

Improving cardiac device therapy: Delivering physiological pacing and improving therapy for tachycardias

Daniel Keene
MBChB MSc MRCP (UK)

A thesis submitted to Imperial College London
for the degree of
Doctor of Philosophy

International Centre for Circulatory Health
National Heart & Lung Institute
Imperial College London
London W12 0HS

Submitted May 2019

Abstract

Since the first implantable device 60 years ago, cardiac device therapy for brady and tachy arrhythmias has shown continued progress. However, despite the substantial benefits that have been realized, they still exhibit significant limitations and pose risks to patients.

Despite the acute benefits that pacemakers confer by providing life-saving ventricular stimulation in patients with ventricular standstill, in the longer-term harm may arise. This harm can occur as both right ventricular pacing and biventricular pacing do not deliver normal physiological activation of the ventricles and a subsequent deterioration in cardiac outcomes can be seen in both observational and randomised studies.

Similarly, Implantable Cardioverter Defibrillators (ICDs) clearly save lives in patients with ventricular arrhythmias by terminating the rhythm disturbance. However, ICDs can also cause harm. Devices may deliver therapies when not absolutely needed. Some therapies may be *inappropriate* (i.e. the device has incorrectly interpreted the recorded electrogram as a ventricular tachyarrhythmia when it is not) or *unnecessary* (i.e. there is indeed a ventricular tachyarrhythmia, but the patient is tolerating it well and a therapy could have been withheld safely). Current available ICD therapies are painful (in the case of shocks) and may worsen the clinical state (in the case of anti-tachycardia pacing accelerating a ventricular arrhythmia).

Improvements in both the pacing and defibrillator sphere of cardiac devices may well have the potential to improve the lives of the one million individuals worldwide that receive new implantable cardiac devices each year.

In Chapter 3, this thesis explores the rationale for delivering cardiac pacing through His bundle pacing. Furthermore, it provides data demonstrating the feasibility of permanent His bundle pacing through data from a large worldwide survey I have conducted.

In Chapter 4, haemodynamic experiments are performed to determine the potential physiological benefit that can be derived from His bundle pacing when compared to the standard bradycardia alternatives – *dual chamber right ventricular pacing* and *pacing avoidance algorithms* in a cohort of patients with intrinsic PR intervals longer than 200ms. This is a group of patients where currently a decision must be made between (a) shortening the atrio-ventricular delay but at the expense of creating ventricular dyssynchrony or (b) maintaining ventricular synchrony but at the expense of atrio-ventricular dyssynchrony. His bundle pacing may allow atrio-ventricular delay to be optimised whilst maintaining ventricular synchrony.

The physiological principles and knowledge derived from these prior chapters will be evaluated in the tachyarrhythmia setting and used to investigate the mechanisms by which ventricular tachyarrhythmias cause harm and subsequent consideration to novel mechanistically-targeted therapies.

In Chapter 5, invasive and non-invasive experiments are performed to determine how the loss of atrio-ventricular and biventricular synchrony contribute to the haemodynamic harm associated with ventricular tachycardias. This thesis then investigates how atrial pacing and His pacing during VT might mitigate this haemodynamic harm, preventing circulatory collapse and potentially allowing spontaneous termination of the ventricular tachycardia which could be a novel strategy for ICDs. In this chapter the first case series of His bundle pacing to terminate ventricular arrhythmias is presented.

In Chapter 6, this thesis tests and investigates a novel algorithm that I have derived, combined with a potentially implantable haemodynamic sensor, namely laser Doppler, to augment the accuracy of arrhythmia detection and the need for therapy to reduce the incidence of potentially harmful *inappropriate* ICDs therapies.

This thesis elucidates the mechanisms by which anti-bradycardia pacing and ventricular tachycardia cause harm; investigates how the novel strategy of His bundle pacing can potentially overcome these; and provides a potential framework by which the next generation of devices could work to enhance the lives of the one million individuals who receive a device each year.

Declaration of originality

I hereby declare that the work presented in this thesis is my own and all else is referenced appropriately

Daniel Keene

Copyright declaration

The copyright of this thesis rests with the author and is made available under a Creative Commons Attribution Non-Commercial No Derivatives license.

Researchers are free to copy, distribute or transmit the thesis on the condition that they attribute it, that they do not use it for commercial purposes and that they do not alter, transform or build upon it. For any reuse or redistribution, researchers must make clear to others the license terms of this work.

Dedication

I dedicate this thesis to my wife Abigail for her constant support, encouragement and patience, our children Rephael, Liora and Amitai who always make me smile and to my parents Miriam and David who have always supported and motivated me throughout my career.

Acknowledgements

I would like to thank my supervisors for their guidance and support: Dr Zachary Whinnett who has encouraged and enthused me from the outset, helping me develop the concepts for this thesis, applying for funding, and for the many involved sessions of data review and manuscript writing. I would also like to thank him for providing invaluable career mentorship and opportunities for career development. Professor Darrel Francis has likewise enthused, encouraged and believed in me to achieve. Without him and his special ability to appraise and communicate data I would not have achieved as much as I have during the time of my PhD and in my career to date.

I am extremely grateful to the excellent research nurses and physiologists who have assisted with data collection, recruitment and troubleshooting, foremost Katherine March, Leah Burden, Nina Davies and Myril Mariveles.

In the cardiac catheter laboratories and in the cardiac rhythm management clinics I have been supported by an outstanding team of cardiac physiologists who have good-naturedly and patiently helped me set up my research equipment and acquire data. These excellent colleagues and friends include: Ian Wright, Elaine Lim, Rob Edwards, Michael Fudge, Michelle Todd, Soraia Almeida and Asha Barnard.

My research fellow colleagues have all helped my research through exchange of ideas, discourse and healthy rebuttal of ideas. I would like to thank Dr Ahran Arnold, Dr James Howard and particularly Dr Matthew Shun-Shin for all their time, patience, effort and encouragement.

I would also like to thank Carol Jones of Medtronic and Berthold Stegemann recently retired from Medtronic, for their support and encouragement particularly relating to providing me with support and resources for establishing His bundle pacing within the UK.

Furthermore, this PhD would not have been possible without the support and fellowship funding from the Imperial Charity and the British Heart Foundation (FS/15/53/31615).

Finally, and most importantly of all, I would like to thank all the patients who have volunteered to act as participants over the course of my degree. They have given of their time to allow me to collect my data and have done this willingly and selflessly.

Table of contents

1	INTRODUCTION	17
1.1	CARDIAC DEVICES: A BRIEF HISTORY	17
1.2	CURRENT CHALLENGES AND POTENTIAL THERAPIES	18
1.2.1	<i>Problems with current pacing landscape.....</i>	18
1.2.2	<i>Problems with the current Implantable Cardioverter Defibrillator landscape.....</i>	35
2	METHODS	44
2.1	INTRODUCTION	44
2.2	MEASUREMENT APPARATUS	44
2.2.1	<i>Non-invasive blood pressures measurement</i>	44
2.2.2	<i>Invasive BP</i>	47
2.2.3	<i>Electrocardiography.....</i>	47
2.2.4	<i>Laser Doppler Perfusion Monitoring.....</i>	47
2.2.5	<i>Implantable Cardiac Devices and Pace-Sense-Analyser/Programmers</i>	50
2.2.6	<i>Customised device to mark transitions of pacing settings.....</i>	50
2.2.7	<i>12-Lead ECG measurements</i>	50
2.3	DATA ACQUISITION SYSTEM FOR HAEMODYNAMIC MEASUREMENTS	50
2.4	ALGORITHM TO MEASURE HAEMODYNAMIC EFFECTS OF DIFFERENT CARDIAC RHYTHMS OR PACING CONFIGURATIONS	51
2.4.1	<i>Analysis software</i>	51
2.4.2	<i>Basis for analysis algorithms</i>	51
2.4.3	<i>Laser Doppler recordings</i>	52
2.4.4	<i>AV delay optimisation assessment</i>	52
2.5	PERFORMING PERMANENT HIS BUNDLE PACING	55
2.5.1	<i>Anatomy of the His Bundle and Implant Technique.....</i>	55
2.5.2	<i>Equipment and Lead Deployment.....</i>	57
2.5.3	<i>Pacing Responses.....</i>	63
2.5.4	<i>My approach to determine pacing response</i>	64
3	RATIONALE, FEASIBILITY, PROCEDURAL AND DEVICE CHARACTERISTICS OF PERMANENT HIS-BUNDLE PACING: 529 PATIENT EXPERIENCE.....	75
3.1	ABSTRACT	76
3.1.1	<i>Introduction</i>	76
3.1.2	<i>Methods.....</i>	76
3.1.3	<i>Results.....</i>	76
3.1.4	<i>Conclusions</i>	77
3.2	INTRODUCTION	79
3.2.1	<i>His bundle pacing: the potential of physiological pacing.....</i>	80
3.2.2	<i>Is His bundle pacing feasible?</i>	80
3.2.3	<i>Aim of Study.....</i>	81
3.3	METHODS.....	82
3.3.1	<i>Study Design</i>	82
3.3.2	<i>Procedural Details.....</i>	82
3.3.3	<i>Clinical outcomes</i>	83
3.4	RESULTS	85
3.4.1	<i>Procedural Characteristics</i>	87
3.4.2	<i>Procedural Success Rates.....</i>	89
3.4.3	<i>Devices, leads and delivery equipment.....</i>	89
3.4.4	<i>Fluoroscopy Time</i>	90
3.4.5	<i>Clinical outcomes</i>	92
3.4.6	<i>Last available Follow Up Thresholds and Programmed Stimulation Outputs.....</i>	97

3.4.7	<i>His Bundle Lead Complications</i>	97
3.4.8	<i>ECG responses</i>	99
3.5	DISCUSSION	102
3.5.1	<i>Implant success rates</i>	102
3.5.2	<i>His Pacing Safety</i>	103
3.5.3	<i>Choice of lead and delivery kit</i>	103
3.5.4	<i>Back-Up Pacing leads</i>	104
3.5.5	<i>Fluoroscopy times are low and show a learning curve</i>	105
3.5.6	<i>Thresholds are low and also show a learning curve.</i>	106
3.5.7	<i>ECG Capture Responses</i>	107
3.5.8	<i>Learning curves</i>	107
3.5.9	<i>Limitations</i>	107
3.6	CONCLUSION	108
4	WITHIN PATIENT COMPARISON OF HIS BUNDLE PACING, RIGHT VENTRICULAR PACING AND RIGHT VENTRICULAR PACING AVOIDANCE ALGORITHMS IN PATIENTS WITH PR PROLONGATION AND A BRADYCARDIA PACING INDICATION: ACUTE HAEMODYNAMIC STUDY	109
4.1	ABSTRACT	110
4.1.1	<i>Introduction</i>	110
4.1.2	<i>Methods</i>	110
4.1.3	<i>Results</i>	110
4.1.4	<i>Conclusions</i>	111
4.2	INTRODUCTION	112
4.2.1	<i>His-bundle pacing allows correction of AV dyssynchrony without inducing ventricular dyssynchrony</i>	113
4.3	METHODS.....	115
4.3.1	<i>His-bundle pacing</i>	115
4.3.2	<i>AV delay optimisation and haemodynamic assessment</i>	115
4.3.3	<i>Pacing Avoidance Algorithm</i>	116
4.3.4	<i>Battery Longevity Assessment</i>	117
4.3.5	<i>Data acquisition and statistical analysis</i>	117
4.4	RESULTS	118
4.4.1	<i>Patients</i>	118
4.4.2	<i>Electrocardiogram Assessment</i>	120
4.4.3	<i>Haemodynamic Assessment</i>	123
4.4.4	<i>Device longevity assessment</i>	128
4.5	DISCUSSION	129
4.5.1	<i>Pacing options in patients with PR interval prolongation and indication for bradycardia pacing</i>	131
4.5.2	<i>Need for a trial</i>	135
4.5.3	<i>Study limitations</i>	136
4.6	CONCLUSIONS.....	138
5	SEPARATING AND QUANTIFYING THE HAEMODYNAMIC HARMFUL COMPONENTS OF VENTRICULAR TACHYCARDIA: THE THERAPEUTIC POTENTIAL, BOTH EXPECTED AND UNEXPECTED	139
5.1	ABSTRACT	140
5.1.1	<i>Background</i>	140
5.1.2	<i>Methods</i>	140
5.1.3	<i>Results</i>	141
5.1.4	<i>Conclusions</i>	142
5.2	INTRODUCTION	143
5.2.1	<i>Potential mechanisms by which VT causes haemodynamic impairment</i>	143
5.2.2	<i>Current Approaches for Device Based Management of VT</i>	145
5.2.3	<i>Pacing interventions to improve cardiac haemodynamics</i>	151
5.2.4	<i>Applicability of a potential new therapy</i>	153
5.3	METHODS.....	155
5.3.1	<i>Patient Population</i>	155
5.3.2	<i>Pacing and Haemodynamic Experiment</i>	155
5.3.3	<i>Data and statistical analysis</i>	161

THE IMPACT OF SIMULATED VT RATE	161
THE POTENTIAL BENEFIT THAT MIGHT BE ACHIEVED THROUGH RESTORATION OF AV AND VV SYNCHRONY	161
5.4 RESULTS	163
5.4.1 Part 1	163
5.4.2 Part 2	173
5.5 DISCUSSION	190
5.5.1 Impact of correcting atrio -ventricular timing	190
5.5.2 Impact of improving ventricular synchrony	191
5.5.3 Future Testing and Application	192
5.5.4 Limitations	193
5.6 CONCLUSIONS	194
6 DEVELOPMENT OF THE ELECTRO-MECHANICAL COUPLING ALGORITHM AND QUANTIFICATION OF ELECTRO-MECHANICAL COUPLING TO PREVENT INAPPROPRIATE IMPLANTABLE CARDIOVERTER DEFIBRILLATOR SHOCKS	195
6.1 ABSTRACT	196
6.1.1 Background	196
6.1.2 Methods	196
6.1.3 Results	197
6.1.4 Conclusions	197
6.2 INTRODUCTION	198
6.2.1 Neither steady state (Running Mean) level nor Oscillatory Height has proved reliable	199
6.3 METHODS	204
6.3.2 Choice of Hemodynamic Sensor	208
6.3.3 Datasets for four conditions per patient	209
6.3.4 Sinus Tachycardia data set	209
6.4 ANALYTICAL ALGORITHM	209
6.4.1 Statistical analysis	227
6.4.2 Study Conduct	228
6.5 RESULTS	229
6.5.1 Patient population	229
6.5.2 Test 1: Confirming onset of VF using continuous Doppler measurement	231
6.5.3 Test 2: Confirming onset of VF without continuous Doppler measurement	234
6.5.4 Test 3: Correct handling of ventricular lead fracture	237
6.5.5 Test 4: Correct handling of Electrogram Double-counting	239
6.5.6 Test 5: Behaviour of algorithms during physical activity	240
6.6 DISCUSSION	243
6.6.1 Limitations	247
6.7 CONCLUSIONS	251
7 SYNTHESIS	252
7.1.1 Future work	254
8 PUBLISHED MANUSCRIPTS FROM THE RESEARCH PERIOD	256
9 APPENDIX:	258
DESIGN OF A MULTICENTRE RCT TO TEST THE ROLE OF AV OPTIMISED HIS BUNDLE PACING FOR CARDIAC RESYNCHRONIZATION FOR HEART FAILURE PATIENTS WITH LONG AV DELAYS AND NARROW COMPLEX QRS	258
9.1 ABSTRACT	259
9.1.1 Introduction	259
9.1.2 Methods	259
9.1.3 Conclusions	260
9.2 INTRODUCTION	261
9.2.1 Prolonged AV delay is pathological in heart failure	261
9.3 PROLONGED AV DELAY CAN BE A TARGET	261
9.3.1 Right Ventricular and Biventricular pacing cause ventricular dyssynchrony in patients with Narrow QRS	262

9.3.2	<i>Evidence that His bundle pacing may be beneficial in heart failure with prolonged AV delay and narrow QRS</i>	266
9.3.3	<i>Aim</i>	266
9.4	METHODS.....	267
9.4.1	<i>Trial Purpose</i>	267
9.4.2	<i>Trial Design</i>	267
9.4.3	<i>Intervention</i>	269
9.4.4	<i>Study Endpoints</i>	274
9.4.5	<i>Endpoint measurements</i>	274
9.4.6	<i>Follow up location</i>	275
9.4.7	<i>Follow up duration</i>	276
9.4.8	<i>Patient flow</i>	276
9.4.9	<i>Randomisation and Allocation Concealment</i>	278
9.4.10	<i>Maintaining blinding during the trial</i>	278
9.4.11	<i>Design of the AV delay haemodynamic optimisation protocol</i>	279
9.4.12	<i>Analysis plan</i>	279
9.4.13	<i>Planned subgroup analysis</i>	280
9.4.14	<i>Sample size calculation</i>	284
9.4.15	<i>Funding</i>	285
9.4.16	<i>Timeline</i>	285
9.5	DISCUSSION AND CONCLUSION	286
10	REFERENCES.....	287

List of tables

TABLE 3-1 BASELINE DEMOGRAPHICS	86
TABLE 3-2 IMPLANT FLUOROSCOPY TIME STRATIFIED BY PROCEDURAL RHYTHM	91
TABLE 3-3 HIS BUNDLE PACING THRESHOLDS, IMPLANT AND FOLLOW UP	98
TABLE 3-4 EFFECT OF HIS BUNDLE PACING ON QRS DURATION	101
TABLE 4-1 PATIENT AND PACING CHARACTERISTICS	119
TABLE 4-2 SUBGROUP DATA ANALYSIS	127
TABLE 5-1 CHARACTERISTICS OF THE 24 PATIENTS INCLUDED IN PART 1	163
TABLE 5-2 CHARACTERISTICS OF THE 11 PATIENTS INCLUDED IN PART 2	174
TABLE 6-1 PATIENT DEMOGRAPHICS AND DEVICE CHARACTERISTICS	230
TABLE 9-1 HOPE HF INCLUSION AND EXCLUSION CRITERIA	268
TABLE 9-2 DIFFERENCES BETWEEN SELECTIVE AND NON-SELECTIVE HIS BUNDLE PACING	273

List of figures

FIGURE 1-1 PROCEDURAL FAILURE RATES OF LV LEAD PLACEMENT	20
FIGURE 1-2 HIS BUNDLE PACING TO REVERSE BUNDLE BRANCH BLOCK	26
FIGURE 1-3 THE EFFECTS OF PACING MODE ON QRS MORPHOLOGY	29
FIGURE 1-4 HIS BUNDLE PACING CORRECTS PR PROLONGATION WITHOUT INDUCING VENTRICULAR DYSSYNCHRONY	32
FIGURE 1-5 EXAMPLE ICD RECORDING SHOWING ATP ACCELERATING VT TO VF.....	37
FIGURE 1-6 EXAMPLE ICD RECORDING SHOWING T-WAVE OVERSENSING	40
FIGURE 2-1 USE OF THE FINOMETER DEVICE	46
FIGURE 2-2 PRINCIPALS OF LASER DOPPLER PERFUSION MONITORING	49
FIGURE 2-3 APPROACH FOR AV DELAY OPTIMISATION	54
FIGURE 2-4 HIS BUNDLE ANATOMY AND PACING APPROACH	56
FIGURE 2-5 THE MEDTRONIC SELECT SECURE 3830 PACING LEAD (USED FOR HIS BUNDLE PACING)	58
FIGURE 2-6 THE C315 HIS CATHETER	58
FIGURE 2-7 UNIPOLAR MAPPING APPROACH FOR HIS BUNDLE PACING	60
FIGURE 2-8 HIS BUNDLE ELECTROGRAM MAPPING APPROACH	62
FIGURE 2-9 BASELINE MEASUREMENTS TO MAKE WHEN A HIS SIGNAL IS LOCATED	65
FIGURE 2-10 HALLMARKS OF SELECTIVE HIS BUNDLE PACING.....	68
FIGURE 2-11 HALLMARKS OF NON-SELECTIVE HIS BUNDLE PACING	70
FIGURE 2-12 DIFFERENCES IN CARDIAC ACTIVATION BETWEEN SELECTIVE AND NON-SELECTIVE HIS BUNDLE PACING	72
FIGURE 2-13 CARTOON SHOWING THE VARIOUS HIS ANATOMICAL VARIATIONS AND THE EFFECT ON PACING RESPONSE WITH VARYING PACING OUTPUTS.....	74
FIGURE 3-1 PRIMARY REASON FOR PACING	88
FIGURE 3-2 WITHIN PATIENT CHANGE IN THRESHOLDS FOR DIFFERENT PACING RESPONSES	93
FIGURE 3-3 HIS BUNDLE PACING LEARNING CURVE METRICS	96
FIGURE 3-4 THE EFFECT OF HIS BUNDLE PACING ON QRS DURATION	100
FIGURE 4-1 12 LEAD ECG EXAMPLES FOR THE THREE PACING MODES FOR AN INDIVIDUAL PATIENT.....	122
FIGURE 4-2 SUMMARY HAEMODYNAMIC DATA	124
FIGURE 4-3 INDIVIDUAL PATIENT HAEMODYNAMIC DATA	125
FIGURE 4-4 POTENTIAL MECHANISM OF BENEFIT WITH AV DELAY OPTIMISATION.....	134
FIGURE 5-1 THE PRINCIPLES UNDERLYING PACING TERMINATION OF RE-ENTRY ARRHYTHMIAS	147
FIGURE 5-2 PRINCIPLES OF " <i>PEELING BACK REFRACTORINESS</i> " FOR SUCCESSFUL VT TERMINATION.....	150
FIGURE 5-3 EXAMPLE OF A PACING CREATED SCENARIO.....	159
FIGURE 5-4 EXAMPLE TRACES SHOWING THE ASSESSMENT OF CHANGE IN SIMULATED VT RATE.....	164
FIGURE 5-5 EXAMPLE TRACE SHOWING THE MECHANISTIC EFFECT OF TRANSITIONING FROM ASYNCHRONOUS VVI PACING AT 125 BPM TO DELIVERING BI-VENTRICULAR SYNCHRONY WITH THE ADDITION OF HIS BUNDLE PACING AT THE SAME RATE.....	165
FIGURE 5-6 IMPACT OF VT RATE ON HAEMODYNAMICS.....	167
FIGURE 5-7 IMPACT OF THE VARIOUS MECHANISMS OF HARM IN VT AT 125BPM.....	169
FIGURE 5-8 IMPACT OF THE VARIOUS MECHANISMS OF HARM IN VT AT 160BPM.....	171
FIGURE 5-9 PATIENT FLOW CHART FOR PART 2.....	175
FIGURE 5-10 EFFECT OF HIS BUNDLE PACING ON ACUTE HAEMODYNAMICS DURING VT	178
FIGURE 5-11 AN EXAMPLE TRACE SHOWING HIS BUNDLE PACING DURING VT AND AN IMPROVEMENT IN SYSTOLIC BLOOD PRESSURE	179
FIGURE 5-12 EXAMPLE TRACE SHOWING HIS BUNDLE PACING DURING VT	180
FIGURE 5-13 EXAMPLE TRACE SHOWING HIS PACING DURING VT.....	181
FIGURE 5-14 EXAMPLE TRACE SHOWING TERMINATION OF VT WITH 15 BEATS OF HIS BUNDLE PACING DELIVERED AT 91% OF THE TACHYCARDIA CYCLE LENGTH	182
FIGURE 5-15 EXAMPLE TRACES OF HIS BUNDLE PACING TERMINATING VT FROM TWO PATIENTS, PATIENT A AND PATIENT B	183
FIGURE 5-16 UTILISATION OF A SINGLE SENSED HIS PACED EXTRA TO TERMINATE VT	184
FIGURE 5-17 EFFECT OF ISOLATED ATRIAL PACING ON ACUTE HAEMODYNAMICS DURING VT	186
FIGURE 5-18 EXAMPLE TRACE SHOWING THE EFFECT OF ATRIAL PACING ON VT	187
FIGURE 5-19 AN EXAMPLE TRACE SHOWING ATRIAL PACING DURING VT	188
FIGURE 5-20 EFFECT OF AV RELATIONSHIP ON HAEMODYNAMICS IN VT	189
FIGURE 6-1 BASELINE VARIABILITY OF LDPM SIGNALS.....	200
FIGURE 6-2 OSCILLATORY HEIGHT MEASUREMENTS ARE SUBJECT TO ARTEFACT	202
FIGURE 6-3 METHODOLOGICAL APPROACH FOR DATA ACQUISITION.....	205
FIGURE 6-4 DATA SAMPLING WINDOWS	207

FIGURE 6-5 ISSUES WITH A RUNNING MEAN BASED ASSESSMENT	211
FIGURE 6-6 THE IMPORTANCE OF OSCILLATORY HEIGHT TO SIGNAL INTERPRETATION.....	213
FIGURE 6-7 FALL IN SIGNAL OSCILLATORY HEIGHT DURING VF	214
FIGURE 6-8 THE ELECTRO - MECHANICAL COUPLING ALGORITHM	216
FIGURE 6-9 THE ELECTRO - MECHANICAL COUPLING ALGORITHM DURING VF	218
FIGURE 6-10 ANALYTICAL ALGORITHMS ISSUES (1)	220
FIGURE 6-11 ANALYTICAL ALGORITHMS ISSUES (2)	221
FIGURE 6-12 EXAMPLE OF THE ELECTRO - MECHANICAL COUPLING ALGORITHM IN AF	223
FIGURE 6-13 THE ELECTRO - MECHANICAL COUPLING ANALYTICAL APPROACH	226
FIGURE 6-14 DISCRIMINATIVE CAPABILITY OF LASER DOPPLER TO DIFFERENTIATE SINUS RHYTHM FROM VF.....	233
FIGURE 6-15 RECEIVER OPERATOR CHARACTERISTICS FOR THE DIFFERENT ANALYTICAL METHODS	235
FIGURE 6-16 EXAMPLES OF FAILURE OF OSCILLATORY HEIGHT AND RUNNING MEAN	236
FIGURE 6-17 CUT OFF THRESHOLDS FOR THE ANALYTICAL APPROACHES.....	238
FIGURE 6-18 THE ELECTRO-MECHANICAL COUPLING APPROACH IN SITUATIONS WHERE INAPPROPRIATE THERAPIES MAY OTHERWISE RESULT.	242
FIGURE 6-19 PILOT DATA OF SIGNALS ACQUIRED FROM MATURE DEVICE POCKET.	246
FIGURE 6-20 HEART RATE ALONE IS NOT AN ADEQUATE DISCRIMINATOR FOR HAEMODYNAMIC HARM	249
FIGURE 9-1 POTENTIAL PACING METHODS FOR ATRIOVENTRICULAR (AV) DELAY OPTIMISATION.....	265
FIGURE 9-3 DIFFERENCES BETWEEN SELECTIVE AND NON-SELECTIVE HIS BUNDLE PACING.	271
FIGURE 9-4 HOPE HF STUDY FLOW DIAGRAM.....	277
FIGURE 9-5 POTENTIAL MECHANISMS FOR RBBB REVERSAL.....	282

1 Introduction

1.1 Cardiac Devices: A Brief History

The first fully implantable cardiac pacemaker was inserted in Sweden on October 8th, 1958 as a treatment for recurrent Stokes-Adam Attacks (Aquilina 2006). This involved an approach that was revolutionary at the time, utilizing epicardial leads and an abdominally placed implantable pulse generator that delivered fixed output pacing at a fixed rate. Since that time developments have been ongoing to improve the field of implantable cardiac rhythm management devices.

