen uptake, which can vary significantly, particularly in respiratory pathology.

<table>
<thead>
<tr>
<th>Oxygen flow rate; l.min(^{-1})</th>
<th>Respiratory rate; breaths.min(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>42.00</td>
</tr>
<tr>
<td>4</td>
<td>59.33</td>
</tr>
<tr>
<td>6</td>
<td>65.33</td>
</tr>
<tr>
<td>8</td>
<td>74.33</td>
</tr>
<tr>
<td>10</td>
<td>82.00</td>
</tr>
<tr>
<td>15</td>
<td>88.33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxygen flow rate; l.min(^{-1})</th>
<th>Respiratory rate; breaths.min(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>35.80</td>
</tr>
<tr>
<td>4</td>
<td>46.87</td>
</tr>
<tr>
<td>6</td>
<td>50.70</td>
</tr>
<tr>
<td>8</td>
<td>56.44</td>
</tr>
<tr>
<td>10</td>
<td>61.33</td>
</tr>
<tr>
<td>15</td>
<td>65.37</td>
</tr>
</tbody>
</table>
If we consider only the EIOCcorr for the Hudson mask at Vt 500 ml and oxygen flow rate of 4 l.min⁻¹, we can use the derived formula to approximate the effect of altering the VD : VA ratio assuming that EᵣO₂ is maintained at 30%. This is summarised in Table A3 and shown graphically in Fig. A1.

The results of the calculations confirm that introduction of a correction factor further reduces the EIOC that the mask delivers. Also, increasing the contribution of the dead space gases and vapours by increasing the proportion of Vt that is VD reduces the EIOC still further. This simplistic view of mixing of gases in the model relies on significant assumptions and the values derived for EIOCcorr can only be viewed as a guide for the real mask performance in vivo.

C. Example 2: Hudson mask Vt 500 ml.
Effect of varying the value of EᵣO₂
The derived formula for calculating EIOCcorr to allow for the effect of dead space gases and vapours relies on an approximation of EᵣO₂ as a reflection of oxygen consumption and carbon dioxide production. The value of EᵣO₂ is predominantly dependent upon the FᵣO₂ and oxygen consumption. Oxygen consumption can vary widely in pathology and so for the purpose of this example we present calculations based on a spectrum of Table A4

Table A3 The Hudson mask with oxygen flow rate of 4 l.min⁻¹ and a Vt of 500 ml. The effect on EIOCcorr of altering the VD : VA ratio assuming a constant EᵣO₂ of 30%.

<table>
<thead>
<tr>
<th>VD : VA ratio</th>
<th>Respiratory rate; breaths.min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>No correction</td>
<td>59.33</td>
</tr>
<tr>
<td>20 : 80</td>
<td>49.80</td>
</tr>
<tr>
<td>30 : 70</td>
<td>46.87</td>
</tr>
<tr>
<td>40 : 60</td>
<td>43.93</td>
</tr>
<tr>
<td>50 : 50</td>
<td>41.00</td>
</tr>
<tr>
<td>60 : 40</td>
<td>38.07</td>
</tr>
</tbody>
</table>

Table A4 Hudson mask at 500 ml delivering 4 l.min⁻¹ oxygen flow rate. Effect of varying the EᵣO₂ on the EIOCcorr if the VD : VA ratio is constant at 30 : 70.

<table>
<thead>
<tr>
<th>EᵣO₂: %</th>
<th>Respiratory rate; breaths.min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>No correction</td>
<td>59.33</td>
</tr>
<tr>
<td>15</td>
<td>42.37</td>
</tr>
<tr>
<td>20</td>
<td>43.87</td>
</tr>
<tr>
<td>25</td>
<td>45.37</td>
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<tr>
<td>30</td>
<td>46.87</td>
</tr>
<tr>
<td>35</td>
<td>48.37</td>
</tr>
<tr>
<td>40</td>
<td>49.87</td>
</tr>
</tbody>
</table>

Figure A1 The effect of varying the VD : VA ratio on the EIOCcorr for a Hudson mask delivering oxygen at 4 l.min⁻¹ to a Vt of 500 ml with an assumed EᵣO₂ of 30%. 60 : 40 (X), 50 : 50 (□), 40 : 60 (○), 30 : 70 (△), 20 : 80 (□) and no correction (●).

Figure A2 The effect of varying the EᵣO₂ on the EIOCcorr for a Hudson mask delivering oxygen at 4 l.min⁻¹ to a Vt of 500 ml with an fixed VD : VA ratio of 30 : 70. 0.15 (+), 0.2 (X), 0.25 (□), 0.3 (○), 0.35 (△), 0.4 (□) and no correction (●).
possible $E_tO_2$ values. This represents the best and worse case scenarios depending upon the value of $E_tO_2$ as a representation of oxygen consumption, and its contribution to the concentration of oxygen in the dead space gases.

Using the Hudson mask again at 500 ml and 4 l.min$^{-1}$ oxygen flow rate, the EIOC$_{corr}$ values obtained with the $E_tO_2$ varying between 40% and 15% are represented in Table A4 and Fig. A2.

Table A4 and Fig. A2 also confirm that assuming a lower oxygen concentration in the expired gas will produce a further reduction in delivery by the oxygen systems, and that the greater the difference between the oxygen concentration delivered and the $E_tO_2$, the lower the corrected EIOC. Once again, we caution that the above calculations only represent true values in vivo, as their derivation depends upon assumptions about $E_tO_2$ and $V_A : V_D$ ratio, both of which are potentially extremely variable in the patient population. However, the above tables and figures do demonstrate the possible effects of the dead space on the delivery of oxygen to the alveoli and how that would further undermine the performance of the mask in reality as opposed to this bench model.