These improvements have included: transition to transvenous endocardial pacing routes, improvements in battery technology, lead technology, device miniaturization and the development of advanced algorithms which in the most basic form allowed the delivery of demand pacing rather than fixed rate asynchronous pacing.

Implantable cardiac rhythm management diversified, going beyond simply providing ventricular stimulation to treat bradycardia. In 1980 Mirowski introduced the revolutionary implantable defibrillator which for the first time allowed ventricular tachy arrhythmias to be treated too (Mirowski et al. 1980). This field has had a multitude of developments in its short history including the emergence of anti-tachycardia pacing (ATP) as a means of attempting to terminate ventricular tachycardia in a painless manner, thus avoiding cardiac defibrillation.

More recently biventricular pacing which was first reported in 1994 by Cazeau and colleagues in France (Cazeau et al. 1994) has been utilised to deliver pacing not necessarily as a means to treat bradycardia but rather to improve cardiac chamber coordination and thus cardiac function. Biventricular pacing has been shown to be effective at improving cardiovascular outcomes, however there remains scope for improvement and the population that this benefit extends to is limited. The patients in whom benefit has been seen is those with heart failure symptoms, impaired ventricular

function and broad QRS predominately with a LBBB morphology. Major advances in this field to date have included the transition from bipolar to quadripolar leads and algorithms that aim to maximize the time spent biventricular pacing.

Biventricular pacing has also been considered as a more advantageous means to provide pacing therapy for bradycardia indicated patients for those with high pacing burdens rather than the standard pacing sites in the right ventricle (Curtis et al. 2013). The proposed mechanism underlying this approach is that biventricular pacing avoids or at least reduces the adverse effects of right ventricular pacing on cardiac mechanical function.

Over the 60 years since the first devices were implanted for the sickest patients, indications for cardiac implantable rhythm management devices have increased and more patients are able to benefit from this field of technology. Device improvements and developments remain ongoing as there still remains a number of unmet needs.

This thesis intends to explore a number of these needs and test possible novel solutions.

1.2 Current Challenges and Potential Therapies

1.2.1 Problems with current pacing landscape

1.2.1.1 *Difficulties with introducing novel pacing approaches*

Right Ventricular Pacing

The first report of cardiac pacing from the UK by Sutton and colleagues involved 53 patients with complete heart block and Stokes-Adams attacks. The survival in this group after five years was ~50% which at the time was regarded as high. These patients suffered with a range of device related complications including lead fractures, unpredictable stimulation threshold rises, generator failure and high infection rates. Potential explanation for these complications could relate to the rudimentary technology being used, the fact physicians were performing a novel procedure without a global

experience to draw from, and the implant procedures being performed in non-dedicated pacing environments. These complications meant most patients spent more than 6 months of the subsequent 5 year follow up period as inpatients having treatments for infections, lead displacements and revisions. (Sutton 2018)

We have progressed beyond these difficulties such that right ventricular pacing is now often regarded as standard of care for patients with a bradycardia indication as it is a safe procedure with near 100% successful device implantation and excellent long-term safety data (Kirkfeldt et al. 2014). Nevertheless, the journey to get to this point should not be forgotten.

Biventricular Pacing

There was a similar iterative progress of improvement, albeit quicker, when biventricular pacing was first introduced into clinical practice, this is demonstrated in Figure 1-1.

High procedural failure rates, long procedural times, lead displacements and capture issues were common (Gamble et al. 2016).

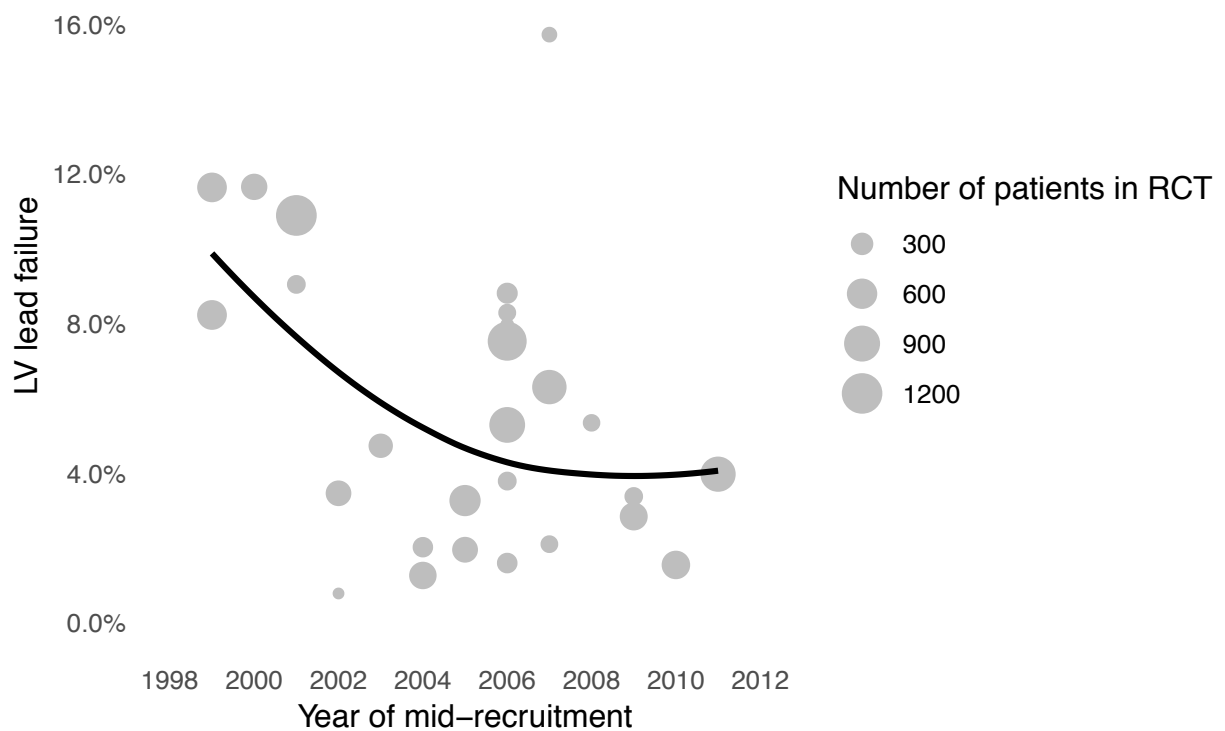


Figure 1-1 Procedural failure rates of LV lead placement

This figure shows the procedural failure rates of LV lead placement reported in RCTs recruiting more than 100 patients. Improvement is made over time but the first RCTs faced a failure rate of 12%. (Other studies [not shown in this graph] despite reporting >10 years after the first LV lead reports still show failure rates of up to 18 percent (Higgins et al. 2003; Doshi et al. 2005)

The physiological promise of this technique meant that the initial issues associated with the procedure were deemed acceptable. Over time this has improved (Schuchert et al. 2013; Gamble et al. 2016). This may be due to superior physician experience and also the development of a wide range of implant tools and techniques from the competing device manufacturers. Even still, in the modern era device related complications occur more frequently with biventricular pacing than with RV pacing (Poole et al. 2010; Kirkfeldt et al. 2014) but due to its physiological benefits this is accepted.

Innovation in pacing often involves iterative revision to maximise the benefits and minimise the risks of the new procedure. Past experience has shown that early difficulties should be expected, and innovation can be worthwhile even though the maximum benefit is to future patients who undergo the most refined procedures.

His bundle pacing

Permanent His bundle pacing can provide physiological ventricular activation by stimulating the His-Purkinje system. This may well represent a physiological advantage over right ventricular and even biventricular pacing for both bradycardia and heart failure indicated patients.

Although right ventricular pacing clearly saves lives in the short term, it can, in some lead to left ventricular impairment in the longer term (Manolis 2006), increasing the rate of heart failure and death as demonstrated famously in two trials.

The MOST trial found that in patients with normal ventricular function and a bradycardia indication for pacing, that right ventricular pacing increased heart failure hospitalizations (HR 1.37; 95% CI 1.05– 1.79; P=0.02). Most startling was the observation that every 10% increase in RV pacing, was associated with a 20% increase in these admissions (Lamas et al. 2002).

Even more dramatic was the DAVID trial. This showed that RV pacing in patients with left ventricular impairment dramatically increased heart failure and death from 16.1% to 26.7% (HR 1.61; 95% CI 1.06-2.44; $P < 0.03$) (Wilkoff et al. 2002).

Alternate strategies to RV apical pacing were therefore proposed.

One proposal was to limit the amount of ventricular pacing using pacing avoidance algorithms in order to limit the harm. However, meta-analysis of this strategy in 4119 patients shows no clinical advantage (Shurrab et al. 2017). In part this approach is not of value in those with high grade AV block as they still will pace the ventricle a high proportion of the time. Furthermore, in those with prolonged PR intervals (but not permanent high-grade AV block), although ventricular dyssynchrony is not induced by RV pacing, AV dyssynchrony remains which may well be of equal (or greater) harm than the ventricular dyssynchrony that is avoided.

A second solution was biventricular pacing.

Biventricular pacing in patients with severe left ventricular dysfunction where the alternative cardiac activation pattern was either from broad intrinsic LBBB (Cleland et al. 2013) or right ventricular pacing (Curtis et al. 2013) has been shown to reduce death and heart failure hospitalizations in RCTs. However in patients with an intrinsic narrow QRS, biventricular pacing is a less than ideal solution as it induces ventricular dyssynchrony (Ploux et al. 2015) which may explain why it increased mortality in patients with heart failure who do not have a broad QRS as seen for example most famously in the ECHO-CRT trial (Ruschitzka et al. 2013).

Moreover, in a patient population without severe left ventricular systolic dysfunction (mean EF 55%) i.e. people with relatively normal LV function and a bradycardia pacing indication, the BIOPACE trial of biventricular pacing showed no advantage over the alternative of RV pacing (Beck and Curtis 2016).

1.2.1.2 A novel approach: His bundle pacing offers physiological ventricular activation

His bundle pacing activates the ventricles via their natural conduction system. This approach means bradycardia can be treated whilst maintaining normal physiological ventricular activation (Catanzariti et al. 2006). This has not been achieved by any other pacing approach to date.

The first report of permanent His bundle pacing was in 2000, this ground-breaking study demonstrated the feasibility of permanent His bundle pacing (Deshmukh et al. 2000). It is worth noting in this first report implant success was only 66%, with high thresholds ($2.4 \pm 1.0V$ at 0.5ms) and long procedural times.

Implant success rates are currently reported to be in the region of 80-92% (Vijayaraman, Naperkowski, et al. 2017; Sharma et al. 2017; Ajijola et al. 2017; Sharma et al. 2015; Abdelrahman et al. 2018) but this data comes from small numbers of patients in just a few centres.

Short term physiological studies have found improved electrical activation of the ventricles with His bundle pacing. This has corresponded with improved cardiac function, compared with right ventricular pacing (Catanzariti et al. 2006; Deshmukh et al. 2000; Kronborg et al. 2014; Barba-Pichardo et al. 2013; Occhetta et al. 2006; Zanon et al. 2008; Barba-Pichardo et al. 2010; Yu et al. 2017; Zanon et al. 2018).

1.2.1.3 His Pacing for bradycardia

His bundle pacing to facilitate AV node ablation

The first report of permanent His bundle pacing was in a group of 18 patients who received AV node ablation to allow rate control of atrial fibrillation (Deshmukh et al. 2000). All patients had pre-existing impairment of left ventricular function. Despite not having dedicated implant tools, permanent His bundle pacing could be achieved in 66%

of patients. Pacing thresholds remained stable over the follow up period and encouragingly left ventricular function improved even with chronic ventricular pacing activation.

His bundle pacing to treat bradycardia due to conduction system disease

The observation that His bundle pacing is feasible following AV node ablation was an important step forward. For more distal disease, however, there were initial concerns about whether His pacing would provide reliable capture. Encouragingly a number of observational studies have demonstrated that His pacing seems to be feasible in this population of patients, including patients with permanent complete heart block (Sharma et al. 2015; Vijayaraman, Naperkowski, et al. 2017; Abdelrahman et al. 2018).

In a recently published long-term observational study of patients with a bradycardia indication for pacing, 304 patients (92% of those attempted) received His pacing and were compared to 433 patients who received right ventricular pacing. During mean follow-up of 725 ± 423 days His pacing was found to be reliable. It was noted that pacing thresholds were higher in the His pacing group, $1.30 \pm 0.85V$ at $0.79 \pm 0.26ms$ vs $0.59 \pm 0.42V$ @ $0.5 \pm 0.03ms$; $P < 0.01$ and the sensed R wave was also lower in the His pacing group, but this did not appear to result in significant clinical consequences.

This observational comparison showed that the His pacing group experienced significantly lower death, heart-failure hospitalizations or a need to upgrade to biventricular pacing compared to the right ventricular pacing group (25% vs 31.6%, $p=0.02$), this difference was most pronounced in patients who had a higher burden ($>20\%$) of ventricular pacing (25.3% vs 35.6% $p 0.02$). (Abdelrahman et al. 2018)

1.2.1.4 His Cardiac Resynchronization Therapy in patients with Bundle Branch Block

Biventricular pacing is proven to reduce morbidity and mortality when delivered to patients with impaired left ventricular systolic function and left bundle branch block

(Cleland et al. 2005; Cleland et al. 2013; Moss et al. 2009). However, despite treatment, symptom burden and mortality rates remain high (Cleland et al. 2005; Cleland et al. 2013; Moss et al. 2009).

Biventricular pacing delivers imperfect ventricular resynchronization, with only modest reductions in QRS duration and ventricular activation time in patients with left bundle branch block (Ploux et al. 2015). More effective ventricular resynchronization has the potential to deliver additional improvements in cardiac function, over and above those seen with current biventricular pacing (Jones et al. 2017).

His bundle pacing shows promise as an alternative method for delivering ventricular resynchronisation therapy. In patients with bundle branch block His pacing may overcome the branch block and result in normalization of ventricular activation time and pattern (Teng, Massoud, et al. 2016; Teng, Lustgarten, et al. 2016; Arnold et al. 2018).

There are several hypotheses for how His bundle pacing can overcome bundle branch block. The simplest is that bundle branch block often occurs as a result of fascicular conduction block or delay within the His bundle. Which can be overcome by positioning the pacing lead distal to the site of block and thus permitting electrical bypass and reversal of the block. Figure 1-2

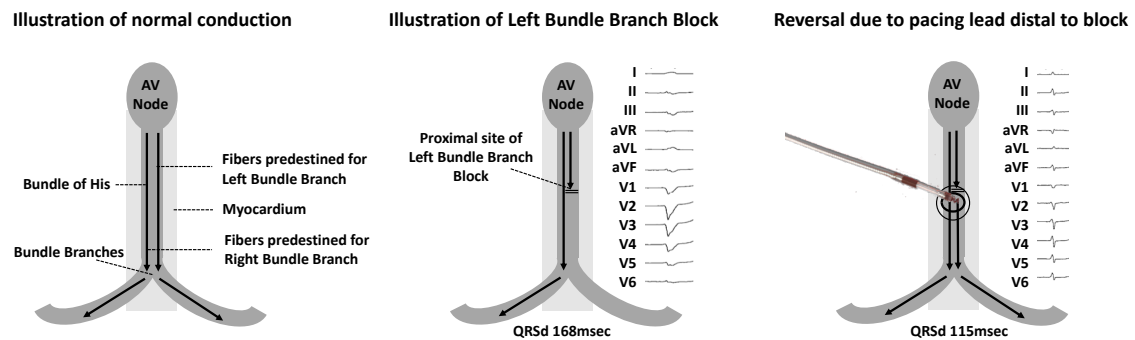


Figure 1-2 His bundle pacing to reverse Bundle Branch Block

His bundle pacing is frequently able to overcome bundle branch block. Multiple hypotheses have been proposed, the simplest (shown here) is that the His lead is placed distal to the site of the block, thereby allowing it to achieve capture of both the left and right bundle branches.

Dramatic improvements in QRS duration have been observed in 70- 90% of patients with bundle branch block (Ajijola et al. 2017; Sharma et al. 2017; Lustgarten et al. 2015). In a recently published study QRS duration was reduced from $157\pm 33\text{ms}$ to $117\pm 18\text{ms}$ (Sharma et al. 2017). In these observational studies improvements in left ventricular ejection fraction and symptoms were observed.

In the study by Sharma et al His pacing was attempted as an alternative to BiV pacing, either when the operator failed to insert an LV lead, if the patient was felt to be a non-responder to biventricular pacing or in patients with AV block, bundle branch block, or with an existing high ventricular pacing burden. During mean follow-up of 14 months, significant narrowing of QRS was observed and this was associated with an increase in left ventricular ejection fraction from $30\% \pm 10\%$ to $43\% \pm 13\%$ ($P = 0.0001$), and improvement in NYHA functional class from 2.8 ± 0.5 to 1.8 ± 0.6 ($P = 0.0001$) with His pacing. (Sharma et al. 2017)

In another study, patients with class 1 indications for CRT received a His lead rather than a biventricular pacing system. Of the 21 patients in whom implantation was attempted, His bundle pacing was successfully implanted in 16. A significant reduction in mean QRS was observed, with narrowing from $180 \pm 23 \text{ ms}$ to $129 \pm 13 \text{ ms}$ ($P < 0.0001$). During the follow-up period, median NYHA functional class improved from III to II ($P < 0.001$), and mean LVEF and LV internal dimensions in diastole improved from $27\% \pm 10\%$ to $41\% \pm 13\%$ ($P < 0.001$) and from $5.4 \pm 0.4 \text{ cm}$ to $4.5 \pm 0.3 \text{ cm}$ ($P < 0.001$) (Ajijola et al. 2017).

These findings support the notion that His-Resynchronisation therapy may be an alternative method for delivering ventricular resynchronisation.

His pacing has the advantages that contrast is not required during the procedure, phrenic nerve stimulation does not occur, and implantation is not limited by the constraints of the coronary sinus anatomy.

1.2.1.5 Is His bundle pacing feasible for mainstream adoption?

Observational studies have demonstrated the feasibility of His bundle pacing. However, published data to date comes from a limited number of centres and there have been concerns about whether with current technology it is feasible for His bundle pacing to be adopted more widely.

In Chapter 3 I assess contemporary global practice in His bundle pacing focusing particularly on length of learning curve, procedural characteristics and clinical outcomes.

1.2.1.6 The challenge of Prolonged PR interval, a new target for pacing therapy for heart failure?

PR prolongation is associated with adverse outcomes, this has been observed both in observational studies in people with ischemic heart disease (Crisel et al. 2011) and patients with heart failure (Stockburger et al. 2016; Salden et al. 2017). In the MADIT-CRT trial, non-LBBB patients in the control group had a threefold higher risk of death or heart failure if their PR interval was prolonged (Stockburger et al. 2016).

Acute studies have shown that improving left ventricular filling by shortening AV delay improves acute cardiac function, as reflected by changes in LV dP/dt_{max} , stroke volume, coronary artery flow and systolic blood pressure (Nishimura et al. 1995; Kyriacou et al. 2012; Whinnett et al. 2013; Z I Whinnett et al. 2006). Indeed much of the beneficial effect of biventricular pacing appears to be delivered through improvements in ventricular filling occurring as a result of shortening a pathologically long left sided mechanical atrioventricular delay. (Jones et al. 2017)

A prolonged PR interval may therefore represent an alternative target for pacing therapy for heart failure. Shortening prolonged PR intervals with pacing is a well-established concept, however, when delivered to patients with a normal QRS duration both right ventricular and biventricular pacing result in non-physiological ventricular activation

and ventricular dyssynchrony. This is likely to offset some of the beneficial effects obtained through shortening of AV delay optimisation. (Figure 1-3 demonstrates this)

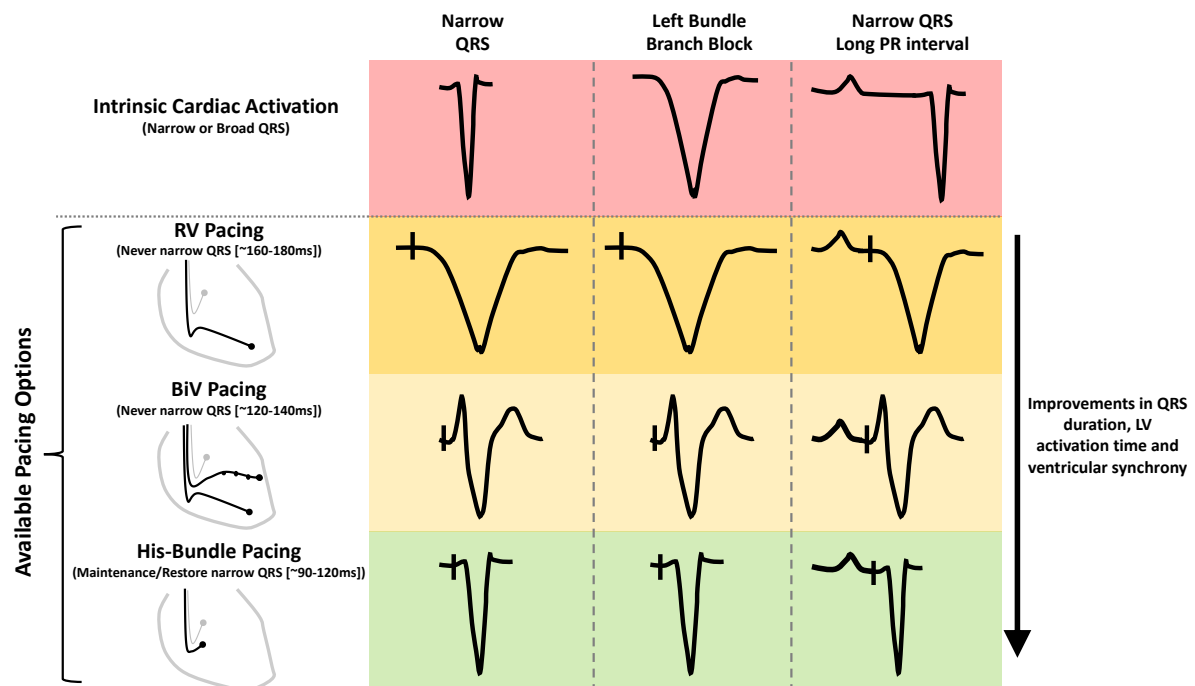


Figure 1-3 The effects of pacing mode on QRS morphology

Redrawn from my publication (Keene, Shun-Shin, et al. 2018)

His bundle pacing is able to provide physiological ventricular activation in patients with narrow QRS or left bundle branch block.

In patients with a long PR interval and narrow QRS, His bundle pacing allows correction of the AV delay without inducing ventricular dyssynchrony.

His pacing, allows AV delay to be shortened without introducing ventricular dyssynchrony (Arnold et al. 2017). AV delay optimisation delivered with His bundle pacing to patients with a prolonged PR interval, a normal QRS or RBBB and heart failure resulted in acute haemodynamic improvements (Sohaib et al. 2015).

Currently the longer term effects of AV optimised His pacing in this population of patients are being investigated in the HOPE-HF trial (Keene, Arnold, et al. 2018). The study design and rationale for this study is detailed within the appendix of this thesis.

PR prolongation and Bradycardia Pacing Indications

In patients who have intermittent higher degree conduction block and a long PR interval there are two major considerations when selecting a pacing strategy. A prolonged PR interval compromises cardiac function (Nishimura et al. 1995) and shortening pathologically prolonged PR intervals has the potential to improve cardiac function. However utilizing right ventricular pacing to shorten prolonged PR intervals can bring its own problems, namely ventricular dyssynchrony which itself compromises cardiac function, increases AF (Sweeney et al. 2007) and increases mortality (Wilkoff et al. 2002). Therefore, in patients with only intermittent bradycardia it is currently common practice (Brignole et al. 2013) to minimize ventricular pacing in order to utilize biological ventricular activation wherever possible.

In many patients with a long PR interval and an intermittent ventricular pacing requirement due to higher degree conduction block, we are therefore faced with the choice of continuous right ventricular pacing (which causes undesirable ventricular dyssynchrony) or taking steps to minimize ventricular pacing (which leaves the patient with undesirable Atrio-Ventricular (AV) dyssynchrony). Results of trials comparing these strategies suggest that the two undesirable desynchronies are of approximately

equal size so that outcomes are the same with both options (Maurer 2003; Shurrab et al. 2017).

His-bundle pacing though provides a potential alternative to the two established pacing strategies. By directly stimulating the His-bundle, normal physiological ventricular activation via the conduction system can be maintained in patients with intrinsic narrow QRS (Catanzariti et al. 2006). Therefore, His-bundle pacing can allow AV delay to be shortened without causing ventricular dyssynchrony as shown in Figure 1-4.

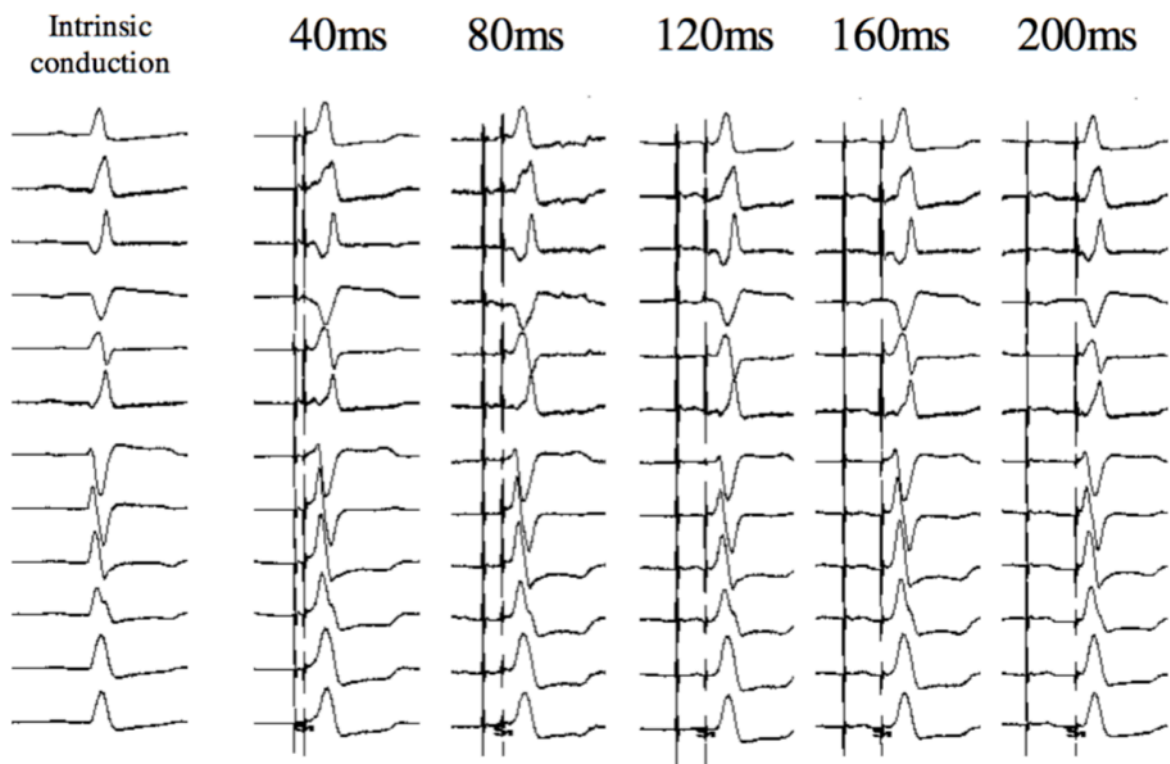


Figure 1-4 His bundle pacing corrects PR prolongation without inducing ventricular dyssynchrony

Here a prolonged intrinsic PR interval can be seen, however utilising dual chamber His bundle pacing a range of programmed AV delays can be programmed which allows for an optimal AV delay setting to be derived and set. Note that the QRS complex and ventricular activation remains unchanged compared to intrinsic activation with His bundle pacing.

In Chapter 4, a group of patients with long PR intervals, who had a bradycardia indication for pacing in whom both a His lead and RV lead were implanted are studied. High precision acute haemodynamic within-patient comparison is performed between: (a) His-bundle pacing to normalize PR interval, (b) RV pacing to normalize PR interval and (c) ventricular pacing-avoidance algorithms. The device energy utilization and effect on predicted battery longevity between the different pacing strategies is also investigated.

1.2.1.7 Conduction system pacing; future directions – Left Bundle Pacing

His bundle pacing is one approach when seeking to deliver physiological pacing and might resemble a physiological ideal if feasibility can be demonstrated (stable and low capture thresholds for pacing and bundle-branch reversal, acceptable sensing and with long-term stability).

However, it is possible that inducing fusion by combining His bundle pacing activation together with activation via a pacing lead within the coronary sinus in the case of LBBB or in the right ventricle in the case of RBBB may provide the most effective approach to narrow QRS complexes, this is a concept termed *Hot CRT* [*His optimised CRT*] (Vijayaraman et al. 2019). This approach may be useful in the future pursuit of physiological pacing but requires further study and testing particularly as the approach requires additional pacing leads to be sited which is not without risk and current implantable generators are also not able to readily accommodate the 4 leads which may be required (RA, RV defibrillator lead, LV lead and His lead).

Furthermore, it is also possible that pacing at alternate sites within the conduction system, namely at the left bundle or in close proximity to it, may provide an alternate approach to provide conduction system pacing, and this too is already being explored. Exploration of pacing at alternate sites within the conduction system may have been prompted due to difficulties encountered from the His location overcoming conduction block (perhaps because block is too distal in location) or due to issues relating to sensing which are not helped by the lack of dedicated device algorithms and high thresholds which with current device battery technology may mean some patients need earlier generator changes.

The first case report of left bundle pacing was published in 2017 by Huang et al. (Huang et al. 2017) The case presented is of a patient with LBBB and left ventricular impairment in whom the operators could not successfully deploy an LV lead via the coronary sinus and although they could achieve His bundle capture, this could not shorten or reverse the LBBB. As such a pacing lead was deployed through the inter-ventricular septum at a site more distal along the conduction system than the His bundle and pacing was performed from a site where a left bundle potential was observed. This allowed capture of the left bundle at a site presumed distal to the site of the block with resultant shortening of the QRS and improvement in patient symptoms were reported.

Hou and colleagues this year presented their observational experiences of left bundle pacing compared to His bundle pacing. They demonstrated larger R waves and lower thresholds with left bundle pacing than with His pacing, but they did observe longer QRS durations with left bundle pacing than with His pacing. It is worth noting that although longer QRS durations were noted when compared to His pacing this was still far shorter for left bundle pacing when compared with right ventricular septal pacing. (Hou et al. 2019)

There is very limited published data on the long-term safety of this approach which needs to be considered as this approach can induce a (partial) right bundle branch block type morphology which could be detrimental and there is a risk of perforation into the LV cavity which could be harmful particularly as this may not be readily apparent.

For the delivery of conduction system pacing in the future it is conceivable that a hierarchical approach may be utilised that includes His bundle pacing as the physiological ideal and transitions to Hot CRT if required to more adequately reverse bundle branch block or to left bundle branch pacing to deliver pacing at a site more distal along the conduction system if the His site is seemingly too proximal to conduction system block or if thresholds are too high or R waves too low.

1.2.2 Problems with the current Implantable Cardioverter Defibrillator landscape

1.2.2.1 ICDs save lives

Implantable Cardioverter Defibrillators (ICDs) are established as an important treatment for patients at increased risk of sudden cardiac death due to ventricular arrhythmias and have well-established mortality benefits (Moss et al. 2002; Bardy et al. 2005). ICDs currently have two methods for attempting to end ventricular arrhythmias. Firstly, they can deliver shocks. Secondly, they can deliver ATP if the rhythm is ventricular tachycardia. ATP was a significant advance for ICDs as this treatment can treat ventricular arrhythmias in a painless way often without the patient being aware which is not only psychologically beneficial but furthermore can avoid shock therapies with potential resultant pathophysiological benefit too. While ATP and defibrillation frequently do restore sinus rhythm when acutely required, we now know they can also be potentially harmful both acutely and in the longer term too (Scott et al. 2014; Gasparini et al. 2013; Moss et al. 2012).

1.2.2.2 Adverse effects of ICD therapy

Morbidity and Mortality: Both ATP and shocks are associated with increased mortality and increased hospitalizations (Gasparini et al. 2013; Moss et al. 2012; Scott et al. 2014). Programming a longer detection window leads to fewer treatments. A meta-analysis of randomised controlled trials, which included 4896 patients, found that delaying the delivery of ICD treatments, compared to conventional short detection windows, reduced shocks by 50% and was associated with a 25% reduction in all-cause mortality (Scott et al. 2014).

Quality of Life (QOL): Shocks reduce QOL (Schron et al. 2002; Mark et al. 2008), increase anxiety, distress and depression (Schron et al. 2002; Dougherty 1995; Namerow et al. 1999; McCready and Exner n.d.) and can even cause post-traumatic stress disorder (Ladwig et al. 2008). In turn, anxiety and depression have the potential to adversely affect cardiac function. They activate the hypothalamus-pituitary-adrenal axis, which increases sympathetic activity and decreases vagal tone. This may result in worsening cardiac function, malignant ventricular arrhythmias and even induction of cardiac ischaemia (Cevik et al. 2009; Kop et al. 2002; Whang et al. 2005). These mechanisms may be an important factor in the increased mortality which is observed in patients with heart failure who suffer with depression (Cassano and Fava 2002; Moussavi et al. 2007).

Harmful effects of Anti-Tachycardia Pacing (ATP): ATP was designed to result in painless termination of ventricular tachycardia. However, it is not always successful and may actually accelerate tachycardia (even benign SVTs) into faster, more unstable rhythms including ventricular fibrillation (Grimm et al. 1993) [Figure 1-5]. This has been observed to occur in up to 8.5% of ATP deliveries (Schukro et al. 2013). Tachycardia acceleration can cause haemodynamic instability, syncope and shock delivery.

In an 1170 patient registry, accelerated tachyarrhythmias were found to be independently associated with higher all-cause mortality (HR 1.76; 95% CI 1.29-2.41; $p < 0.001$) (Schukro et al. 2013). Perhaps surprisingly the majority of non-fatal syncope occurred not from primary VT or VF but from ATP mediated acceleration of a tachycardia which may or may not be VT (Grimm et al. 1993). Even when it does not accelerate the tachycardia, ATP is associated with higher all-cause mortality. (Moss et al. 2002)

Shocks cause myocardial damage: At an observational level, patients with ICDs who receive shocks, both appropriate (potentially lifesaving, particularly in the short-term) and inappropriate, have a worse prognosis than those who do not receive shocks (Bardy et al. 2005; Moss et al. 2002). However, this does not tell us the shocks themselves are harmful since there may be some underlying pathology that causes the harm and the shocks in parallel.

The unfortunate Medtronic Sprint Fidelis lead fracture saga provides a window though into the direction of causation. The lead fractures caused inappropriate shocks, and these were found to result in rises in troponin levels. The troponin rises were proportional to the number of shocks received (Sham'a et al. 2014). Furthermore, reductions in cardiac index have been observed following defibrillation threshold testing in patients with LVEF $< 30\%$ (Steinbeck et al. 1994) and data from humans and animal models provides evidence that shocks produce histological evidence of cellular damage (Wilson et al. 1988; Epstein et al. 1998; Tung et al. 1994; Singer et al. 1987).

Furthermore, it is apparent that the most common cause of death among patients who have received an ICD shock is progressive heart failure (Poole et al. 2008). There are many possible mechanisms: Shocks cause endocardial fibrosis and increased permeability of the cellular membrane allowing calcium overload with resultant cellular hyper-contraction and cell necrosis. In parallel, cell death can be mediated by a catecholamine surge after receipt of a shock (Tung et al. 1994; Sham'a et al. 2014; Epstein

et al. 1998). Moreover, fibrosis increases defibrillation thresholds which means that subsequent shocks are less likely to be successful. Fibrotic areas can also facilitate further arrhythmias as they may produce re-entry circuits (Singer et al. 1987).

Inappropriate Therapies: In MADIT II almost 1 / 3 of shocks were inappropriate, i.e. not precipitated by ventricular arrhythmia (Moss et al. 2002). The majority occurred as a result of misclassification of supraventricular tachycardias, over-sensing of normal cardiac electrograms or due to lead damage (Daubert et al. 2008; van Rees et al. 2011) [Figure 1-6 shows an example trace]. Inappropriate shocks are associated with adverse mortality and morbidity as described above.

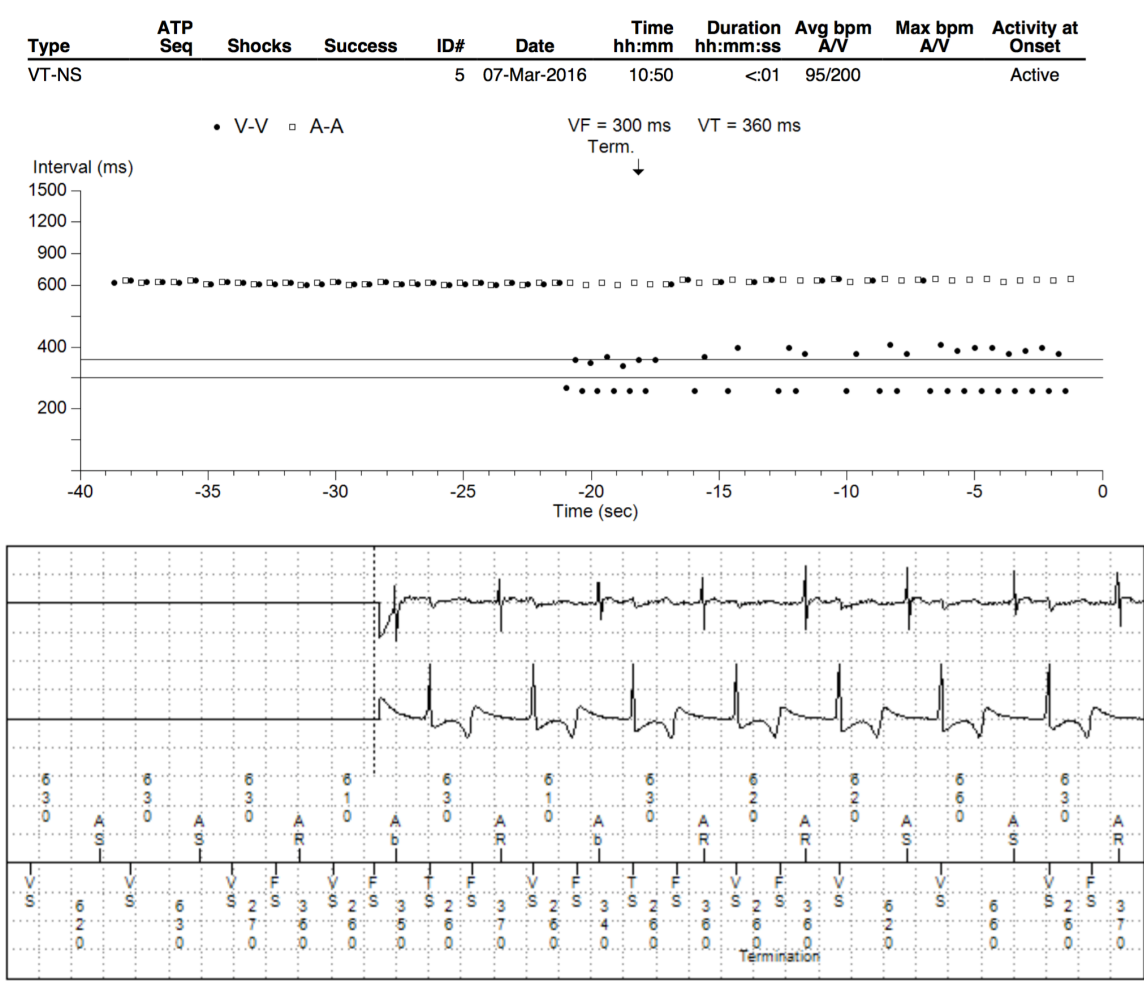


Figure 1-6 Example ICD recording showing T-wave oversensing

A Medtronic device EGM obtained with consent from a patient seen at Imperial College NHS Hospitals Trust. The trace highlights an example of an inappropriate diagnoses from an ICD of a ventricular rhythm disturbance. The EGM dot-plot shows the classic “tramline” pattern associated with T wave oversensing and this is also clearly seen too in the associated EGM trace.

1.2.2.3 Current approaches to avoid harmful therapies

Current approaches rely on three facets:

- 1) Improved electrogram based diagnostics of the rhythm disturbance to ensure the rhythm is truly VT and not supraventricular tachycardias or other mimickers of high ventricular rates for example double counting of electrogram components. Although improvements have been made, room for improvement remains.
- 2) Delaying therapies by allowing VT to persist longer in the hope that this will allow time for a VT to stop spontaneously before the episode becomes too long and causes severe symptoms and ventricular failure. Prolonged episodes unfortunately have been shown to reduce the likelihood of ATP being able to successfully terminate the rhythm disturbance (Arenal et al. 2016).
- 3) Setting a very high rate threshold for treatment to avoid treating slower VTs, in the expectation that all lower rate VTs will be hemodynamically tolerated. This approach does not allow for the fact that slower VT may still be harmful or that the same VT rate may cause haemodynamic collapse on one occasion but not on another, in the same patient.

1.2.2.4 Improving Understanding of Ventricular Tachycardia to Improve treatment options

A novel approach to reducing therapy would be for the device to improve cardiac function during VT, rather than only attempting to end the VT.

If this could be achieved there would be several advantages. By preserving cardiac output, the negative impact VT has on cardiac function due to reduced coronary perfusion could be minimized. By preserving cerebral perfusion, episodes of syncope or pre-syncope could be avoided. As a result of this, it would be possible to delay ATP or shock therapy even further than is currently carried out in clinical practice. This would

allow more time for spontaneous termination. It is likely that this will ultimately lead to a reduction in the requirement for ATP and shock therapies compared with currently practice. This would be expected to have major beneficial consequences in terms of quality of life, morbidity and possibly also mortality.

To design therapies that could improve cardiac function during VT we first need a better understanding of the exact mechanisms and relative contribution through which VT impairs cardiac function.

Harmful mechanisms at play in VT can be divided into four component factors:

1. The very high heart rate
2. Loss of atrial contribution to ventricular filling
3. Loss of ventricular synchrony
4. Patient status - including left ventricular function, presence of coronary artery disease and the patients posture at the time of an episode.

The relative effects of these factors can be determined by simulating the top three mechanisms with pacing leads positioned within the heart. Potential VT treatment methods (which may include His bundle pacing to restore ventricular synchrony) can then be explored to determine the benefits during VT episodes.

In Chapter 5, experiments are performed exploring the haemodynamic effects of loss of atrio-ventricular and biventricular synchrony during tachycardia. Investigation is then performed to assess if pacing manoeuvres including His pacing during VT can mitigate some of the haemodynamic harm during VT, potentially allowing spontaneous termination of the ventricular tachycardia which could be a novel strategy for ICDs.

1.2.2.5 Reducing inappropriate and unnecessary ICD therapies

Forty percent of ICD shocks in clinical practice are inappropriate (Theuns et al. 2018; Turakhia et al. 2017), i.e. delivered in the absence of a ventricular arrhythmia. A further proportion are unnecessary, that is they are delivered albeit in the presence of an appropriate diagnosis of VT, but when a given patient is tolerating the rhythm disturbance without significant haemodynamic instability. In this situation it is possible that the net effect of ICD treatment could cause more harm than either allowing the VT to continue or utilising alternative medical therapies to treat the clinical scenario.

ICD treatments cause unpleasant symptoms, increase healthcare costs (Bhavnani et al. 2014; Turakhia et al. 2017; Borne et al. 2013) and are associated with increased mortality. (Proietti et al. 2015; Borne et al. 2013; Li et al. 2016) Despite increasingly sophisticated electrogram analysis algorithms, it has not been possible to reduce the rate of inappropriate shocks below ~3% per year, even in carefully recruited, attentively managed clinical trial patients. (Gasparini et al. 2013; Moss et al. 2012) Rates appear to be even higher in clinical practice, affecting up to 41% of ICD recipients. (Watanabe et al. 2017) These rates suggest that there remains a major opportunity to reduce inappropriate therapies in order to make ICDs safer and more acceptable to people at risk of sudden cardiac death.

In Chapter 6, I develop and test an algorithm for assessment of a haemodynamic signal that could be potentially incorporated into future ICD iterations and form part of the therapy decision tree. If this novel approach reliably detects adverse haemodynamic consequences during ventricular fibrillation, this could in the future lead to a considerable reduction in inappropriate shocks.

2 Methods

2.1 Introduction

In this thesis many of the pacing techniques, measurement techniques, data acquisition approaches, and methods of data processing will be used in multiple chapters. This chapter describes these methods.

Methods unique for an individual Chapter will be detailed in the appropriate chapter.

2.2 Measurement apparatus

2.2.1 Non-invasive blood pressures measurement

Non-invasive beat-to-beat blood pressure were measured for a number of experiments in this thesis.

Measurements were made using a NOVA Finometer (Finapres Medical Systems, Amsterdam, Netherlands). FINAPRES is an acronym for 'Finger Arterial Pressure' and it is this quantity that was measured. The device used is a digital photoplethysmograph which uses an inflatable finger cuff and applies a Volume Clamp technique as described by the Czech physiologist Penaz (Molhoek et al. 1984) to derive a continuous arterial pressure waveform.

In brief the Volume Clamp method used by the Finapres is as follows:

A small cuff is placed around a finger. This cuff has both a light emitting source sited on one side of the cuff and a light detector on the opposite side, and both are housed within an inflatable bladder.

The device first determines the unloaded diameter of the finger arteries. This is the point where the finger-cuff pressure and intra-arterial pressure are equal. At this point the artery is dynamically clamped by the inflatable bladder within the finger cuff thus enabling a constant artery unloaded diameter. This is achieved by varying the pressure of the finger cuff bladder relative to the arterial pressure detected. A servo-controller

system defines the target unloaded diameter and measured values are then compared to this set point. The intra-arterial pressure is measured by assessing the cuff pressure required to exactly counteract the change in intra-arterial pressure (Imholz et al. 1998) and the measured values are determined by changes in the amount of light absorbed.

Deriving the unloaded diameter of the finger artery correctly is critical for measurement accuracy. This can be affected by changes in autonomic tone and arterial smooth muscle tone. For these reasons' intermittent verification and calibration of the unloaded diameter of the artery must be made.

2.2.1.1 Practical Methodology

An appropriately sized finger cuff for a patient was applied to the middle phalanx of the middle finger of the right hand and allowed to calibrate until a consistent pressure trace is obtained. If this finger did not yield an acceptable trace an alternate finger was used.

This can occur due to poor peripheral circulation and/or cool peripheries. If needed either the middle finger of the left hand or the index finger of the right hand were used.

The Finometer initially performs a calibration test every 10 seconds and extends the time period between calibrations as the trace consistency improves. Once at least 30 seconds of a consistent pressure trace had been observed I manually paused the calibration process to allow recordings to be made that were not affected by calibration artefact. This is shown in Figure 2-1.

The participants during the experiments were requested to keep their hand and finger still and at a constant height in relation to the heart throughout all recordings.

Signals from the Finometer were extracted via an analogue output channel. This allowed real time extraction of signals to my data acquisition set-up so that it could be synchronously acquired with all the other signals and measurements being recorded.

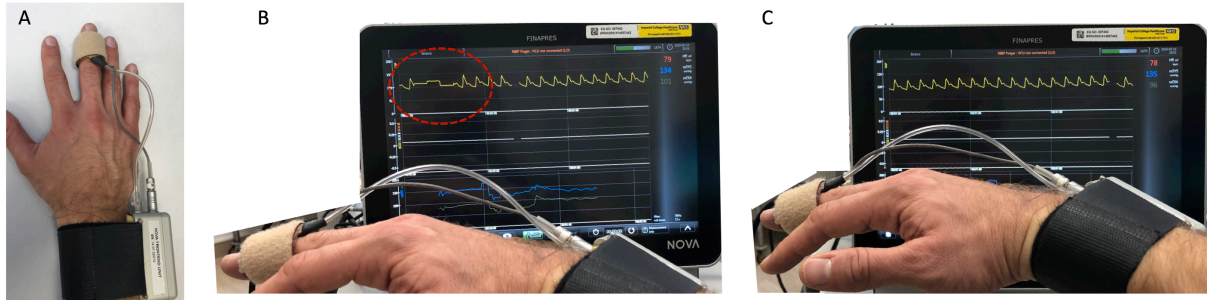


Figure 2-1 Use of the Finometer Device

A Finometer cuff positioned on the middle finger of the right hand for measurements

B The Nova device with evidence of calibration artefact (red circle)

C The Nova device with consistent stable pressure traces and the calibration mode disabled

2.2.2 Invasive BP

For a number of experiments conducted within the cardiac catheter laboratory invasive beat-to-beat blood pressure was recorded. This was recorded from a sheath positioned in either the radial or femoral artery. Pressure was transmitted via fluid filled tubing to a fluid filled column connected to an external pressure transducer. The transducer was fixated at a standardised height to prevent inaccurate recordings. Pressure recordings were made utilising the Fukuda Denshi DS 7100 Monitor (Fukuda Denshi, Tokyo, Japan). Real time extraction of signals via an analogue output to my data acquisition set-up was performed so that the signal can be synchronously acquired with other signals and measurements.

2.2.3 Electrocardiography

Where needed a three-lead surface ECG was recorded using the Fukuda Denshi DS 7100 Monitor (Fukuda Denshi, Tokyo, Japan). Leads were positioned in the following standard positions: right shoulder, left shoulder, right hip. Real time extraction of signals was performed via an analogue output to my data acquisition kit so that the signal could be synchronously acquired with other signals and measurements.

2.2.4 Laser Doppler Perfusion Monitoring

Laser Doppler is a method for assessing peripheral tissue perfusion.

This thesis seeks to explore whether interpretation of biological signals from this sensor could provide potential added value to cardiac rhythm management devices. It may be able to provide a measure of perfusion as part of a feedback loop that could improve device tachyarrhythmia diagnostics and trigger responses in device behaviour.

Unlike measures of beat-to-beat arterial pressure, laser Doppler relies on changes in reflected light rather than on a pressure sensor sited within or near to an artery.

Laser Doppler quantifies blood flow by assessing changes in Doppler velocity from the reflected change in wavelength of a laser signal directed into tissue containing moving red blood cells. Pulsatility of blood flow is then detected and quantified.

The laser Doppler perfusion monitoring technique is based upon the emission of a beam of laser light carried by a fibre optic cable. The light is scattered at the tissue interface and partially absorbed by the tissue being studied. Light hitting moving red blood cells undergoes a change in frequency (Doppler shift) whilst light hitting static objects is unchanged. Both the magnitude and frequency distribution of these Doppler shifts directly relates to the number and velocity of red blood cells in the sampling volume. This information which in essence is a measure of perfusion is picked up by a returning fibre optic cable, converted into an electronic signal and then analysed. The principle of Laser Doppler monitoring is shown in Figure 2-2.

In this thesis the commercially available Perimed Periflux 5000 laser Doppler equipment is utilised (Perimed, Sweden). The probes used have a standard fibre separation of 0.25mm and emit laser light with a wavelength of 780nm. The measurement depth will increase depending on the presence or lack of blood in an area, with measurement depth increasing if there is a lack of blood medium. A typical measurement depth will be in the order of 0.3-0.5 millimetres.

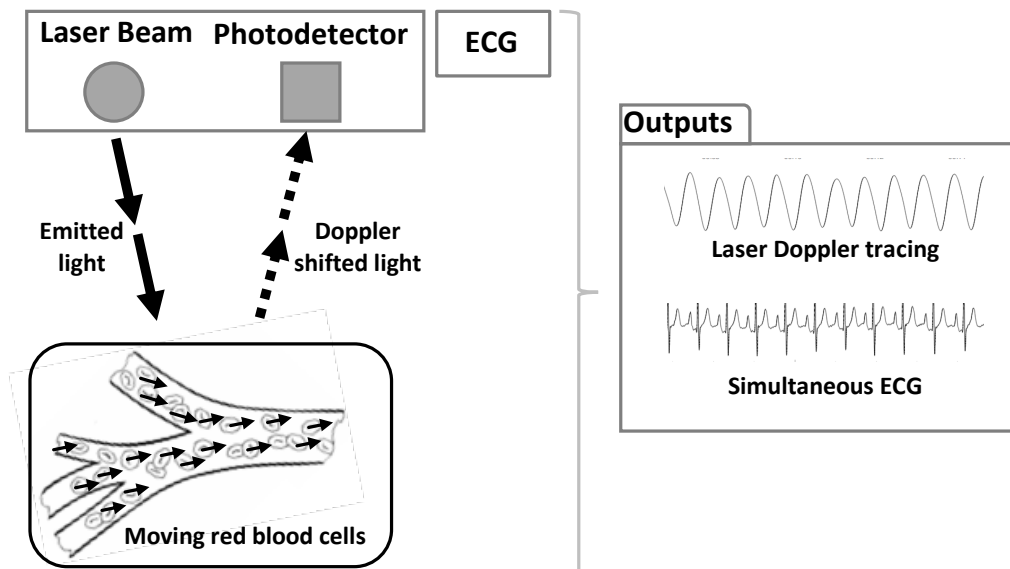


Figure 2-2 Principals of Laser Doppler perfusion monitoring

A laser light is emitted from the laser Doppler perfusion monitoring device.

Should this hit moving red blood cells the light undergoes a change in frequency (Doppler shift) whilst light hitting static objects is unchanged. Both the magnitude and frequency distribution of these Doppler shifts directly relates to the number and velocity of red blood cells in the sampling volume. This information provides a measure of perfusion. This is detected by a returning fibre optic cable, converted into an electronic signal and displayed as an oscillatory trace. The size of the oscillations reflects high and low perfusion states.

It is noteworthy that these oscillations occur in synchrony with the heart beat as seen by the simultaneous ECG trace recorded.

2.2.5 Implantable Cardiac Devices and Pace-Sense-Analyser/Programmers

Pacemakers and implantable cardioverter defibrillators were used in many experiments discussed in this thesis. Devices included both dual chamber ICDs and pacemakers and triple chamber ICDs and pacemakers. Devices used were manufactured by either Medtronic (Minneapolis, MN, USA) or Boston Scientific (Natick, MA, USA).

Programmers from these manufacturers were used to induce ventricular fibrillation, adjust paced heart rate, to control the delivery of pacing stimuli at various sites within the heart and to allow adjustment of Atrio-Ventricular (AV) delay. Lead signals and marker channels were able to be extracted in analogue format from the Medtronic PSA for real-time input into my acquisition kit.

2.2.6 Customised device to mark transitions of pacing settings

To allow for notarisation on the data acquisition system where changes in pacemaker programming had occurred; for example, when there was a change in programmed AV delay which may not be obviously assessable, a purpose-built transition marker box was used. This box connected to the acquisition kit outputs a continuous voltage output, but by toggling a switch at the time of a change in pacing configuration triggers a change in the voltage output. This is recorded on the acquisition system thus marking the time of transitions.

2.2.7 12-Lead ECG measurements

12 lead ECG measurements were printed using a GE MAC 1200 ST ECG machine (GE Healthcare, Buckinghamshire, UK)

2.3 Data acquisition system for haemodynamic measurements

A custom designed data acquisition system was utilised for all haemodynamic measurements. Recording equipment was selected if they allowed output of analogue

signals. This includes the toggle box, electrocardiography, invasive and non-invasive blood pressure and laser-Doppler. The analogue signals were taken from all recording equipment and digitised utilising a signal acquisition system (National Instruments USB 6251 Austin, Texas USA) and stored on a computer. Data files were stored as zipped text files.

Whilst signals were being acquired they were monitored and viewed using a custom display program developed using Labview (National Instruments). All signals were converted from analogue inputs to digital signals at a sampling rate of 1000 per second thus ensuring high fidelity signals were available for analysis.

2.4 Algorithm to measure haemodynamic effects of different cardiac rhythms or pacing configurations

2.4.1 Analysis software

Data analysis was performed with software designed by our research group using the Python open access platform (Python Foundation, USA). Separate methodological approaches were used for (1) performing AV delay optimisation determination, and (2) for assessing perfusion state by Laser Doppler recordings.

2.4.2 Basis for analysis algorithms

The haemodynamic data acquisition protocols were designed to reliably and with narrow error bars distinguish differences in observed haemodynamics in individual patients even when the observed differences are small. It is known with regard to AV delay optimisation that these differences although small in numerical size can be highly clinically relevant.

2.4.3 Laser Doppler recordings

Three approaches were used for laser Doppler analysis. Two have been well described elsewhere; the “Running Mean” method (Compton et al. 2012) and the “Oscillatory Height” method (Turcott and Pavsek 2008; Turcott and Pavsek 2010; Nabutovsky et al. 2012). As a major part of this thesis I derived a third approach (namely the Electro - Mechanical Coupling method). This new method is resistant to many of the issues the former methods face. This approach is described in detail in Chapter 6.

2.4.4 AV delay optimisation assessment

Systolic Blood Pressure has previously been shown to be a highly reliable marker of changes in haemodynamic function triggered by changes in AV delay and as such this measure was chosen for this purpose (Z I Whinnett et al. 2006; Manisty et al. 2012).

When considering AV delay optimisation assessment, the approach utilised must be robust enough to reliably detect numerically small changes (0-10mmHg) in observed haemodynamics resulting from changes in programmable settings. The approach must be robust against haemodynamic effects caused by natural beat-to-beat variability in blood pressure. It must also be designed to be as immune as possible to the longer term effect of peripheral vasodilation which is shown to occur after a rise in systolic pressure caused by increased cardiac output (Manisty et al. 2012).

Natural fluctuations occur within a blood pressure trace even in seemingly stable conditions; some may be predictable like cyclical respiratory driven changes, but others may be caused by other internal physiological processes which do not have a predictable or cyclic pattern.

As the observed effect of a change in AV delay may be small, multiple measurements must be performed so to be sure of its true value.

To account for fluctuations in haemodynamics two approaches are utilised. Firstly, multiple beats are assessed and averaged in a given 'transition', from a *control* state to a *test pacing* mode. Secondly, multiple transitions are performed between the *control* state to the *test pacing* mode and back again.

To account for the decay in systolic blood pressure (this occurs as vasodilation occurs) the analysis is focused only on the 8 heart beats either side of a transition. (Whinnett et al. 2008)

2.4.4.1 Practical Methodology

The method utilises repeated alternations between *test* settings (the available programmable AV delays) and a *control or reference* setting, all conducted at a constant atrial based pacing rate. AV delays of 40ms, 80ms, 120ms, 160ms, 200ms, 240ms, 280ms and 320ms etc were tested until fusion occurred. The reference setting used was atrial based pacing with the same programmed heart rate as the *test* settings. Each transition between the *reference* setting, the *test* setting and then back to the *reference* setting was notarized by means of a toggle box as mentioned above in 2.2.6.

The relative change in mean systolic blood pressure between the *reference* setting (8 beats of the reference setting immediately before transitioning to a test setting) and the *tested* setting (8 beats immediately after the transition to a tested AV delay) was calculated. A minimum of six transitions are performed between the reference setting and the atrial synchronous dual chamber pacing mode at a given AV delay. The overall mean relative change for that particular programmed AV delay as compared with the reference setting was then calculated. The blood pressure changes for all the tested AV delays are then plotted on a parabola and the optimal AV delay derived. The optimal AV delay was defined as the one that gave the greatest increment in cardiac function relative to the reference setting.

The above described approach can be seen with a worked example in Figure 2-3.

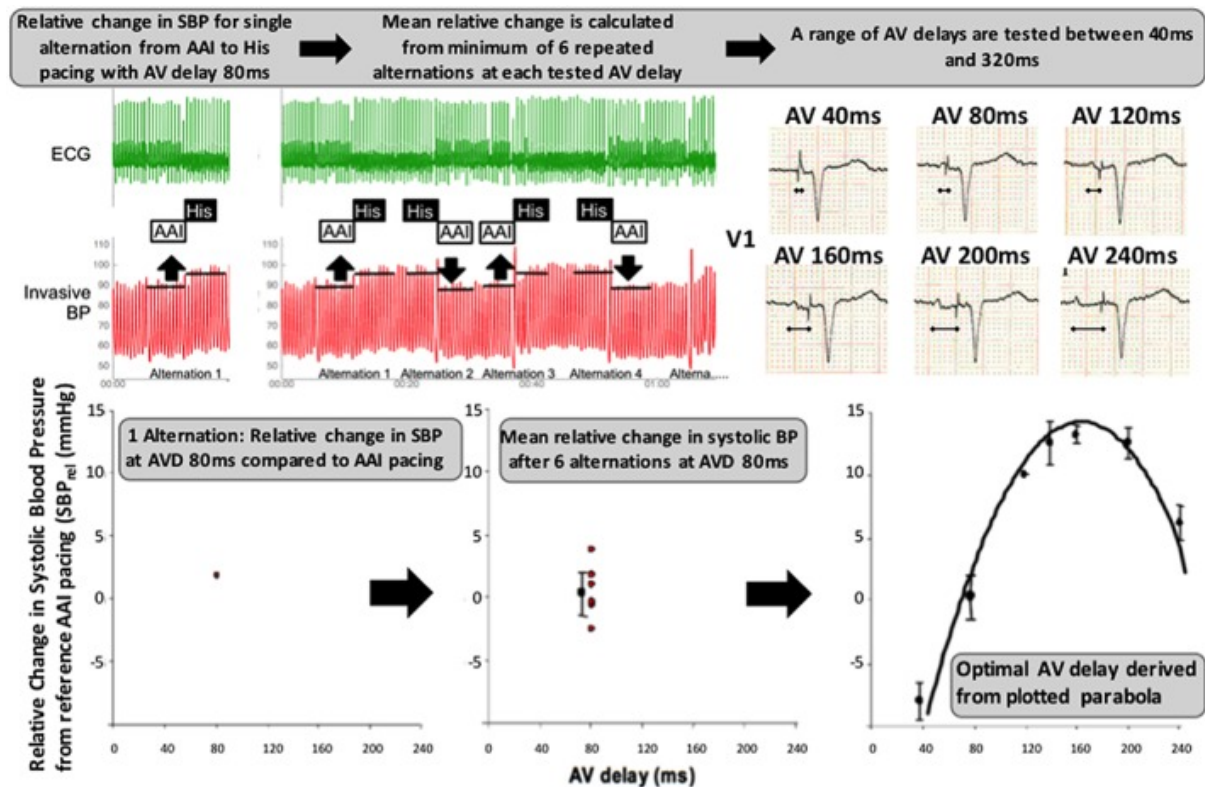


Figure 2-3 Approach for AV delay optimisation

The relative change in systolic blood pressure (SBP) between 8 beats of AAI pacing and 8 beats of dual chamber atrial synchronous–pacing at a given atrioventricular delay (AVD) is determined [AV delay = 80 ms in this example (top left)]. This is a single alternation (plotted bottom left). A minimum of six alternations are made for each AVD (middle sections top and bottom). This process is repeated for each AV delay between 40 and 320 ms (less if intrinsic AV conduction occurs before 320 ms). The optimal AV delay is then derived from the plotted parabola (bottom right). In this example, the optimal AV delay was 160 ms.

BP, blood pressure; ECG, electrocardiogram.

2.5 Performing permanent His bundle pacing

The effects of providing or restoring physiological ventricular activation are central to many chapters in this thesis. In this section a detailed description of my approach to obtaining and confirming His bundle capture is presented.

2.5.1 Anatomy of the His Bundle and Implant Technique

The His bundle is a cord like structure, made up of multiple filaments contained within a fibrous sheath. These internal filaments are described to be longitudinally dissociated from one and other. Each filament is predetermined for either the right or left bundle from the point at which they exit the AV node. (Narula 1977)

The non-branching section of the His bundle extends from the compact AV node within the membranous septum before dividing in to its respective bundle branches and crossing the AV junction. This non-branching section is approximately 15 to 20 millimetres in length. (Correa de Sa et al. 2012) It is this region that a pacing lead is targeted to. This region is at the inferior septal margin of the right atrium.

Anatomically the mitral valve sits more basally to the tricuspid valve. This means that the inferior septal region of the right atrium in which the pacing lead is deployed is a right atrial – ventricular septum interface. It is at this site that a pacing lead is targeted to and allows atrial and ventricular signals to be sensed due to the proximity of the different tissue types in this area.

Figure 2-4 provides an overview of where the His pacing lead is placed electrically and anatomically.

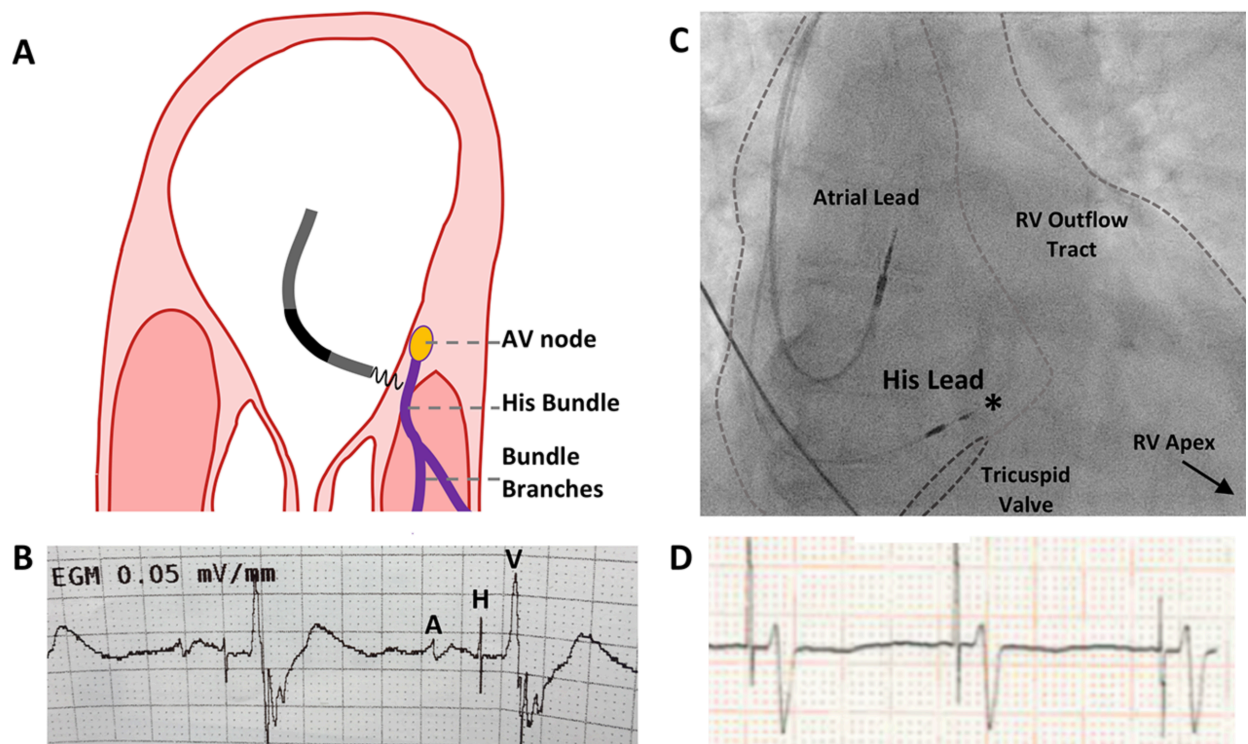


Figure 2-4 His bundle anatomy and pacing approach

A: The His-bundle arises from the AV node on the atrial side of the tricuspid valve. As the tricuspid valve is more apical than the mitral valve, some ventricular tissue is located in the vicinity of the proximal His bundle.

B: Fluoroscopy showing the anatomical landmarks for His bundle pacing.

C: Unlike right ventricular pacing, His bundle pacing requires electrical positioning. Clear atrial (A), His (H), and ventricular (V) signals are seen, with the ventricular signal having a greater amplitude than the atrial.

D: Surface ECG during His bundle pacing.

2.5.1.1 Described His Bundle Anatomical Variants

Understanding His bundle anatomy and its variations can help to understand pacing responses. Autopsy studies in 105 Japanese men identified three anatomical variants. The three variations have different responses to pacing. (Kawashima and Sasaki 2005)

The majority of patients (~ 50%) are described as having a *type 1* anatomy. These are the patients in whom the His bundle has just a thin layer of myocardial cells covering the His bundle.

In contrast *type 2* patients (~ 30%) have a higher riding muscular septum which their His bundle is located within. The implication of this means that there is a thicker muscular layer separating the pacing lead from the His Purkinje fibres.

Finally, in *type 3* patients (~ 20%) have no muscular covering over the His bundle in contrast to *type 1* (thin myocardial covering) and *type 2* (thick myocardial covering) and it is described as *naked*. The pacing lead can theoretically therefore easily engage with the His bundle fibres in these patients.

These anatomical variations can be seen in the cartoon illustration in Figure 2-13.

2.5.2 Equipment and Lead Deployment

The pacing lead used for permanent His bundle pacing in this thesis is the Medtronic SelectSecure 3830 lead (Medtronic, MN, USA) [Image shown in Figure 2-5]. This lead is a 4.1 French lead that is non-stylet driven and therefore requires a delivery sheath to deploy it to the selected site. The lead is an active fixation lead with an exposed helix screw mechanism. The screw tip (unlike other active pacing leads) in this lead is the tip (cathode) electrode. This means that if the lead screw can penetrate the fibrous capsule surrounding the His bundle it can bring about stimulation directly of the His bundle fibres. The screw tip delivers a single dose of dexamethasone to reduce inflammation following deployment.



Figure 2-5 The Medtronic Select Secure 3830 pacing lead (used for His bundle pacing)

The lead is standardly delivered by a non-deflectable fixed dual curve catheter (C315 43cm, Medtronic). The first curve aims to bring the delivery system forward to the tricuspid valve and the second curve then aims to point the delivery system in a septal direction arriving at the septum in a perpendicular fashion. This is demonstrated in Figure 2-6. There are other catheters that can be considered should this catheter fail to be successful.

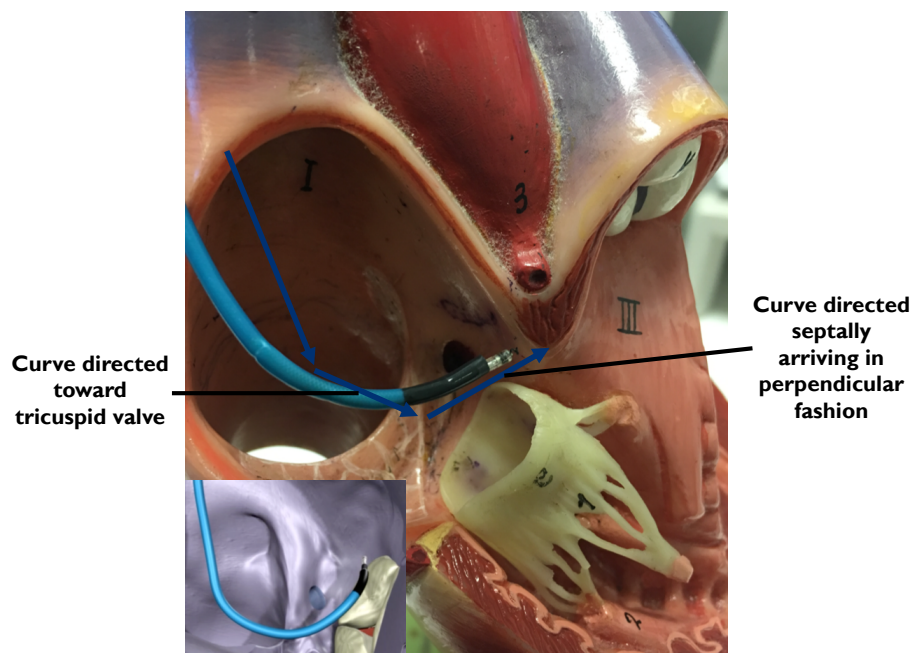


Figure 2-6 The C315 His catheter

This dedicated His pacing catheter has two fixed curves. The first brings the lead forward toward the tricuspid valve and the second curve points the lead septally to arrive at the location of the His in a perpendicular orientation. This orientation is optimal for deploying the lead at this location.

Unlike traditional pacing lead placement which requires fluoroscopic guidance His lead placement primarily relies on electrical sense mapping (or less frequently pace mapping response) to identify the appropriate site.

2.5.2.1 Sense Mapping

Signal sense mapping is performed in a unipolar fashion. In this way only the very tip of the pacing lead needs to be exposed beyond the end of the delivery sheath. This has two advantages:

1) should it be exposed further it may have a higher likelihood of catching on surrounding cardiac structures or trapping myocardial strands within it, these may impair the leads ability to deploy adequately.

2) When deploying the lead, it is important to have the delivery catheter as close as possible to the lead-myocardial interface to provide support for deploying the lead.

Should mapping be performed in bipolar fashion the lead would need to be exposed at least 1cm outside the delivery catheter. This could mean that when an appropriate site is found and one wishes to move the catheter forward to give support for lead deployment there is a risk of micro or macro lead displacement and loss of the sensed site. The approach for Unipolar sense mapping is shown in Figure 2-7.

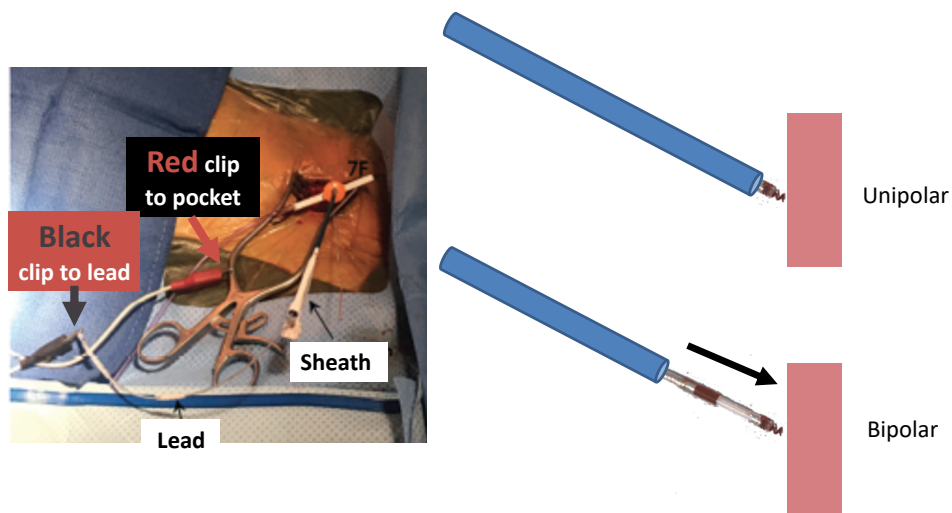


Figure 2-7 Unipolar Mapping approach for His bundle pacing

This figure demonstrates how unipolar mapping is conducted with the red crocodile clip of the Pace-Sense cable connected to the pocket and the black crocodile clip connected to the cathode of the lead. Unipolar mapping has the advantage of only requiring the lead tip to be exposed to map whereas bipolar mapping would require more lead to be exposed which has associated disadvantages.

An electrogram detected by the lead tip is displayed during mapping either via a Pace-Sense Analyser or via a dedicated electrophysiology system. This second approach allows mapping of the signal with real-time alignment with a 12 lead ECG recording. This is of particular value when assessing the response to pace stimulation at selected sites.

A His electrogram is targeted which is surrounded by a preceding atrial component and followed by a ventricular electrogram. The more distal the site along the conduction system the smaller the atrial component and the larger the ventricular component. More distal sites are often favoured due to improved ventricular sensing and less risk of inadvertent atrial tissue capture. More distal sites may allow the His pacing lead to be distal to localised conduction system block that may be present in the proximal His bundle location. It is the subjective opinion of many highly experienced operators that I have interacted with that the optimal ratio of atrial signal amplitude to ventricular amplitude is 1:3 with a His electrogram between the two, this is shown in Figure 2-8.



Figure 2-8 His bundle electrogram mapping approach

A His electrogram has been mapped (lowest tracing) with an optimal ratio of small atrial component and larger ventricular component. This has been mapped using an electrophysiology system so the relationship of the signals to the entire 12 lead ECG can easily be seen.

2.5.2.2 Catheter manipulation to optimise site for deployment.

Clockwise rotation of the delivery sheath points the sheath towards the superior atrio-ventricular septum and towards the right ventricle. This movement enables movement distally along the conduction system. Conversely, anticlockwise rotation will direct the delivery system towards the mid/posterior septum and the atrial region.

2.5.2.3 Lead Deployment

Once a suitable site has been found, the lead is deployed with support from the delivery catheter by at least 4-5 complete rotations of the lead. Fixation can be determined by tactile feedback secondary to a build-up of torque within the lead body as it is deployed.

Once the lead is deployed it is important to initially confirm that the electrograms observed in the unipolar configuration remain satisfactory. Next the delivery catheter should be pulled back whilst applying forward pressure to the pacing lead in a “*push-pull*” approach to allow slack to be present on the lead and to expose both the anode and the cathode. The delivery catheter is then brought back to the level of the mid or high right atrium. At this point the response to pace stimulation can be tested. If sensing and pacing responses are satisfactory the delivery sheath can then be slit in the standard way.

2.5.3 Pacing Responses

Consensus documentation now exists as to how to classify pacing responses (Vijayaraman, Dandamudi, Zanon, et al. 2017).

To confirm successful conduction system capture via the His bundle a 12 lead ECG and the lead electrogram are used. Assessment is made of the relationship between the pacing stimulus and QRS on the lead electrogram and the paced QRS morphology response on the 12 lead ECG. These responses are compared with the intrinsically observed His signal and relationship with native QRS and the native QRS itself. A number of responses may be observed.

2.5.4 My approach to determine pacing response

When an optimal His site has been located. It is advised to make note of the following measurements. (Figure 2-9)

- First; The “H-V” time; the time taken from the His potential to the first part of the QRS in the earliest of the ECG leads. This is representative of the time taken for electrical activation to travel down the His-Purkinje network before ventricular break out and activation. A time of 35-55ms would be considered normal in health but in patients with conduction disease it is not uncommon to see longer HV times.
- Second; the QRS duration as a reference
- Third; ascertain the time taken for overall completion of ventricular activation from the moment of His activation i.e. a signal exiting the AV node to completion of ventricular activation. This is measured from the His electrogram to the latest terminal component of the QRS on the 12 lead ECG. This measurement should not be lengthened by His bundle pacing regardless of the type of His bundle capture achieved. However, should myocardial capture occur (rather than His pacing) this total activation time would be extended.

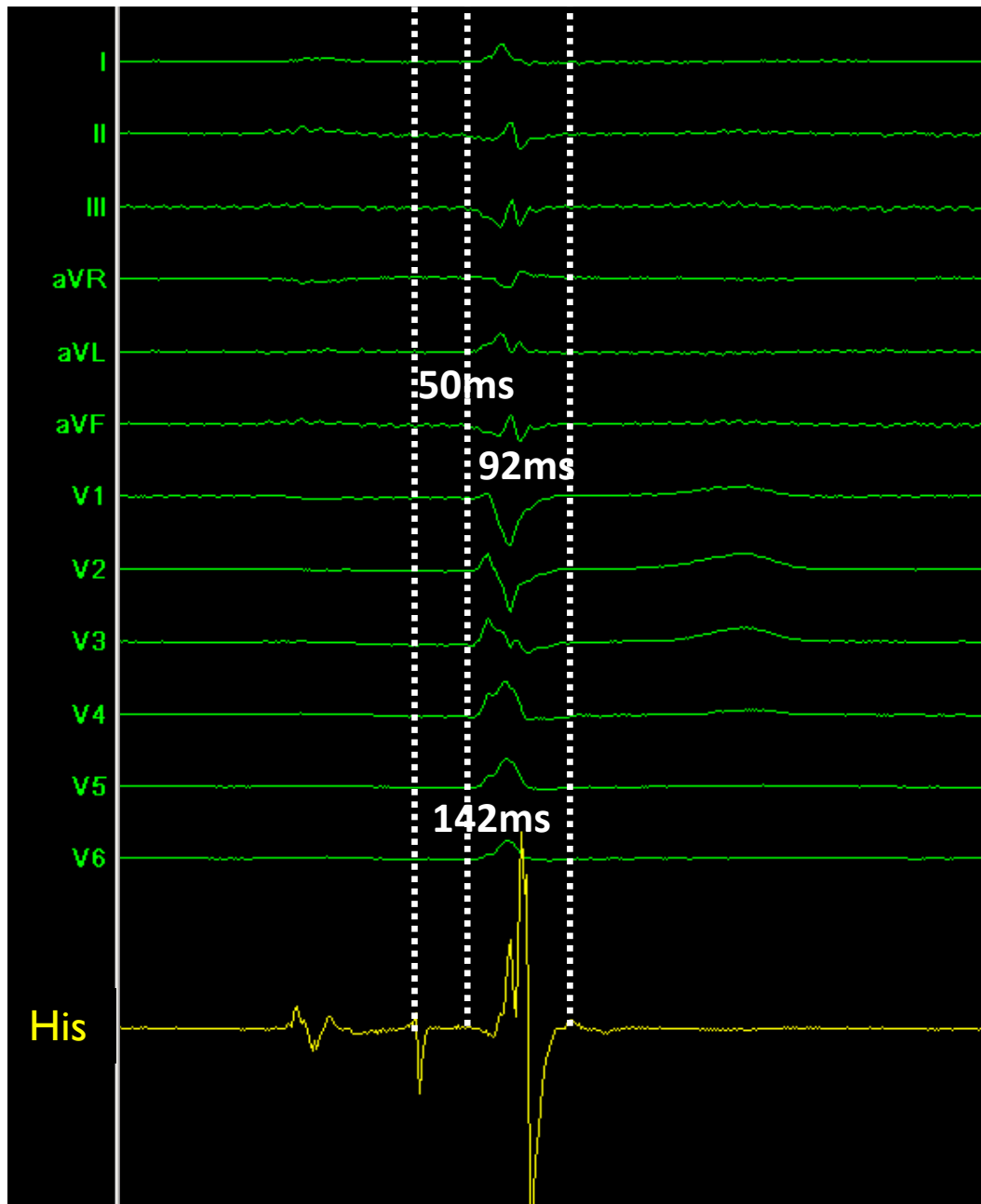


Figure 2-9 Baseline measurements to make when a His signal is located

Recommended baseline measurements to make: 1, HV interval 2, QRS duration and 3, His to end of QRS duration as a measure of total ventricular activation

2.5.4.1 *His pacing electrophysiological responses*

When I attempt to pace at the His bundle there are a number of measures to make to compare with the reference data in order to determine the pacing response.

- First, is the time taken from stimulation artefact, to the start of the QRS first observed on the surface ECG. Assessment is made whether it is isoelectric or upsloping. Comparison is also made as to whether the time taken is the same as the HV time measured intrinsically.
- Second, measurement of the paced QRS is performed, and assessment made whether it is the same or different to the intrinsic one.
- Finally, the pacing stimulus to the end of the QRS time is measured. Assessment is made to see if it differs from the His to end of QRS time measured intrinsically. With His pacing we would expect it to be either the same as intrinsic or perhaps shortened. If shorter it means overall ventricular conduction has occurred more quickly than intrinsic conduction – this could occur if intrinsically bundle branch block was present. However, if this time is prolonged, this would suggest that activation has not occurred down the native conduction system rather cardiac activation has occurred simply as a result of myocardial capture.

2.5.4.2 *Selective Capture response*

Previously this type of capture has been referred to as direct or specific capture but selective is now the agreed nomenclature. It can be defined as ventricular activation occurring solely over the His Purkinje system in exactly the same way that an intrinsic impulse is transmitted through the conduction system in a healthy individual.

When a pacing stimulus is delivered activation spreads down the native His Purkinje conduction system, and, initially whilst current is flowing through the His bundle prior

to ventricular myocyte activation there is an isoelectric interval on the ECG. This is then followed by rapid depolarisation and activation of the ventricle giving a normal and narrow QRS complex distinct from the pacing stimulus. Hallmarks of Selective capture are shown in Figure 2-10.

Selective His Bundle pacing

1. Isoelectric interval between stimulus and QRS onset
2. HV interval = stimulus – V interval or a shorter stimulus – V interval if QRS narrowing occurs in BBB
3. QRS identical to native morphology or narrower QRS (if intrinsic BBB) with concordance of the T wave complexes
4. Discrete local ventricular electrogram on HBP lead
5. Widening of the QRS at higher outputs as local myocardium is captured (2/3 of cases)

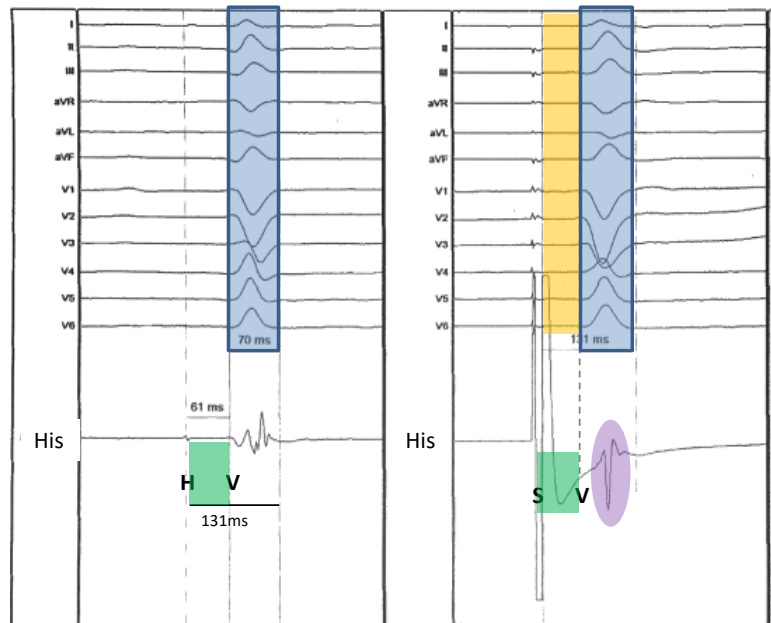


Figure 2-10 Hallmarks of Selective His bundle pacing

2.5.4.3 *Non-Selective Capture Response*

This previously has been referred to as para-hisian pacing, indirect or non-specific pacing. The consensus nomenclature is now that of Non-Selective capture. In contrast to Selective capture, Non-Selective capture involves activation of surrounding myocardium overlying the His bundle in addition to engaging the His bundle. This results in initial fusion between local ventricular capture in the basal anteroseptal right ventricular region and His bundle activation.

When a pacing stimulus is delivered there is immediate activation of the His Purkinje system like there is with Selective pacing BUT also, simultaneously, activation of the local surrounding myocytes next to the His bundle. This accounts for the observation of a superimposed delta wave on the ECG, (in contrast to the isoelectric interval seen with Selective capture) this represents the presence of the surrounding myocardial cells activating prior to the His Purkinje system overtaking and continuing the activation of the heart. Hallmarks of Non-Selective capture are shown in Figure 2-11.

Non-Selective His Bundle pacing

1. Interval from stimulus to end of the QRS = His to end of QRS during native conduction
2. Shorter stim to end QRS interval in normalisation of BBB.
3. Pseudo delta wave after stimulus reflecting basal anteroseptal ventricular capture
4. Electrical axis of the paced QRS must be concordant with the electrical axis of the native QRS
5. More likely narrowing of QRS with high output

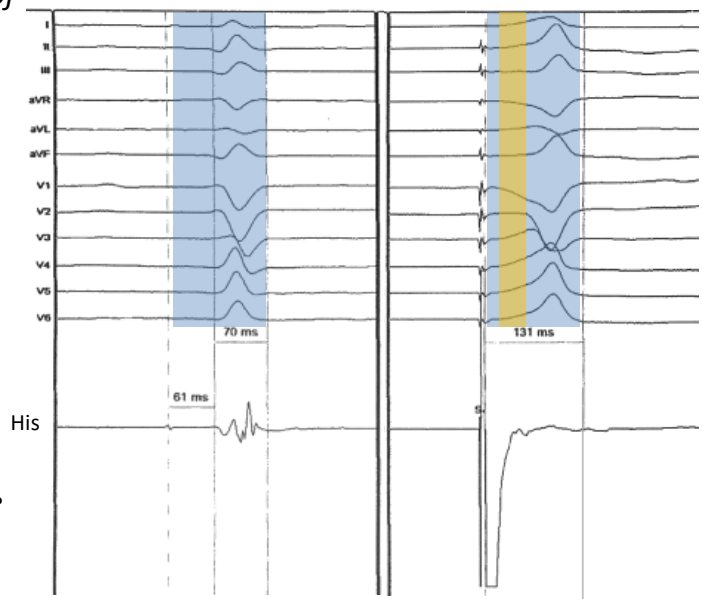


Figure 2-11 Hallmarks of Non-Selective His bundle pacing

2.5.4.4 Differences in LV activation with Selective vs Non-Selective capture

The activation of the RV is different with non-selective His capture. The basal and mid RV are activated earlier which can be seen in the Figure 2-12 below (Arnold et al. 2016; Keene, Arnold, et al. 2018). However, it is important to note LV activation time and pattern remains entirely homogenous and the same as Selective capture, suggesting that this LV activation pattern is not affected by Selective or Non-Selective capture.

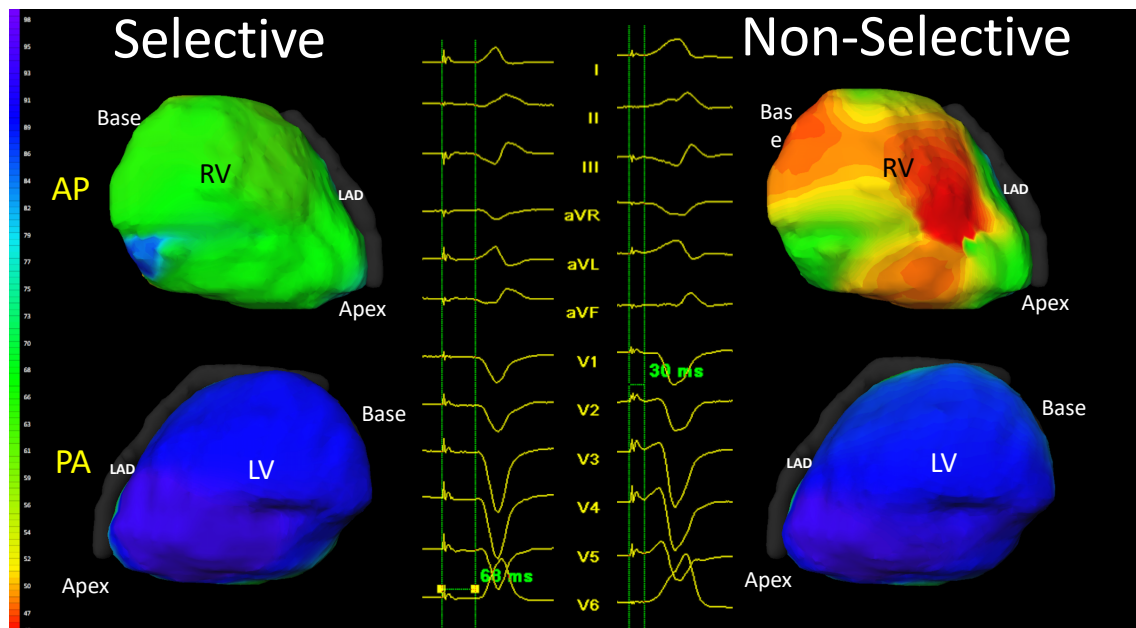


Figure 2-12 Differences in Cardiac Activation between Selective and Non-Selective His bundle pacing

The left image shows Selective pacing, there is homogenous activation of both the RV and the LV and an isoelectric interval on the ECG. All the ventricular activation results from His Purkinje activation.

The right image in contrast shows Non-Selective pacing. The ECG shows the presence of a pseudo delta wave which represents local myocardium activating in close proximity to the pacing lead and the subsequent cell-to-cell advancement of an electrical wavefront. This is eventually overtaken by the high speed His Purkinje system and as such the LV is activated rapidly (by the His Purkinje system) with exactly the same appearance as for Selective capture.

2.5.4.5 *Effect of Anatomy on pacing observed response*

Patients with *type one* anatomy, i.e. those with only a minimal amount of myocardium covering the His bundle, Selective capture can commonly be achieved. This typically occurs with lower energy delivery. However, with increased pacing output it is likely that this additional energy would capture both the His and the small amount of surrounding myocardium leading to Non – Selective capture.

In those patients with a *type two* anatomy, where the His bundle is deep within the muscular septum, Selective capture is impossible to achieve. Non-selective capture can be achieved but likely only with higher pacing outputs and conversely with lower outputs not enough energy will be delivered to capture the His Purkinje system rather just the surrounding myocardium resulting in myocardial capture only.

In those patients with a *type three* anatomy, with a *naked* His bundle, engagement of the pacing lead with the His bundle is common, capture thresholds are observed to be low, Selective capture results and large injury pattern components are seen during deployment.

Figure 2-13 outlines the pacing responses that can be observed.

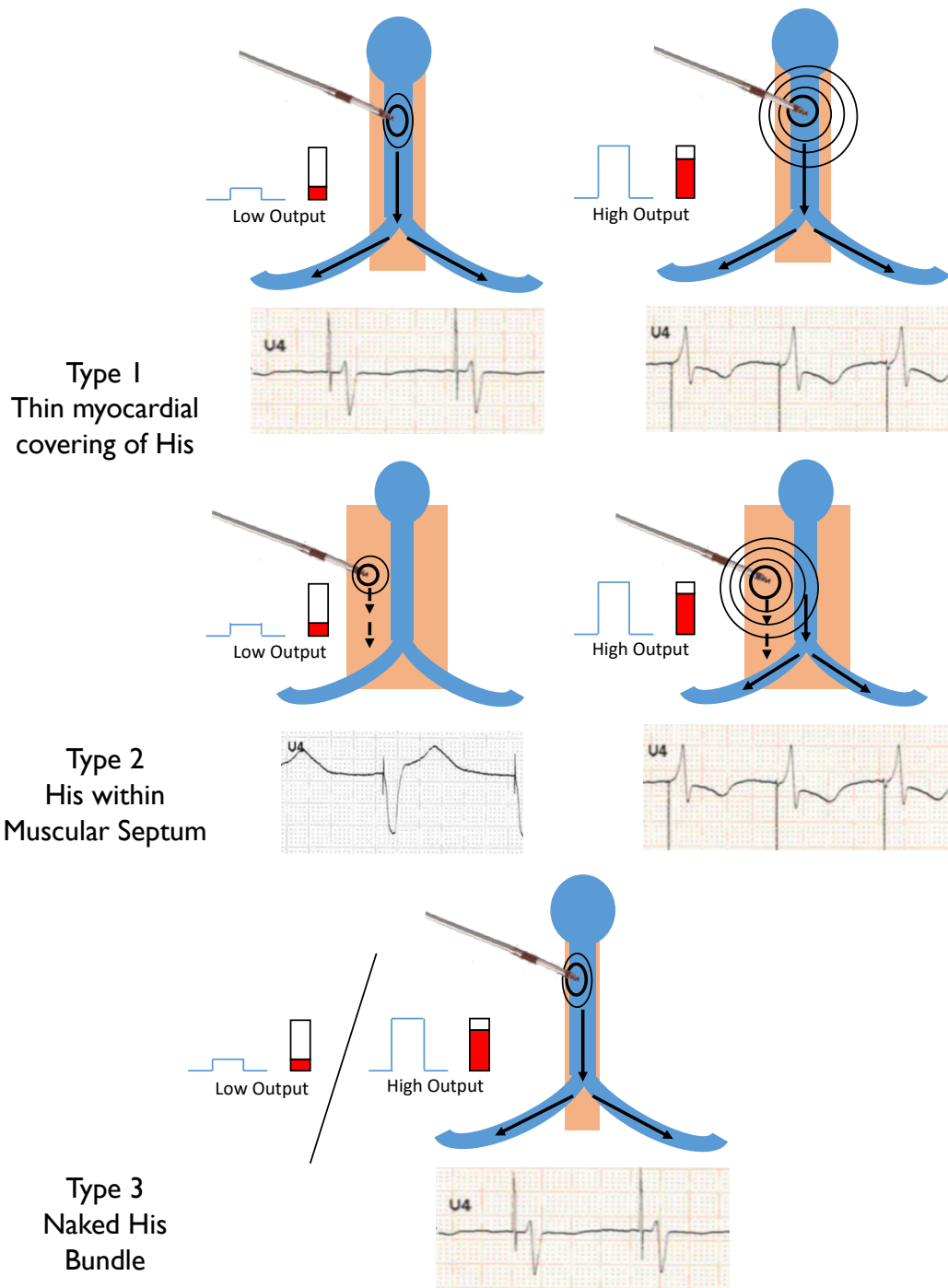


Figure 2-13 Cartoon showing the various His anatomical variations and the effect on pacing response with varying pacing outputs

3 Rationale, Feasibility, Procedural and Device characteristics of permanent His-Bundle pacing: 529 patient experience

3.1 Abstract

3.1.1 Introduction

His bundle pacing stimulates the His-Purkinje system to activate the ventricles physiologically, shortening activation time in bundle branch block and preserving activation time when QRS is intrinsically narrow. In principle these may be advantages over conventional pacing approaches. However, His bundle pacing has been reported to have low implant success rates, high fluoroscopy times and pacing thresholds that are high and rise with time.

This Chapter delineates the potentially beneficial role His bundle pacing may have and then report contemporary global practice in His bundle pacing. The Chapter focuses particular attention on length of learning curve, procedural characteristics and clinical outcomes to determine the current viability of His bundle pacing as an alternative to right ventricular or biventricular pacing.

3.1.2 Methods

Presented here is a retrospective, multi-centre, observational study of patients undergoing attempted permanent His bundle pacing, for any indication, at seven centres. The following procedural characteristics and clinical outcomes were recorded: pacing indication, pre-existing device, lead / delivery equipment, lead-generator configuration, fluoroscopy time, His bundle pacing thresholds, programmed stimulation energy and QRS duration. Where centres had systematically recorded implant success rates from the outset, these were also collated.

3.1.3 Results

529 patients underwent attempted His bundle pacing during the study period (2014-19) with mean follow-up of 217 ± 303 days. 49.5% were for high-degree atrioventricular block,

27.8% for slow atrial fibrillation, 8.9% sinus node dysfunction, 6.6% pre-AV node ablation and 7.2% for cardiac resynchronisation.

In the three centres with systematic longitudinal collation of all attempts, overall implant success rate was 81% which improved to 87% after completion of 40 cases.

All seven centres reported data on successful implants. In 88.6% of cases the C315 delivery sheath was successfully used. Mean fluoroscopy time was 11.7 ± 12.0 minutes. Mean implant His bundle capture threshold was 1.4 ± 0.9 V at 0.8 ± 0.3 ms. At last device interrogation mean threshold was 1.3 ± 1.2 V at 0.9 ± 0.2 ms, which was not significantly different from implant ($p=0.32$).

Overall, His bundle pacing did not prolong QRS duration (intrinsic 116 ± 31.6 ms vs paced 115 ± 23.8 ms, $p=0.5$) but when intrinsic QRS was >120 ms, His bundle pacing reduced it (intrinsic 150 ± 21.6 ms vs paced 127 ± 24.5 ms, $p<0.001$).

His bundle pacing lead re-intervention or deactivation (for lead displacement or rise in threshold) occurred in 7.5% of successful implants.

Both fluoroscopy time and His bundle capture threshold showed a learning curve with falling fluoroscopy time and threshold with greater operator experience levelling out between 30 and 50 cases.

3.1.4 Conclusions

In this, the largest observational study of His bundle pacing to date, it was found that it is feasible to establish a successful His bundle pacing program using the currently available implantation tools. Implant success and complication rates may be acceptable given the potential haemodynamic benefit. There is a clear learning curve for His lead implantation with a progressive reduction in fluoroscopy times and implant thresholds

with greater experience. The learning curve plateaus at ~30-50 cases, which may help inform His bundle pacing training standards.

3.2 Introduction

For 60 years right-ventricular pacing has been the standard of care for patients with bradycardia who require cardiac pacing. However, while right-ventricular pacing is very effective in preventing bradycardia, it produces non-physiological ventricular activation. The ventricular activation wave-front proceeds slowly via cell-to-cell conduction from the pacing site within the right ventricle, resulting in electrical dyssynchrony with delayed left ventricular activation. This non-physiological activation can lead to left ventricular impairment (Tops et al. 2009; Tse and Lau 1997). In the Predict HF study (Chen et al. 2013) which enrolled patients with normal ventricular function at the time of device implant, there was a clear correlation seen between paced QRS width and increased heart failure events. Furthermore, as previously mentioned right ventricular pacing when delivered to patients with ventricular impairment increases the incidence of both heart failure (Sweeney et al. 2003; The DAVID Trial Investigators* 2002) and death (The DAVID Trial Investigators* 2002).

Methods to mitigate the detrimental effects of ventricular pacing have included programming strategies to reduce exposure to right ventricular pacing. These device-based algorithms can successfully reduce right ventricular pacing but do so at the expense of allowing abnormally long, non-physiological, AV delays (Shurrab et al. 2017). Moreover, these algorithms are not useful in pacing dependent patients.

Alternative ventricular pacing sites, such as septal pacing, deliver a narrower QRS duration, but ventricular activation still occurs predominantly via slow cell-to-cell conduction and produces non-physiological ventricular activation patterns. This may explain why it has not consistently been found to be superior to right ventricular pacing (Kypka et al. 2008; Kaye et al. 2015).

Biventricular pacing delivers more rapid ventricular activation compared with right-ventricular apical pacing, however, activation is still significantly longer than during

normal physiological activation (Ploux et al. 2015; Jones et al. 2017). Therefore, when applied to patients with narrow QRS, biventricular pacing causes ventricular dyssynchrony which may explain the harmful effects seen when applied to this population (Ruschitzka et al. 2013).

3.2.1 His bundle pacing: the potential of physiological pacing

Since the first report of successful permanent His bundle pacing in 2000 by Deshmukh et al (Deshmukh et al. 2000), His bundle pacing has emerged as an alternative to both right ventricular myocardial pacing for patients with a bradycardia indication or as an alternative for cardiac resynchronization. The physiological ventricular activation pattern it delivers is desirable assuming it can be delivered in a safe and feasible manner. It is worth noting though that the first report of His bundle pacing demonstrated success in only 66% of patients with high thresholds ($2.4 \pm 1.0V$ at 0.5ms) and long procedural times (Deshmukh et al. 2000). With the arrival of dedicated delivery kit and a more established procedural approach, implant success rates are currently reported to be in the region of 80-92% (Vijayaraman, Naperkowski, et al. 2017; Sharma et al. 2017; Ajijola et al. 2017; Sharma et al. 2015; Abdelrahman et al. 2018) but this data comes from small numbers of patients in just a few centres.

3.2.2 Is His bundle pacing feasible?

Large randomised-controlled-trials showing a clear clinical benefit of His pacing are not yet available. However, data from observational studies does show promising results with respect to feasibility and importantly safety (Vijayaraman, Naperkowski, et al. 2017; Sharma et al. 2017; Ajijola et al. 2017; Sharma et al. 2015; Abdelrahman et al. 2018).

The His bundle pacing pioneers encountered several challenges during the early years of His bundle pacing, such as low procedural success rates, and high and rising thresholds (Deshmukh et al. 2000). However, with the arrival of specialized delivery equipment and a more suitable pacing lead, published His bundle pacing success rates appear to have improved accompanied by improvements in the time taken to position the lead, capture thresholds and ventricular sensing (Zanon et al. 2018; Vijayaraman, Naperkowski, et al. 2017). This published experience includes relatively small numbers of patients from a limited number of expert centres. Therefore, there have been concerns about whether, with current technology, it is feasible for His bundle pacing to be adopted more widely.

3.2.3 Aim of Study

This Chapter aims to determine whether *real-world* practice reflects the success reported by highly experienced operators. Furthermore, it aims to determine for the first-time data relating to the learning curve for His bundle lead implantation. It reports the experience of seven international centres who have adopted His bundle pacing, with a particular focus on the learning curve for performing His bundle pacing, acute implant success rates as well as acute and longer term His bundle pacing thresholds.

3.3 Methods

3.3.1 Study Design

This was a retrospective, multi-centre observational study designed to evaluate contemporary real-world practice of permanent His bundle pacing with regard to patient populations, procedural characteristics and device follow-up. The study population were all patients undergoing attempted permanent His bundle pacing, for any indication, at seven implanting centres (1 Germany, 1 Poland, 1 Switzerland, 3 United Kingdom and 1 United States). Baseline patient demographics together with relevant clinical information (QRS duration, NYHA class, LV function, presence of IHD) were recorded. Patients identified as being recruited to blinded randomised controlled trials, including the HOPE-HF double-blind randomised crossover trial (Keene, Arnold, et al. 2018), were excluded from this analysis.

3.3.2 Procedural Details

Procedural characteristics (indication, presence of pre-existing device, procedural success, lead/delivery equipment, lead-generator configuration, fluoroscopy time, His bundle pacing thresholds and programmed stimulation energy) were extracted from procedure reports and pacemaker databases.

Clinical indications for His bundle pacing were classified into five categories: (1) intermittent/permanent high-degree atrioventricular block (HD-AVB, including Mobitz type II second-degree atrioventricular block and complete heart block), (2) prior to atrioventricular nodal ablation (AVNA) for atrial fibrillation, (3) sinus node dysfunction (SND, including tachy-brady syndrome), (4) slowly conducted atrial fibrillation (AF) or (5) cardiac resynchronisation therapy. If patients had more than one indication, only their strongest pacing indication was registered. (For example, if a patient was reported to have both AV block and sinus node disease the indication recorded for the patient would have been AV block. Similarly, if a patient had both AV block and also LV impairment

[and would have been eligible for conventional CRT] although both AV block and CRT may have been noted within the indication, again only AV block would have been recorded as their strongest pacing indication. The pacing indication hierarchy used is the order in which they are listed above.

Procedural success was defined subjectively as a successfully deployed lead with adequate sensing (if required) and clinically acceptable His bundle capture threshold, as determined by the operating physician. Pulse width for His bundle pacing threshold testing was determined at the individual implanting centres. Selective and Non-Selective His bundle capture and myocardial-only capture were defined using previously described standard criteria (Zanon et al. 2018).

His bundle pacing lead delivery method was categorized into three: the fixed curve C315 His sheath (Medtronic, MN), the deflectable C304 delivery sheaths (Medtronic, MN) and the remainder which covered a variety of sheaths and hybrid approaches. The type of lead implanted to deliver His bundle pacing was also recorded.

It is known that fluoroscopy time is longer when more leads are implanted. In order to test the additional hypothesis that the rhythm during implantation might also have an influence on fluoroscopy time, both the number of leads and the rhythm during implantation were documented.

3.3.3 Clinical outcomes

Clinical outcomes (QRS duration, His bundle pacing thresholds and programmed stimulation energy) were extracted from hospital records and pacemaker databases. These outcomes were reported at implant and at the latest recorded follow up. His bundle pacing QRS duration was stratified by whether Selective or Non-Selective capture was achieved. Non-Selective capture of the His bundle results in capture of both the local myocardium, and the His bundle. The capture of the local myocardium with non-

selective pacing produces a pseudo-delta-wave on the ECG which prolongs the surface QRS duration.

Programmed stimulation energy was analysed as voltage and as a function of voltage and pulse width (V^2t , V = voltage, t = pulse width).

3.3.3.1 Statistical Analysis

Descriptive statistics including mean and standard deviation were used, and for within patient changes in parameters, paired t tests were performed for parametric data and Wilcoxon paired tests for non-parametric data. Differences between groups were assessed using ANOVA. To assess the impact of experience on pacing parameters, regression models were constructed (ordinary least squares or proportional odds as appropriate) with a restricted cubic spline with three knots for experience (measured as number of cases performed by that centre). Data analysis was performed using R version 3.3.

3.4 Results

His bundle pacing was attempted in a total of 529 patients, at the seven implanting centres during the study period (2014-19), permanent His bundle pacing was successfully achieved in 466 of these patients. Baseline demographics are displayed in Table 3-1. Mean follow up duration was 217 ± 303 days. 52% of patients were reported to have impaired ventricular function at the time of device implantation.

Table 3-1 Baseline Demographics

Age, years	75 ± 11
Male	363 (69%)
NYHA functional class	1.9 ± 0.9 (n=481)
I	184 (38.3%)
II	157 (32.6%)
III	127 (26.4%)
IV	13 (2.7%)
Left Ventricular Function	n=517
Normal	248 (48.0%)
Mildly impaired	72 (13.9%)
Moderately impaired	91 (17.6%)
Severely impaired	106 (20.5%)
12-lead QRS duration, ms	118 ± 33 (n=513)
Ischaemic Heart Disease	145 (33.9%, n= 428)
Values are mean ± SD or n (%) for all patients in whom permanent His bundle pacing was attempted. Where data is missing, 'n' is provided for the patients in whom data is available. NYHA – New York Heart Association.	

3.4.1 Procedural Characteristics

3.4.1.1 *Clinical Indications*

The majority of His bundle pacing attempts (49.5%) were performed in patients with intermittent or persistent high-degree atrioventricular block, 27.8% were performed for slowly conducted atrial fibrillation. CRT, sinus node dysfunction and AV node ablation were the least common primary indications for His bundle pacing (Figure 3-1). 86.2% of procedures were de-novo device implantations; the remainder were upgrades for previously implanted devices.

Primary Reason for Pacing

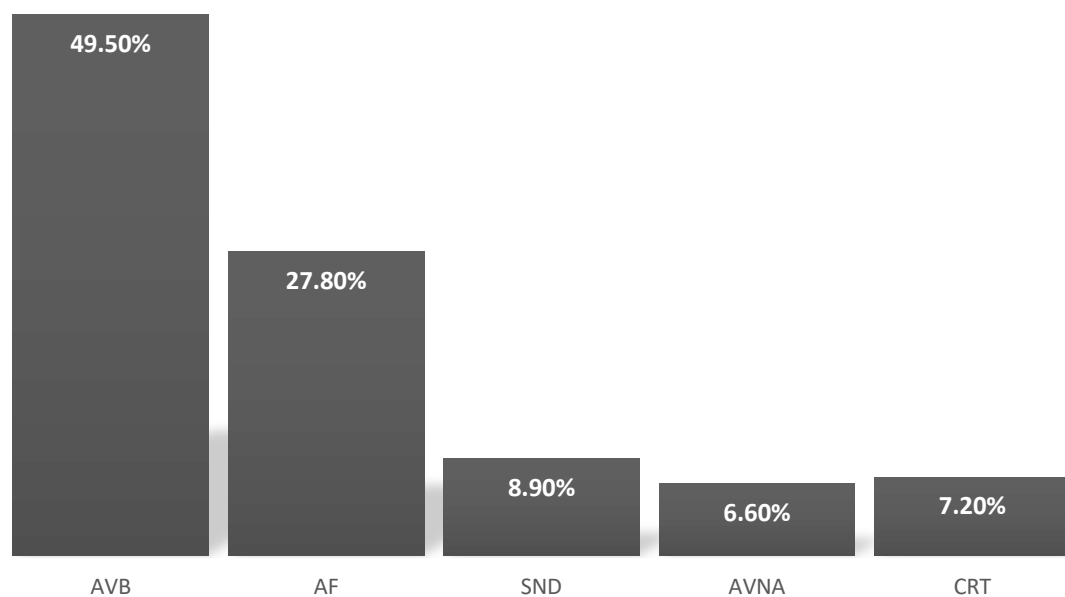


Figure 3-1 Primary Reason for Pacing

Bar chart of clinical indications for His bundle pacing (n=529). AVB: high-degree atrioventricular block, AVNA: pre-atrioventricular node ablation, SND: sinus node dysfunction, AF: atrial fibrillation with slow ventricular response, CRT: cardiac resynchronisation therapy.

3.4.2 Procedural Success Rates

Implant success rates were systematically recorded by 3 centres from the outset. Overall, successful permanent His bundle pacing was achieved in 81% of patients (denominator n=322). The patients in whom His bundle pacing was not achieved were more likely to have intrinsic broad QRS at time of the implant (71% had QRS>120ms) and the mean QRS of all failed implants was 139 ± 33 ms. In 39 cases the specific reason for His bundle pacing failure was not recorded. In the 22 cases where this information was available, the reasons for discontinuing the His pacing attempt were as follows: infra-Hisian block distal to the pacing site at high rates (n=2), unmappable His signal with unsatisfactory pace-mapping (n= 8), lead instability / displacement (n=3), failure to correct bundle branch block (n=7) and His pacing threshold prohibitively high (n=2).

With experience, successful implantation rates were higher, for example being 87% after 40 implant attempts.

3.4.3 Devices, leads and delivery equipment

In all patients the SelectSecure 3830 69cm lead was used to attempt His bundle pacing. In 89.0% of successful His bundle pacing cases the C315 fixed curve sheath successfully delivered the lead. In 10.1% of implants the deflectable C304 sheath was used and in 0.9% a C315 sheath was passed through a modified coronary sinus catheter or a coronary sinus guide catheter alone was used to position the His lead.

65 patients (14% of successful His bundle pacing implants) received a single lead pacemaker with only a His bundle lead. 182 patients (39%) received a dual lead pacemaker. In 36 of these patients, the His bundle lead was connected to the atrial port with a ventricular *'back-up'* lead connected to the ventricular port. In 146 the His bundle lead was connected to the ventricular port with a right atrial lead connected to the atrial

port; in two such patients a right ventricular sensing lead was also implanted and connected to the ventricular port along with a His bundle lead via a Y connector.

219 (47%) patients received triple lead devices. In 152 a CRT-P device was used, and 67 patients received a CRT-D device. In almost all CRT devices an atrial lead was connected to the atrial port, and the His lead and RV ("*back-up*") lead were connected to the ventricular ports, however alternative configurations were used in a small minority of cases.

From the 399 patients who did *not* require a mandatory RV lead for defibrillation purposes, 47% were implanted with a '*back-up*' ventricular pacing lead in addition to the His lead. Back up lead implantation decreased with experience ($p=0.0018$), this is shown in Figure 3-3.

3.4.4 Fluoroscopy Time

Mean fluoroscopy time across all procedures was 11.7 ± 12.0 minutes. Fluoroscopy times, stratified by number of leads and procedural rhythm, are depicted in Table 3-2. Overall, fluoroscopy times were not significantly affected by the underlying rhythm during the implant procedure.

30 implants involved a coronary sinus (CS) lead and were excluded from fluoroscopy time analysis (and Table 3-2) as variation in fluoroscopy use for CS lead implantation, is not relevant to this analysis and could be responsible for differences in overall fluoroscopy time. Fluoroscopy times tended to reduce with increasing His bundle pacing experience ($p=0.15$) as shown in Figure 3-3 with a levelling off after 30-50 cases.

Table 3-2 Implant Fluoroscopy time stratified by procedural rhythm

Device	Procedural Rhythm			
	AF	AVB	SR	All
Single-lead	10.4±12.0	n/a	n/a	10.4±12.0
	(n=63)	(n=0)	(n=0)	(n=63)
Dual-lead	9.7±7.5	9.2 ± 6.3	8.8 ± 7.1	9.2±7.0
*	(n=52)	(n=55)	(n=68)	(n=175)
Triple-lead	13.1±17.2	11.2 ± 13.6	13.8 ± 13.0	12.8±14.4
**	(n=50)	(n=59)	(n=75)	(n=184)
All	11.0±12.9	10.2±10.7	11.4±10.8	11.7±12.0
	(n=165)	(n=114)	(n=143)	(n=422)
Values are fluoroscopy time (minutes) mean ± SD (number of patients with available data). * excludes 4 patients implanted with an LV lead. ** excludes 26 patients implanted with an LV lead [2 patients data missing from single lead device, 3 patients data missing from dual-lead device and 9 patients data missing from triple-lead devices]				

3.4.5 Clinical outcomes

3.4.5.1 *Initial Thresholds and Programmed Pacing Outputs at implant*

The mean threshold of His bundle capture (whether Selective or Non-Selective) was 1.4 ± 0.9 V at 0.8 ± 0.3 ms (data available in 449 cases [96%]). Selective His bundle capture was achieved in 200 patients, with a mean capture threshold of 1.4 ± 0.8 V at 0.7 ± 0.3 ms. In 63 of these patients' Non-Selective capture occurred at pacing outputs above the threshold of selective capture, in these cases the mean threshold of Non-Selective capture was 2.6 ± 1.6 V at 0.7 ± 0.3 ms and the mean threshold of Selective capture was 1.1 ± 0.5 V at 0.7 ± 0.3 ms.

In remaining 249 patients Selective His bundle capture was not observed, the mean threshold of His bundle capture in this group was 1.4 ± 1.0 V at 0.9 ± 0.3 ms. In 64 of these patients a myocardial capture threshold was found to be lower than the Non-Selective threshold with a mean myocardial threshold of 0.9 ± 0.6 V at 0.9 ± 0.2 ms.

In patients with bundle branch block where either the left or right bundle was recruited by His bundle pacing (n=27), the mean threshold for bundle branch recruitment was 2.1 ± 1.0 V at 0.9 ± 0.2 ms and the mean threshold of His bundle capture (without necessarily recruiting both bundles) was 1.6 ± 0.8 V at 0.9 ± 0.2 ms.

Figure 3-2Figure 3-2 depicts the within patient change in thresholds for the different pacing responses seen.

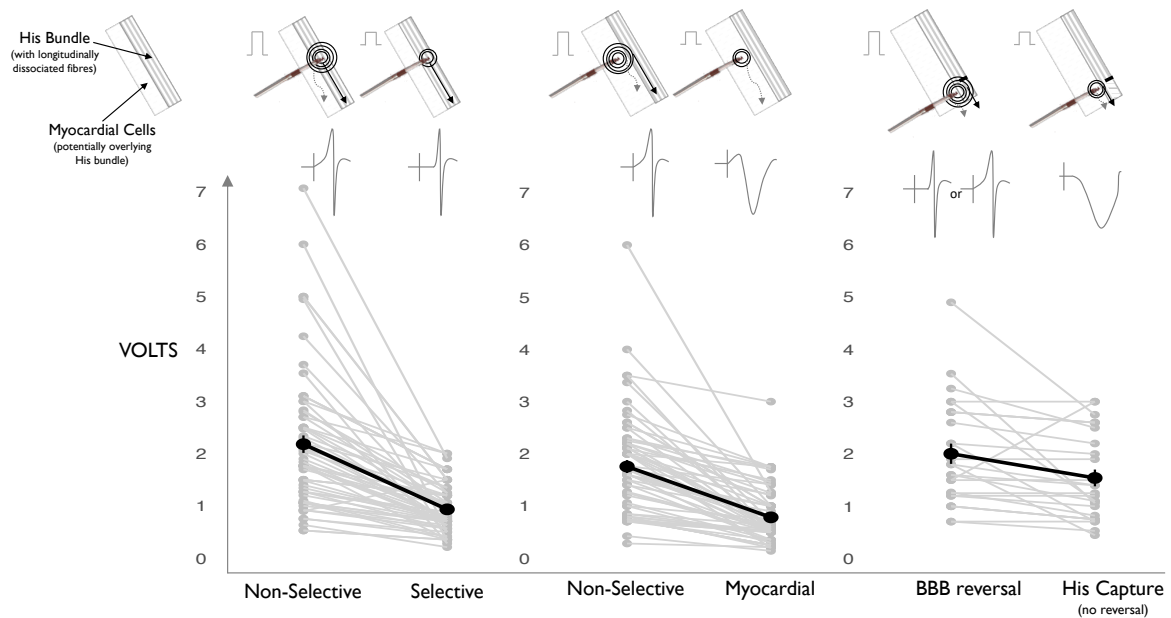


Figure 3-2 Within patient change in thresholds for different pacing responses

Within patient change in thresholds for potential different pacing responses seen with His bundle pacing. Cartoon illustrations are shown above depicting what may be occurring with change in voltage amplitude

The relationship between threshold of His bundle capture and centre experience is shown in Figure 3-3. As experience increased the threshold of His bundle capture reduced, before plateauing ($p=0.04$), again demonstrating a learning curve.

Mean programmed His lead pacing outputs across all cases at implant was 4.2 ± 1 at 0.9 ± 0.2 ms (data available in 322 cases) with a mean safety margin of 2.9 ± 1.2 V above the threshold of His bundle capture.

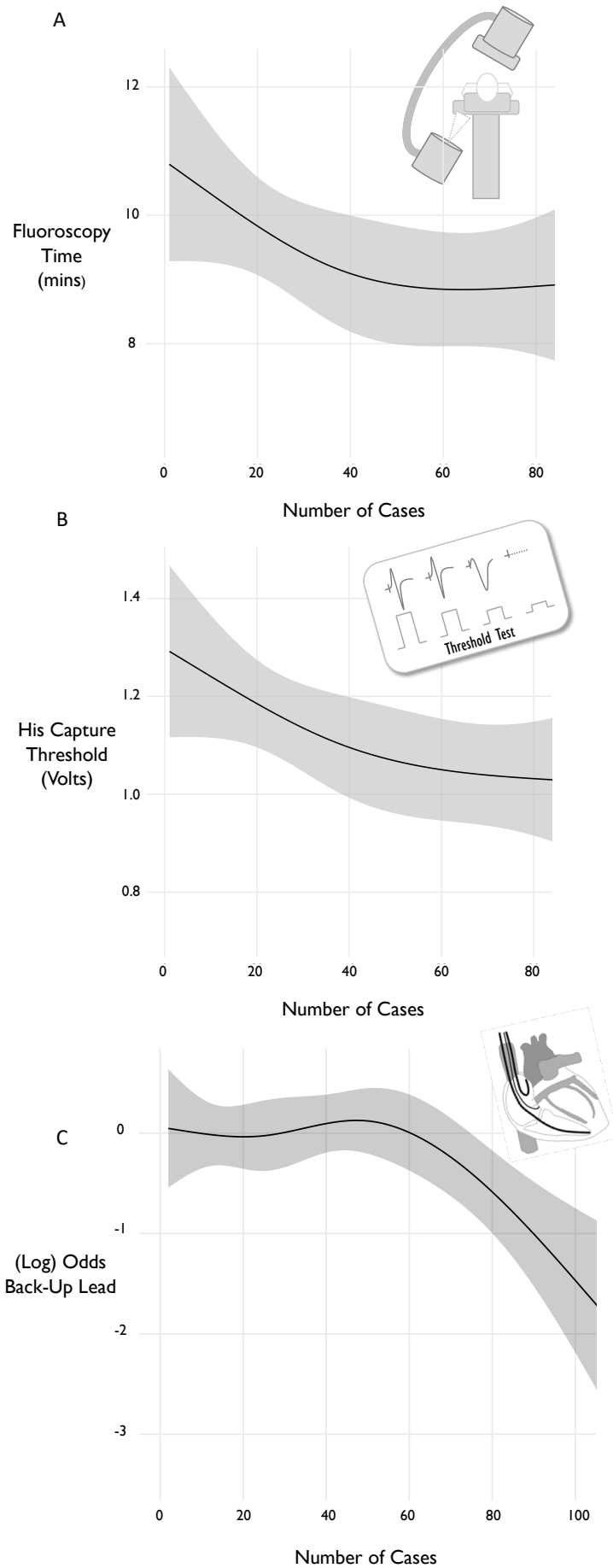


Figure 3-3 His bundle pacing Learning Curve Metrics

A, shows the relationship between fluoroscopy time and centre experience ($p=0.15$).

B, shows the relationship between pacing threshold and centre experience ($p=0.04$).

C, shows the log odds of receiving a back-up pacing lead in the ventricle ($p=0.0018$).

Overall successful implantation rate was 81% which increased to 87% after 40 cases. As number of cases per centre increased, there were reductions in fluoroscopy time and thresholds until a plateau is reached between 30 and 50 cases, and similar fall in the odds of receiving a back-up pacing lead thus demonstrating a learning curve.

3.4.6 Last available Follow Up Thresholds and Programmed Stimulation Outputs

The mean threshold of His bundle capture (whether Selective or Non-Selective) at the last available follow-up was 1.3 ± 1.2 V at 0.9 ± 0.2 ms (n=366). Mean programmed His lead pacing output at follow-up was 3.0 ± 1.1 V at 0.8 ± 0.3 ms with a safety margin of 1.7 ± 1.0 V above threshold of His bundle capture. Details of all thresholds for the various types of His bundle pacing are recorded in Table 3-3.

His bundle pacing threshold data was not available for all patients at follow-up. Reasons for this include: initial implant within 6 weeks and first follow-up not occurred (n=58), data not reported [although no mention of lead related issues included in supplied data set] (n=17), patient death (n=5), patient followed up at different hospital (n=1), pacemaker explanted due to infection (n=1) or explanted due to venous thrombosis (n=1).

There were 17 patients with no follow up capture threshold data reported due to His lead issues. Issues reported included myocardial only capture (n=3) [mean threshold 0.5V at 1ms] or lead deactivated (n=14). Reasons for deactivation include, rise in threshold (n=6), displacement and loss of capture (n=7) and observation of infra-Hisian block with pacing at rates >130bpm (n=1).

3.4.7 His Bundle Lead Complications

In addition to the 17 patients without follow up threshold data reported due to His lead issues, 8 additional patients had undergone lead revisions either due to displacement (n=5) or unsatisfactory threshold rise as defined by the patient's physician (n=3). In a further ten patients the His pacing lead had been deactivated due to displacement and loss of capture (n=3) or due to unsatisfactory threshold rise (n=7). Overall, therefore, 7.5% of initially successful implants experienced issues requiring either a lead revision or lead deactivation.

Table 3-3 His bundle pacing thresholds, Implant and Follow Up

	Initial Threshold	Follow Up Threshold	
<i>Lowest threshold of His bundle capture (selective or non-selective)</i>			
All HBP	1.4 ± 0.9 V 0.8 ± 0.3 ms (N = 449)	1.3 ± 1.2 V 0.9 ± 0.2 ms (N = 366)	
<i>His bundle captured selectively only</i>			
Selective HBP	1.4 ± 0.8 V 0.7 ± 0.3 ms (N = 200)	1.1 ± 1.0 V 0.9 ± 0.2 ms (N = 152)	
<i>Non-selective HBP threshold above selective HBP threshold</i>			
Non-Selective HBP	2.6 ± 1.6 V 0.7 ± 0.3 ms (N = 63)	2.4 ± 1.7 V 1.0 ± 0.1 ms (N = 82)	
Selective-HBP	1.1 ± 0.5 V 0.7 ± 0.3 ms (N = 63)	0.8 ± 0.5 V 0.9 ± 0.2 ms (N = 82)	
<i>His bundle is only captured non-selectively</i>			
Non-Selective HBP	1.4 ± 1.0 V 0.9 ± 0.3 ms (N = 249)	1.5 ± 1.7 V 0.9 ± 0.1 ms (N = 214)	
Pure Myocardial Capture	0.9 ± 0.6 V 0.9 ± 0.2 ms (N = 64)	1.0 ± 0.8 V 1.0 ± 0.2 ms (N = 59)	
<i>Intrinsic BBB corrected by HBP</i>			
BBB correction	2.1 ± 1.0 V 0.9 ± 0.2 ms (N = 27)	2.1 ± 1.1 V 0.9 ± 0.3 ms (N = 21)	
Lowest HBP	1.6 ± 0.8 V 0.9 ± 0.2 ms (N = 27)	1.3 ± 1.0 V 0.9 ± 0.3 ms (N = 21)	
Values are mean threshold (V) ± SD at mean pulse width (ms) ± SD. N is the number of patients with available data. HBP – His bundle pacing			

3.4.8 ECG responses

Mean pre-implant QRS duration across all attempted patients was 118 ± 33 ms and was 116 ± 31 ms in those successfully implanted. There was no difference in overall paced QRS duration which was 115 ± 24 ms ($p=0.5$).

In patients with an intrinsic QRS duration < 120 ms, the mean within-patient change from intrinsic QRS to Selective His bundle capture QRS was $+8 \pm 18$ ms ($n=125$) ($p<0.0001$) and the mean within-patient change from intrinsic QRS to Non-Selective His bundle capture QRS was larger 17.0 ± 23 ms ($n=130$) reflecting the presence of a pseudo-delta-wave on the ECG ($p<0.0001$).

In patients with intrinsic QRSd > 120 ms, the mean within-patient change in QRS duration from intrinsic QRS to Selective His bundle capture QRS was -21 ± 29 ms ($n=60$) and the mean within-patient change in QRS duration from intrinsic QRS to Non-Selective His bundle capture QRS was -27 ± 32 ms ($n=102$) ($p<0.0001$). Figure 3-4 shows the summary ECG changes and full details are provided in Table 3-4.

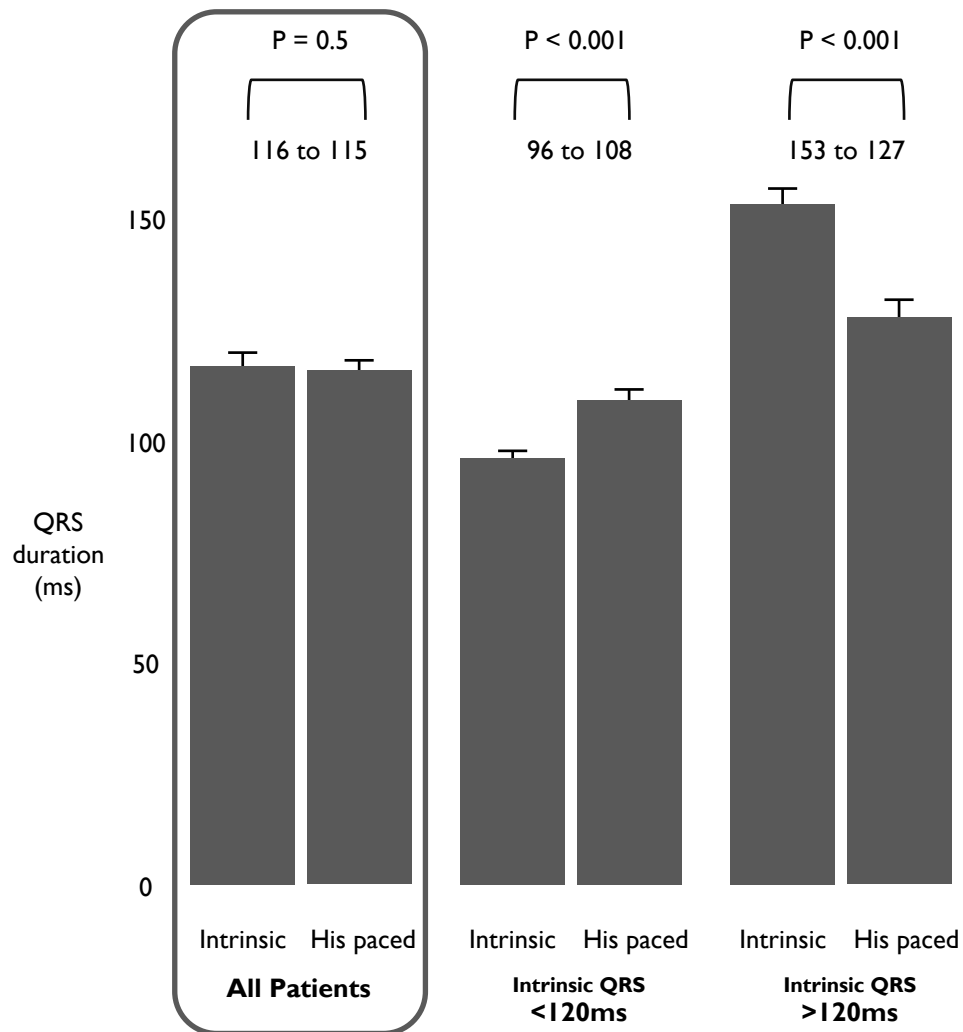


Figure 3-4 The effect of His bundle pacing on QRS duration

Summary of QRS duration changes for all patients receiving His bundle pacing and then stratified according to intrinsic QRS duration; less than or more than 120ms

Table 3-4 Effect of His bundle pacing on QRS duration

Group	QRS duration (msec)
All attempted implants pre-procedure	118 ± 33
All successful implants stratified by His Pacing only	
Pre-successful implant	116 ± 31.6
Post successful implant	115 ± 23.8
All successful implants stratified by Selective or Non-Selective Capture	
Selective capture	Pre 113 ± 28.5 Post 113 ± 22.4
Non-selective capture	Pre 118 ± 33.9 Post 117 ± 24.6
All successful implants stratified by intrinsic QRS duration and by Selective or Non-Selective Capture	
Preimplant QRS <120ms	Pre 97 ± 11.7
Selective capture reported	Post 105 ± 18.4 Diff 7.6 ± 17.5
Preimplant QRS <120ms	Pre 93±12.2
Non- Selective capture reported	Post 111±20.9 Diff 17.0± 23.0
Preimplant QRS >120ms	Pre 149±21
Selective capture reported	Post 127±20.6 Diff – 21.3± 29.0
Preimplant QRS >120ms	Pre 152±22.4
Non- Selective capture reported	Post 126±26.7 Diff – 27. ± 32

3.5 Discussion

In this large observational study of His bundle pacing, covering a period where seven international centres were adopting this pacing technique, we found relatively high implant success rates. There is clear evidence of a learning curve: as operator experience increased fluoroscopy time, His bundle capture thresholds and reliance on back up leads decreased. This learning curve appears to last between 30-50 cases. We found both acute and chronic His pacing thresholds were not excessively high. Loss of His capture or unacceptably high threshold requiring lead re-intervention or deactivation was observed in 7.5% of cases.

3.5.1 Implant success rates

Across the full range of experience, including the very first implants at each centre, the overall success rate of attempted His bundle pacing was 81%. After the first 40 implants at a centre (the median estimate for the learning curve) the success rate was higher at 87%. Other present day reports of His bundle pacing success rates are consistent with this ranging from 80 to 92% (Sharma et al. 2015; Zanon et al. 2018; Zanon et al. 2006). These are a contrast with the pioneering reports of His bundle pacing, which did not benefit from specialised delivery systems, that reported success rates as low as 66% (Deshmukh et al. 2000).

The current 87% success rates that can be expected by patients undergoing implantation at experienced centres are a result of both improvements in lead delivery approach and also growth of experience by implanting centres. It is likely that with further increases in collective operator experience and advancements in delivery tools that His bundle pacing may soon rival the success rates seen by right ventricular pacing and certainly biventricular pacing. His bundle pacing success rates show good progress in the context of other pacing revolutions. After a decade of biventricular pacing (BVP), the previous

such revolution, major RCTs reported success rates similar to those seen in this study: In the randomised PAVE study success rates were 83% (Doshi et al. 2005) and in the RD-CHF study 82% (Leclercq et al. 2007).

Importantly, His bundle pacing leads and delivery equipment can also be used for conventional atrial or ventricular pacing and even distal conduction system pacing where the left bundle itself is directly stimulated, offering flexibility when His bundle pacing capture cannot be achieved (Huang et al. 2017).

3.5.2 His Pacing Safety

In this observational study 7.5% of His pacing leads required either a repeat intervention or were deactivated. The most common reasons for this included either displacement or unsatisfactory threshold rise. Although this initially may appear high, this rate of safety concern must be contextualised. RV leads in the modern era experience issues requiring repeat intervention infrequently with 1.2-2.4% reported in a large Danish cohort study (Kirkfeldt et al. 2014) and a 3% incidence reported in the RV pacing arm of BLOCK HF (Curtis et al. 2013). LV leads, although more evolved than His leads, may represent a better comparator and in meta-analysis LV lead revisions occur in ~7% of cases (Gamble et al. 2016). An adequately powered RCT will be able to inform whether the risks associated with potential rise in thresholds and displacement can be offset by the potential improvement provided by physiological pacing delivery.

3.5.3 Choice of lead and delivery kit

The SelectSecure 3830 lead (Medtronic, USA) has emerged as the dominant lead used in His bundle pacing and was used in every case in this experience. The ability to sense His signals and also pace-map through the delivery sheath appears to be the most successful way of performing His bundle pacing. However, lead and delivery innovations are now on the horizon with most device manufacturers set to introduce new tools.

One advantage of the SelectSecure lead is that the active electrode is incorporated into the screw tip so the screw and the electrode engage together with the His bundle directly. This is in contrast to other leads where the electrode is proximal to the screw, which might impair mapping and capture of the His bundle.

The C315 His fixed curve delivery sheath appears to be sufficient in most cases to facilitate His bundle pacing with a different sheath required in only 11% of cases. The C315 does not allow flexibility in cases of dilated right atria and ventricles where the tricuspid valve and therefore the His bundle region are displaced. But its pre-shaped curves deliver the lead to the His bundle location in most other hearts. In the remainder of cases the deflectable C304 sheath permits the extra flexibility required but our study shows that operators are improvising solution to achieve successful His bundle capture when the C315 and C304 sheaths fail, by using the extra flexibility other coronary sinus sheaths may offer or by achieving extra-reach by constructing a hybrid delivery system involving a coronary sinus catheter that achieves the extra reach with a C315His catheter passed through it to maintain the desired perpendicular arrival at the His bundle.

3.5.4 Back-Up Pacing leads

The utilization of back-up leads is best studied in those patients who do not require a ventricular lead for any other purpose i.e defibrillator lead. In this patient group 46% were implanted with a 'back-up' pacing lead.

Back-up RV leads can offer improved ventricular sensing should the ventricular sensing be inadequate via the His lead. This may be the case if the His lead is in a location which provides an optimal pacing response which the operator does not wish to sacrifice in search of improved sensing. Although this situation is infrequent, it is relevant, not if the R wave is small as R waves $>1.3\text{mV}$ can be safely accepted, but rather if despite optimal

sensing programming the R wave cannot be differentiated from the atrial (or even His) electrogram signal.

Back-up RV leads also offer protection in the event of His lead displacement or loss of any ventricular capture – this potentially serious complication can however occur with any lead positioned in any chamber of the heart. There has also been concern regarding progression of infra-hisian block distal to the location the His lead has been deployed in. Although data regarding this is small, data out to 70 months of follow-up does not suggest that this phenomenon occurs. (Vijayaraman, Dandamudi, Lustgarten, et al. 2017).

Furthermore it is known in patients who have Non-Selective capture i.e they capture basal ventricular myocardial tissue in addition to engaging with the His bundle that in these patients should a micro displacement occur or a change in the His pacing threshold the lead will still maintain myocardial “*cell-to-cell*” ventricular activation in the same way that a septal or apical lead would provide ventricular activation and thus from a safety perspective this can provide reassurance to guard against asystole in the context of high grade AV block.

Our experience shows that operators do initially value the protection of a back-up RV lead despite low acute thresholds and low long-term lead failure rates, and with experience most operators are happy to withhold the back-up lead.

3.5.5 Fluoroscopy times are low and show a learning curve

Fluoroscopy time is important as a measure of procedural feasibility and can also be extrapolated to estimate overall procedure duration. Mean fluoroscopy time for His bundle pacing was acceptably low across all patients.

A key finding from our study is evidence of a learning curve. Fluoroscopy times becomes shorter as operators perform more cases and become more competent and comfortable with the technique. The relationship between fluoroscopy time and number of cases

performed levels out after 30 to 50 cases performed. This levelling out might suggest that this is when operators becoming highly competent with the technique. It is possible that this levelling out may also occur as despite adequate learned skills, operators with experience take on more complex cases (dilated hearts with displaced tricuspid valves, infra-nodal block and LBBB reversal for heart failure treatment) which can inversely affect procedural time. Both explanations invoke a familiarity with the technique as the reason for levelling out. This is the first study to clearly demonstrate a learning curve due to the smaller numbers of cases in previous studies.

3.5.6 Thresholds are low and also show a learning curve.

High His bundle pacing thresholds at implant and rising implants at follow up were previously viewed as problematic and, as discussed, RV back-up leads were often implanted prophylactically to guard against the potential for loss of capture. However, our study shows that His bundle pacing thresholds in contemporary practice are sufficiently low and even with allowing traditional safety margins of twice the His threshold would not prohibitively effect battery longevity (programmed output likely to be lower than battery voltage). The threshold of His bundle capture is low but importantly for those with Non-Selective capture the safety threshold of myocardial capture was even lower in this study. Even bundle branch recruitment appears to acceptably low, despite this previously being thought to require excessive energy. Reassuringly, thresholds on the whole were stable at follow up, which has also previously been a concern.

Reductions in His-capture thresholds at time of implant were seen with increasing experience with a similar pattern to that seen with decreasing fluoroscopy time. Again, further supporting evidence of an operator learning curve that levels out after between 30 and 50 cases.

3.5.7 ECG Capture Responses

ECG responses were in keeping with expected physiological responses. In those with intrinsic narrow QRS duration this was virtually preserved with Selective His bundle pacing but mildly prolonged (due to early activation of basal RV tissue) in those with Non-Selective capture.

Shortening of QRS in those who had QRS >120ms was noted irrespective of the type of capture achieved.

3.5.8 Learning curves

For both fluoroscopy time (and by extension procedural time) and His bundle capture threshold, a learning curve is observed plateauing after between 30 and 50 cases performed. This is useful for setting training standards for new His bundle pacing operators and perhaps also for setting operator experience levels for the urgently needed large, mortality counting, randomised trials of His-bundle pacing which must be the next step for this physiological pacing modality.

3.5.9 Limitations

This is an observational, registry data set reliant on physicians reporting of data not acquired prospectively. Data on R wave sensing was not available from all centres and therefore we were unable to report on sensing in this study. Although most centres were not recruiting into randomised control trials at least three were, this may have a small influence on the data derived for learning curves.

3.6 Conclusion

In this large, contemporary, global experience of His bundle pacing it has been shown that current practice has acceptable procedural success rates, acceptably low fluoroscopy time and low overall reliable His bundle capture thresholds. The current deactivation or reintervention rate is not prohibitive and is similar to that of LV leads. Due to the high number of cases included in this study of His bundle pacing, for the first time a learning curve is evident for falling fluoroscopy time and His bundle capture threshold with increased operator experience, plateauing at 30-50 cases.

- 4 Within patient comparison of His bundle pacing, right ventricular pacing and right ventricular pacing avoidance algorithms in patients with PR prolongation and a bradycardia pacing indication: Acute haemodynamic study

4.1 Abstract

4.1.1 Introduction

Prolonged PR interval can be haemodynamically harmful, but dual-chamber right-ventricular pacing to correct it induces ventricular dyssynchrony, itself harmful.

Therefore, in intermittent heart-block, pacing-avoidance algorithms are often implemented, delivering pacing only if absolutely necessitated. In this Chapter His-bundle pacing is tested as an alternative.

4.1.2 Methods

Out-patients with a long PR interval and intermittent need for ventricular pacing were recruited. I measured within patient differences in high-precision non-invasive haemodynamics between right-ventricular pacing, pacing-avoidance algorithms and His bundle pacing.

4.1.3 Results

18 patients were recruited. Mean left ventricular ejection fraction was $41.3 \pm 9\%$. Mean intrinsic PR interval was $266 \pm 42\text{ms}$ and QRS duration was $123 \pm 29\text{ms}$. Right-ventricular pacing lengthened QRS duration ($+54\text{ ms}$, 95% CI 42 to 67ms, $p < 0.0001$) whilst His bundle pacing delivered a shorter QRS duration than RV pacing (-56 ms , 95% CI -67 to -46ms, $p < 0.0001$).

His-bundle pacing improved acute systolic blood pressure by a mean of 5.0 mmHg (95% CI 2.8 to 7.1mmHg, $p < 0.0001$) compared to right-ventricular pacing and by 3.5 mmHg (95% CI 1.9 to 5.0mmHg, $p = 0.0002$) compared to the pacing avoidance algorithm. There was no significant difference in haemodynamics between right-ventricular pacing and pacing avoidance ($p = 0.055$).

4.1.4 Conclusions

His bundle pacing provides better acute cardiac function than pacing avoidance algorithms and right-ventricular pacing, in patients with prolonged PR intervals and a bradycardia pacing indication. His bundle pacing allows normalization of prolonged AV delays (unlike pacing avoidance) and does not cause ventricular dyssynchrony (unlike right-ventricular pacing). Clinical trials may be justified to assess whether these acute improvements translate into longer term clinical benefits in patients with a bradycardia indication for pacing.

4.2 Introduction

In patients who have intermittent higher degree conduction block and a long PR interval there are two major considerations when selecting a pacing strategy. A prolonged PR interval compromises cardiac function (Nishimura et al. 1995) and shortening pathologically prolonged PR intervals has the potential to improve cardiac function. However utilizing right ventricular pacing to shorten prolonged PR intervals can bring its own problems, namely ventricular dyssynchrony which itself compromises cardiac function, increases AF (Sweeney et al. 2007) and increases mortality (Wilkoff et al. 2002). Therefore, in patients with only intermittent bradycardia it is currently common practice (Brignole et al. 2013) to minimize ventricular pacing in order to utilize biological ventricular activation wherever possible.

In people with preserved ventricular function, current strategies to minimize ventricular pacing include programming long AV delays, setting AV hysteresis or applying dedicated ventricular-pacing avoidance algorithms. However, if AV delay is long, this itself interferes with cardiac function in several ways. First, the energy expended on the atrial kick is wasted, because it occurs too early, either before the E wave (passive ventricular filling) has finished or even during the preceding systole. Second, after the atrial kick, there is a pathologically long delay before systole. This allows blood that had been pumped from the atrium to ventricles to drift back into the atrium since the papillary muscles which tense to seal the mitral valve have not yet been activated by systole. These mechanisms combine to impair ventricular filling and reduce stroke volume (Hu et al. 2013; Nishimura et al. 1995).

In many patients with a long PR interval and an intermittent ventricular pacing requirement due to higher degree conduction block we are therefore faced with the choice of continuous right ventricular pacing (which causes undesirable ventricular

dyssynchrony) or taking steps to minimize ventricular pacing (which leaves the patient with undesirable AV dyssynchrony). Results of trials comparing these strategies suggest that the two undesirable desynchronies are of approximately equal size so that outcomes are the same with both options (Maurer 2003; Shurrab et al. 2017). Biventricular pacing is an alternative option, but is a more complex procedure, which utilizes more expensive technology.

4.2.1 His-bundle pacing allows correction of AV dyssynchrony without inducing ventricular dyssynchrony

His-bundle pacing provides a potential alternative to the two established pacing strategies. By directly stimulating the His-bundle normal physiological ventricular activation via the conduction system can be maintained in patients with intrinsic narrow QRS (Catanzariti et al. 2006). His-bundle pacing may even improve ventricular activation time and pattern in people who have bundle branch block and are indicated for pacing (Sharma et al. 2017; Sharma et al. 2018).

Therefore, His-bundle pacing allows AV delay to be shortened without causing ventricular dyssynchrony. Our research group have previously observed acute haemodynamic improvements in patients with a long PR interval and ejection fraction below 35% (Sohaib et al. 2015). What is not known is whether acute haemodynamic improvements occur when patients are selected on the basis of a bradycardia indication for pacing rather than wholly for resynchronisation.

His bundle pacing has the potential to have an increased energy utilization cost compared to the other pacing strategies. Compared to pacing-avoidance algorithms, AV optimised His bundle pacing will lead to a higher proportion of ventricular pacing. Compared to right ventricular pacing, His bundle pacing capture thresholds may be higher, which may also lead to increased energy utilisation (Sharma et al. 2015).

In this Chapter a group of patients with long PR intervals, who had a bradycardia indication for pacing in whom both a His lead and RV lead were implanted were studied. In this study acute within patient comparisons between AV optimised; His-bundle pacing, RV pacing and ventricular pacing-avoidance algorithms, using high precision acute haemodynamic measurements were performed. Furthermore, comparison of the device energy utilisation and effect on predicted battery longevity between the different pacing strategies was assessed.

4.3 Methods

18 patients with sinus rhythm and an intrinsic PR interval >200ms who had devices with pacing leads in the right atrium, His bundle and right ventricle (RV leads were sited either for pacing back-up or defibrillator capability) were recruited. All recruits were ambulatory outpatients who presented for a device check at least 3 months after their device implant and had evidence of at least 5% ventricular pacing despite the prior programming of pacing-avoidance algorithms.

All patients gave written informed consent for the study which was approved by the local research ethics committee.

4.3.1 His-bundle pacing

His-bundle pacing was always delivered using a Medtronic SelectSecure 3830 lead (Medtronic, MN, USA). His-bundle capture was confirmed using established criteria (Vijayaraman, Dandamudi, Zanon, et al. 2017) before enrolment. Both Selective and Non-Selective capture were acceptable for enrolment. We did not recruit patients with typical LBBB whose QRS duration was above 140ms. If the intrinsic QRS demonstrated either right bundle branch block (RBBB) or non-specific inter-ventricular conduction delay (IVCD) this was noted and any effect of shortening QRS duration by His bundle pacing recorded.

4.3.2 AV delay optimisation and haemodynamic assessment

AV delay optimisation was performed using a validated, high precision, non-invasive haemodynamic method which has been previously described in Chapter 2 (Zachary I Whinnett et al. 2006; Keene, Arnold, et al. 2018). In brief, this uses continuous non-invasive beat-by-beat blood pressure from the Finapres Nova device (Finapres Medical Systems, The Netherlands). The method is designed to minimise the effect of noise on

calculation of the optimal AV delay, through repeated alternations between test settings (the available programmable AV delays) and a reference setting, all conducted at a constant atrially based rate, in this case 80bpm. The aim was to test AV delays of 40ms, 80ms, 120ms, 160ms, 200ms, 240ms, 280ms and 320ms etc until fusion occurred. The reference setting was the pacing avoidance algorithm with the same programmed heart rate.

The relative change in mean systolic blood pressure between the reference setting (8 beats of the reference setting immediately before transitioning to a test setting) and the tested setting (8 beats immediately after the transition to the tested AV delay) was calculated. A minimum of six such transitions were performed between the reference setting and the atrial synchronous dual chamber pacing mode at each AV delay. The mean of all of these alternations was used to calculate the relative change for that particular programmed AV delay compared with the reference setting. The blood pressure changes for all tested AV delays were plotted on a parabola and the optimal AV delay derived, defined as the one that gave the greatest increment in cardiac function relative to the pacing avoidance algorithm.

Thus, the mean change in systolic blood pressure from the reference state to each dual-chamber pacing mode at the optimal AV delay was calculated. This permitted the haemodynamics of the three pacing modes (His dual-chamber pacing, RV dual-chamber pacing and the pacing-avoidance algorithms) to be compared *within each patient*.

4.3.3 Pacing Avoidance Algorithm

The pacing avoidance algorithm utilised in this study was the Managed Ventricular Pacing (MVP) algorithm (Medtronic MN, USA). In brief this algorithm operates in an AAI/(R) mode whilst monitoring for the presence of AV conduction. Should a persistent

loss of AV conduction be detected the device then switches to a dual-chamber pacing mode until consistent AV conduction returns.

Should AV conduction be transiently lost, the algorithm allows the device to initially remain in an AAI/(R) mode but provides a backup ventricular paced beat after one missed ventricular sensed event has been detected. Should two out of four A-A intervals not have a sensed ventricular event between them the algorithm initiates a switch in pacing mode to a dual-chamber pacing mode. The algorithm then performs periodic checks for resolution of intrinsic AV conduction, and if detected will return to the AAI/(R) mode.

4.3.4 Battery Longevity Assessment

Lead impedance, pacing thresholds and programmed lead output with suitable safety margins were known. For each patient the projected device longevity in each of the three modes was calculated. The calculation was based on a Medtronic Azure XT device (Medtronic MN, USA) with a programmed rate of 60bpm. The states compared were: (1) Pacing-Avoidance Algorithm with 50% atrial pacing and 5% RV pacing, (2) Dual-chamber His pacing with 25% atrial pacing and 100% His pacing and (3) Dual-chamber RV pacing with 25% atrial pacing and 100% RV pacing.

4.3.5 Data acquisition and statistical analysis

Haemodynamic and electrocardiographic data were acquired by using an analogue-to-digital card (National Instruments, Texas) and Labview (National instruments, Texas). The data were then processed with custom software written in Python. Statistical analyses were performed in R version 3.0.2 (R Project, Austria). Baseline characteristics were summarised as means and standard deviations. Paired and unpaired t-tests were used as appropriate.

4.4 Results

4.4.1 Patients

The 18 patients had a mean left ventricular ejection fraction 41.3% (SD±9) , of whom 8 had a CRT-defibrillator (Atrial, His and RV defibrillator leads) implanted and the others a 3-chamber pacemaker (CRT-P: Atrial, His and RV pacing leads) (Table 4-1). All patients were implanted with a His lead due to evidence of intermittent AV block and a degree of LV dysfunction and all patients had received at least 5% ventricular pacing despite the programming of pacing avoidance algorithms. During un-paced conduction, 2 patients had right bundle branch block and 2 patients had non-specific interventricular conduction delay.

Table 4-1 Patient and Pacing Characteristics

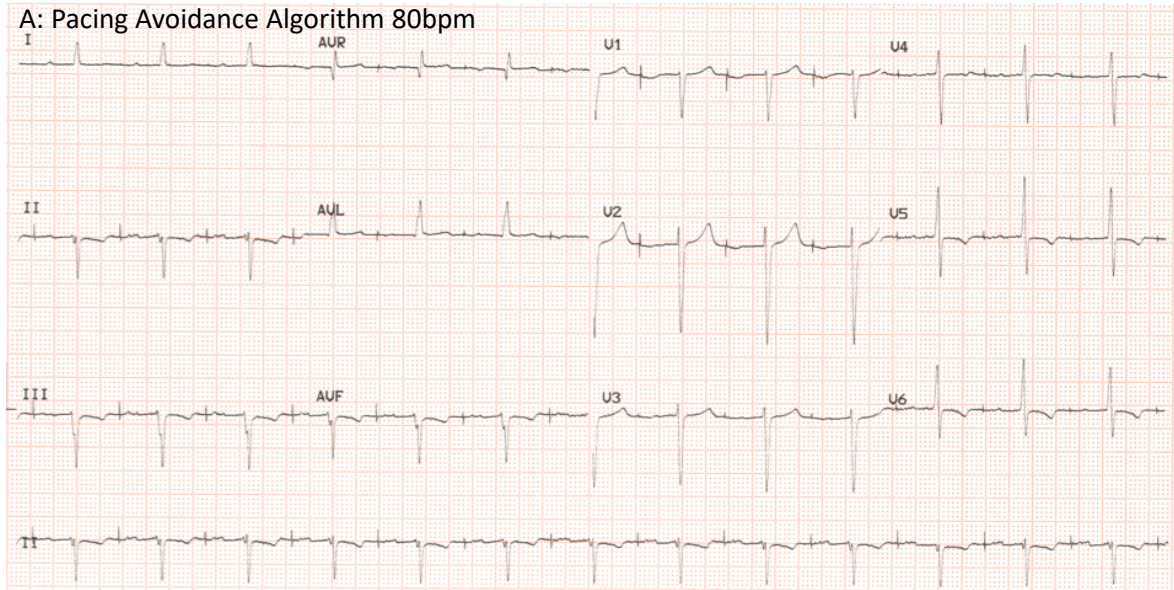
Patient and Pacing Characteristics of the 18 patients	
Male n (%)	15 (83%)
Age years	65.5 ± 8.6
Left Ventricular Ejection Fraction (%)	41.3 ± 8.8
Intrinsic PR interval (ms)	266 ± 42
Intrinsic QRS (ms)	123 ± 29
IVCD (n) % mean QRS (ms)	2 (11%) 140 ± 2.8
RBBB (n) % mean QRS (ms)	2 (11%) 188 ± 8.5
CRT-D implanted	8 (44%)
CRT-P implanted	10 (56%)
His pacing characteristics	
Selective capture	9 (50%)
Non-selective capture	9 (50%)
Paced QRS duration (ms)	121 ± 17
Lead impedance (ohms)	315 ± 54
Threshold (V) at (ms)	0.75 ± 0.5 at 0.83 ± 0.3
Output (V) at (ms)	2.27 ± 0.5 at 0.87 ± 0.3
RV pacing characteristics	
Paced QRS duration (ms)	178 ± 17
Lead impedance (ohms)	459 ± 85.6
Threshold (V) at 0.4ms	0.72 ± 0.32
Output (V) at 0.4ms	2.17 ± 0.30
RA pacing characteristics	
Lead impedance (ohms)	476 ± 65.0
Threshold (V) at 0.4ms	0.70 ± 0.39
Output (V) at 0.4ms	2.10 ± 0.57
IVCD – Interventricular conduction delay RBBB – right bundle branch block	

4.4.2 Electrocardiogram Assessment

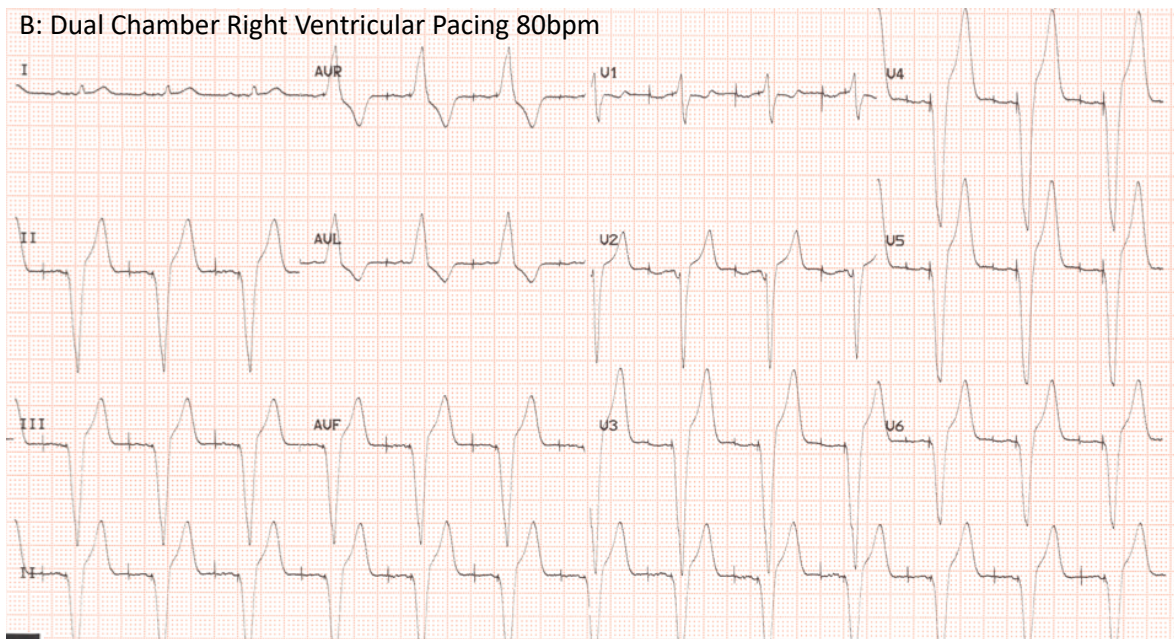
Both of the dual-chamber modes resolved the PR prolongation. Dual-chamber RV pacing however increased QRS duration from 123 ± 29 to 177 ± 17 ms (+54 ms, 95% CI 42 to 67ms, $p<0.0001$) whilst dual-chamber His bundle pacing had no significant effect on QRS duration compared to intrinsic conduction (123 ± 29 vs 121 ± 17 ms, -2.6 ms, 95% CI -8 to 13ms, $p=0.6$). As compared to RV pacing, His pacing delivered a significantly shorter QRS duration (-56 ms, 95% CI -67 to -46 ms, $p < 0.0001$). Figure 4-1 shows a single patient ECG example of the three pacing modes.

The effect of His bundle pacing on QRS duration depended on two factors. First, the pacing response achieved, this could be either Selective or Non-Selective capture. 9 patients with His bundle pacing had evidence of Non-Selective capture and the presence of a pseudo-delta wave which resulted in prolongation of the measured QRS. Or, secondly whether bundle branch block was present at baseline. In the two patients with RBBB, QRS duration shortened from 188 to 133ms (-55 ms, 95% CI -93 to 17ms, $p=0.035$). In those without bundle branch block, QRS duration overall was only minimally increased from 115 to 119ms (4 ms, 0.3 to 8.3ms, $p=0.07$) reflecting Non-Selective capture and the addition of a slurred upstroke between pacing stimulus and onset of QRS.

A: Pacing Avoidance Algorithm 80bpm



B: Dual Chamber Right Ventricular Pacing 80bpm



C: Dual Chamber His-Bundle Pacing 80bpm

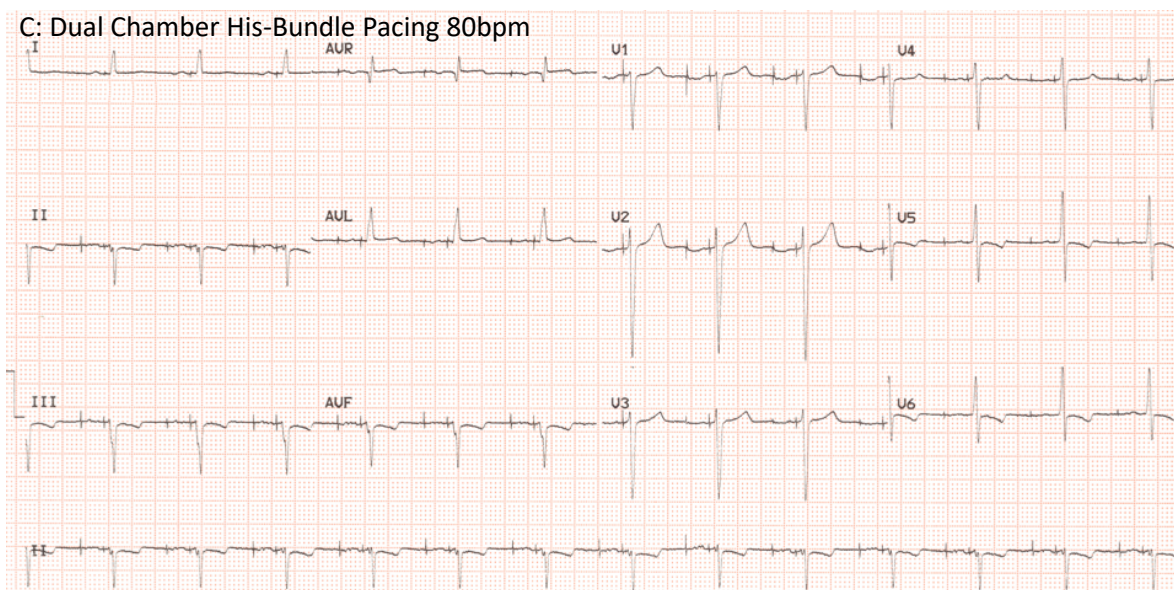


Figure 4-1 12 lead ECG examples for the three pacing modes for an individual patient.

A, shows the ECG during pacing avoidance algorithm. This shows an atrially paced rhythm at 80bpm with intrinsically activated QRS but with a prolonged PR interval.

B, shows the ECG during dual chamber RV pacing at 80bpm. This shows correction of the prolonged PR interval but the presence of ventricular dyssynchrony induced by right ventricular apical pacing.

C, shows the ECG during dual chamber His-bundle pacing at 80bpm. This shows correction of the prolonged PR interval and the presence of physiologically activated synchronous QRS complexes

4.4.3 Haemodynamic Assessment

His bundle pacing produced significantly higher acute systolic blood pressure compared with right-ventricular pacing by 5.0 mmHg (95% CI 2.8 to 7.1 mmHg, $p<0.0001$). There was no significant difference in acute systolic blood pressure when dual-chamber right-ventricular pacing was used to shorten AV delay compared with the pacing avoidance algorithm [-1.5 mmHg (95% CI -3.1 to 0.0 mmHg, $p=0.055$)]. Dual-chamber His bundle pacing produced a significant increase in systolic blood pressure 3.5 mmHg (95% CI 1.9 to 5.0 mmHg, $p=0.0002$) compared with the pacing avoidance algorithm.

Figure 4-2 shows a summary of the acute haemodynamic change at the optimal AV delay for all patients and Figure 4-3 shows the individual patient data.

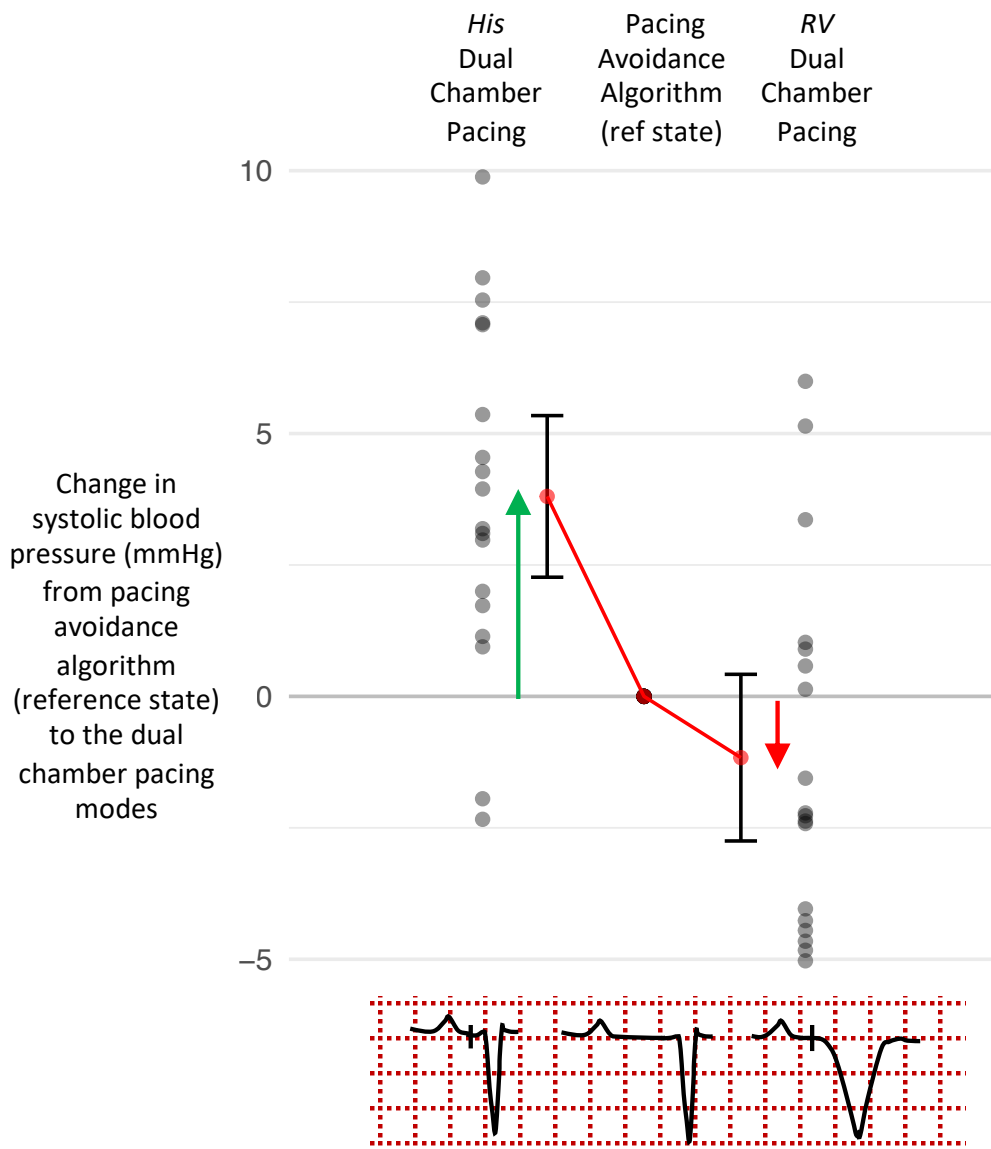


Figure 4-2 Summary Haemodynamic Data

Summary data for all 18 patients is displayed here. The mean change in systolic blood pressure at the optimal AV delay during both dual chamber His and RV pacing is plotted for each patient relative to the haemodynamic response during the pacing avoidance algorithm mode. Overall dual chamber His pacing improved acute haemodynamic response and RV pacing reduced it.

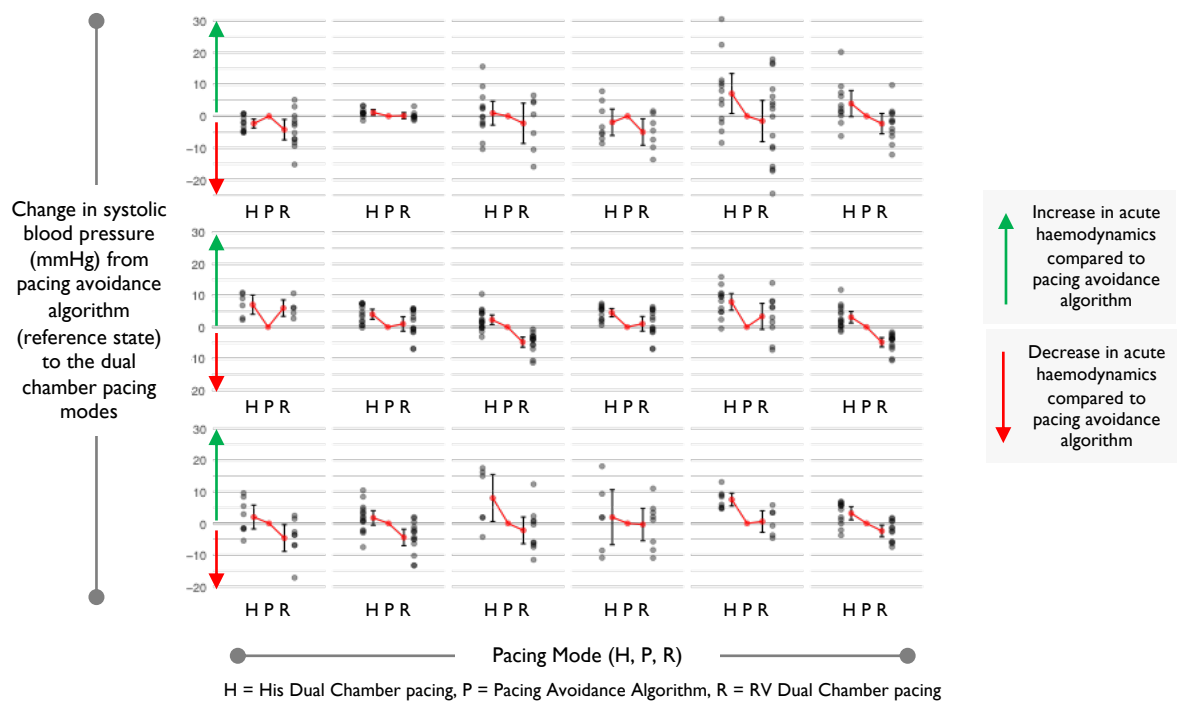


Figure 4-3 Individual Patient Haemodynamic Data

Individual patient data for each of the 18 patients is shown here comparing the changes in acute systolic blood pressure for each patient between AV optimised dual chamber His pacing and RV pacing relative to the pacing avoidance algorithms.

In 16/18 (89%) patients, His-bundle pacing performed best out of the three pacing modes. In the remaining 2 patients, it was pacing avoidance that performed best. RV pacing did not deliver the best haemodynamic response in any of the patients.

In six patients AV delay shortening with dual chamber right-ventricular pacing as compared to pacing avoidance algorithm resulted in an improvement in acute haemodynamics. No significant differences in ECG parameters were found between these two small groups (Table 4-2). Furthermore, across the whole cohort, there was no significant association between the haemodynamic benefit of RV pacing and either longer intrinsic PR interval or broader QRS ($p=0.4$ and $p=0.2$ respectively).

Table 4-2 Subgroup Data Analysis

	Pacing avoidance superior to dual chamber RV Pacing	Dual Chamber RV pacing superior to pacing avoidance	p
N (%)	12 (67%)	6 (33%)	
Acute haemodynamic effect of dual chamber RV pacing compared to Pacing Avoidance (mmHg)	- 3.4 ± 1.3	+ 2.0 ± 2.2	NA
Intrinsic PR (ms)	256 ± 41	284 ± 40	0.2
Intrinsic QRS (ms)	116 ± 17	138 ± 42	0.3
Baseline left ventricular ejection fraction % (SD)	42.3 ± 10.0	39.2 ± 6.1	0.42
Reduction in surface PR interval to the optimal AV delay with dual chamber RV pacing (ms)	61 ± 31	78 ± 56	0.51
Prolongation in surface QRS duration with dual chamber RV pacing (ms)	62 ± 19	39 ± 31	0.14

4.4.4 Device longevity assessment

Mean lead impedances, thresholds and programmed outputs for the right atrial, right ventricular and His leads are shown in Table 4-1. Duration of pacing stimulus was 0.4ms for right-ventricular and right-atrial leads but typically 1.0 ms for His leads to deliver better energy efficiency as per strength-duration principles (Coates and Thwaites 2000). Right-atrial and right-ventricular lead outputs were set using the device's auto adjustment process, with the proviso of being at least twice the threshold and a minimum output of 2 Volts. For the His lead, each patient had a fixed output programmed based on similar principles.

With dual-chamber His-bundle pacing, calculated battery longevity was 3.5 years shorter (9.3 ± 2.3 years) than with pacing-avoidance (12.9 ± 0.7 years, $p < 0.0001$) and 2.6 years shorter than with dual chamber RV pacing (12.0 ± 1.0 years, $p = 0.003$).

4.5 Discussion

This Chapter presents the first within patient comparison of AV optimised right ventricular pacing, a ventricular pacing avoidance algorithm and AV optimised His bundle pacing, using high precision haemodynamic measurements in patients with conduction system disease and a bradycardia indication for pacing. This chapter found that His bundle pacing delivers a significantly shorter QRS duration compared with RV pacing and that this more rapid ventricular activation translates into significant improvements in acute haemodynamic function.

Shortening AV delay using His bundle pacing also produced a significant improvement in acute haemodynamic function compared with a pacing-avoidance algorithm. Whereas using RV pacing to shorten AV delay did not improve cardiac function.

His bundle pacing compared with right-ventricular pacing

This study found that His bundle pacing produced a significantly shorter QRS duration compared with right-ventricular pacing and resulted in significant improvements in acute systolic blood-pressure.

Right-ventricular pacing is a very reliable method for preventing bradycardia in people with higher degree conduction block. However, right-ventricular pacing is known to be harmful when delivered to patients with left-ventricular impairment. In the DAVID trial RV pacing resulted in a ~50% increase in mortality. Chronic right-ventricular pacing can also lead to left-ventricular impairment in patients with previously normal ventricular function (Abdelrahman et al. 2018).

The mechanism of harm for right-ventricular pacing is believed to occur as a result of dyssynchronous non-physiological ventricular activation. This occurs because with direct

stimulation of right-ventricular myocardial cells the activation wavefront spreads slowly via cell-cell conduction.

His bundle pacing has been proposed as an alternative pacing strategy, which aims to produce physiological ventricular activation by utilizing the hearts natural conduction system which produces rapid and synchronous ventricular activation.

There is a growing body of evidence from observational studies that His bundle pacing is technically feasible, associated with a narrow QRS duration and associated with encouraging outcomes including heart failure hospitalisations and death when compared to alternate pacing modes in clinically similar patients (Zanon et al. 2018; Sharma et al. 2017; Ajijola et al. 2017; Sharma et al. 2015; Abdelrahman et al. 2018; Vijayaraman, Naperkowski, et al. 2017).

This study is the first to perform a within patient comparison of His-bundle pacing with RV pacing using high precision haemodynamic measurements. The finding that His-bundle pacing results in significantly higher acute haemodynamic function, suggests that the observed beneficial effect of His-bundle pacing are delivered through improvements in cardiac function. These improvements in cardiac function are most likely to be delivered as a result of more efficient ventricular activation, this is supported by our finding that His-bundle pacing produced a significantly shorter QRS duration compared to RV pacing. Our research team recently found that when His pacing is used for ventricular resynchronisation therapy in patients with LBBB and left ventricular impairment, that this produces a greater acute haemodynamic response compared to biventricular pacing. We demonstrated an incremental response between reduction in ventricular activation time and acute haemodynamic response. (Arnold et al. 2018)

Padeletti et al unexpectedly did not find a beneficial haemodynamic difference with His pacing compared to RV pacing (Padeletti et al. 2007). It may be that this apparent difference can be explained by differences in methodology. In the previous study

haemodynamic measurements were acquired from only a single alternation from AAI pacing to the tested pacing mode rather than calculating the mean from multiple alternations as was the case in our study. It is known that when acute haemodynamic measurements are used to assess the effect of pacing interventions that if multiple repeated measurements are not made this can result in wide error bars and a less reliable assessment of acute response. (Francis 2013; Whinnett et al. 2013)

This acute haemodynamic study supports the concept that delivering more physiological ventricular activation using His bundle pacing avoids the negative effects that right-ventricular pacing has on cardiac function. This supports the need for randomised-control-trials to prospectively assess this treatment approach on hard clinical endpoints.

4.5.1 Pacing options in patients with PR interval prolongation and indication for bradycardia pacing

When dual-chamber pacing with a right-ventricular lead is used to treat patients who have a long PR interval and intermittent conduction block, there are two competing physiological considerations. On the one hand while it is very effective in normalising PR interval, chronic right-ventricular pacing is known to be potentially harmful. RV pacing increases hospitalisations (e.g. HR 1.37, $P=0.02$, in MOST trial) (Lamas et al. 2002) and increases the risk of death and heart-failure (HR 1.61, $P<0.03$ in DAVID trial) (Wilkoff et al. 2002). Therefore, ventricular pacing-avoidance algorithms have been developed and utilised to mitigate this problem. However, pacing-avoidance algorithms permit the existence of very long PR intervals which can be detrimental to cardiac function since long PR interval impairs ventricular filling, because it disrupts efficient diastole.

This study investigated the within patient effect of AV delay optimisation using RV pacing and His bundle pacing. AV optimisation delivered using right-ventricular pacing did not significantly change acute haemodynamic function, indeed there was a non-significant trend for a decrease in acute cardiac function. This suggests that the benefits

of AV optimisation were outweighed by the detrimental effects of right-ventricular pacing. A randomised cross-over study assessing quality of life, LV function and exercise capacity measured by cardio-pulmonary exercise testing in 14 patients previously showed approximate equivalence between pacing-avoidance algorithms and dual-chamber RV pacing, which is consistent with our findings (Maurer 2003).

AV optimised His-bundle pacing resulted in a significant improvement in acute systolic blood pressure. This suggests that if physiological ventricular activation can be maintained then there is the opportunity to improve cardiac function in this group of patients, which has the potential to lead to an improvement in symptoms.

Our research group previously found a haemodynamic improvement with AV optimised His bundle pacing in patients with severe left ventricular dysfunction and no bradycardia pacing indication (Sohaib et al. 2015). His optimised pacing in this group of patients is currently being evaluated in the HOPE-HF trial (Keene, Arnold, et al. 2018). Details of the trial design and rationale are included in the Appendix of this thesis. In the current study we investigated patients who had a bradycardia indication for pacing, LV function was not an entry criterion for the study and therefore we included a spectrum of different LV function. My findings that shortening a pathologically long AV delay in this group of patients improves acute cardiac function supports further investigation of the role of AV optimised His bundle pacing in patients with a long PR interval regardless of underlying LV function.

Long PR interval can be detrimental to cardiac function since it impairs ventricular filling by disrupting efficient diastole. The effects on ventricular filling and subsequent reductions in stroke volume and cardiac output seemingly though can be offset by shortening the PR delay with pacing that allows physiological ventricular activation. This is illustrated in Figure 4-4.

	Prolonged AV delay	Optimised AV delay
ECG		
Pulse Wave Doppler Mitral inflow		
2D Echo		
Continuous Wave Doppler Trans-mitral		
Aortic VTI		
Acute Systolic Blood Pressure		

Figure 4-4 Potential Mechanism of Benefit with AV Delay optimisation

The left side of the figure demonstrates the physiological effects of prolonged AV delay and the right side of the figure the positive haemodynamic effects of correcting this. Ideally there is a passive early diastolic phase of ventricular filling followed by an atrial kick and then immediately ventricular contraction (without leaving any time for the blood pushed into the ventricle by the atrial kick to passively drain back into the atrium). When the PR interval is abnormally long, the atrial kick occurs earlier (with respect to the preceding ventricular relaxation and the succeeding ventricular contraction). This has dual disadvantage. First, the atrial kick occurs during the E wave, wasting the opportunity for maximum spontaneous filling at no energy cost, or even earlier, during late ventricular systole which is even more wasteful. Second, after the atrium has forced blood into the ventricles there is a pathological pause before the ventricles and papillary muscles contract sealing the mitral valve. This pathological pause permits blood to drain backward from ventricle to atrium (diastolic mitral regurgitation). Both mechanisms reduce ventricular filling and thereby reduce stroke volume and cardiac output, and both waste energy. These detrimental effects are corrected by dual chamber pacing at an optimal AV delay if the pacing mode does not induce its own dyssynchrony.

Patients with long PR interval have been seen in population studies to have an association with increased (1) mortality, (2) atrial fibrillation, (3) heart-failure, (4) coronary artery disease and (5) progression of conduction disease. (Cheng et al. 2009; Magnani et al. 2013; Blackburn et al. 1970; Crisel et al. 2011; Nielsen et al. 2013) Similar findings have also been reported in subgroup analyses of randomised controlled trials. (Holmqvist et al. 2014; Nielsen et al. 2012)

Biventricular pacing (although not tested in this study) is an alternative method of resolving AV dyssynchrony while producing less ventricular dyssynchrony than RV pacing. Results with biventricular pacing studies of patients with bradycardia have been mixed, with improved clinical outcomes in the BLOCK HF trial of patients with impaired LV function (Curtis et al. 2013) and neutral results in the BIOPACE trial in patients with relatively normal LV function (Funck et al. 2014; Beck and Curtis 2016). Caution should be exercised when postulating potential benefit of biventricular pacing in patients other than in those with broad QRS and LV impairment due to the increased mortality seen in the ECHO CRT trial which looked at patients with heart failure, objective mechanical dyssynchrony and narrow QRS (Ruschitzka et al. 2013).

4.5.2 Need for a trial

In patients with long PR, His bundle pacing results in distinctly better haemodynamics in almost all cases but involves continuous ventricular pacing, thereby consuming more energy than the pacing-avoidance algorithms. His pacing thresholds also tend to be higher than RV pacing thresholds. Both of these factors mean that chronic AV optimised His pacing would lead to greater battery usage, which would mean more frequent generator changes. A trial is needed to determine whether the improved haemodynamics seen translate into better patient outcomes even in spite of current higher energy requirements.

Future developments could improve the energy demands of His-bundle pacing. For example, the Medtronic SelectSecure 3830 is the most commonly used lead to pace the His bundle but it has a lower impedance than other pacing leads, which means more energy is wasted. As another example, there are no reliable automatic capture management algorithms for dynamically determining the pacing output threshold to safely permit minimization of energy utilization on His leads, this could also be a major step forward in reducing energy wastage in the future as currently fixed outputs with adequate safety margins are mandated.

4.5.3 Study limitations

This is a short-term within patient comparison focusing on cardiac function, rather than a long-term endpoint trial.

Whether the energy price of His bundle pacing is worth paying depends on whether the haemodynamic benefits translate into clinical benefits. Determining the later requires a suitably sized randomised-controlled-trial.

This study was conducted in an outpatient environment in patients who already had a His pacing device. It therefore could only compare modes achievable by that implanted system which did not include biventricular pacing. Therefore, this trial and any other in an outpatient setting cannot compare within patient differences of His-bundle to traditional biventricular pacing. However, separately, our research team have carried out an invasive, haemodynamic comparison of His pacing versus biventricular pacing in a cohort with heart failure and LBBB at the time of device implant. (Arnold et al. 2018) In this study, both His pacing and biventricular pacing improved haemodynamics but His pacing achieved significantly better haemodynamics than biventricular pacing (4.6mmHG to 12.4mmHG, $p=0.04$).

The patients recruited into this study had a range of LV function, ranging from normal to severely impaired. It was however, encouraging that acute haemodynamic improvements were observed in patients with normal ventricular function as well as those with impaired cardiac function.

4.6 Conclusions

This mechanistic study using high precision haemodynamic measurements and within patient comparison found that His bundle pacing leads to improved acute haemodynamics compared with right-ventricular pacing in patients with a bradycardia indication for pacing. Interestingly, the findings also suggest that in patients with a long PR interval that AV optimised His-bundle pacing is advantageous compared with a ventricular pacing avoidance algorithm. The His pacing strategy does however come at the cost of greater device energy requirements compared with the other two strategies. The study supports the need for randomised trials to assess whether the beneficial effects on cardiac function outweigh the risks associated with the requirement for more frequent pacing generator changes.

- 5 Separating and quantifying the haemodynamic harmful components of Ventricular Tachycardia: the therapeutic potential, both expected and unexpected

5.1 Abstract

5.1.1 Background

The haemodynamic effects of Ventricular Tachycardia can differ greatly between patients and even between episodes of similar rates within the same patient. There are various potential mechanisms by which VT causes impaired haemodynamics and consequently there may be cardiac pacing interventions that could target these different mechanisms to support haemodynamic function within episodes of tachycardia.

Therapies that terminate tachycardia are well established and include Anti-Tachycardia Pacing and defibrillation. However, the former is not always successful and may cause acceleration of the rhythm disturbance, and the latter is painful and causes both pathological and psychological harm to patients.

His bundle pacing may, in principle, assist haemodynamics during VT by improving ventricular coordination. The size of any such effect has not been established.

This Chapter aims to examine the various mechanisms by which VT impairs cardiac function, and quantify the potential benefit of novel pacing therapies including His bundle pacing in VT.

5.1.2 Methods

5.1.2.1 *Part 1: Mechanisms of Haemodynamic Harm during VT determined by simulated VT*

24 patients with LV systolic dysfunction were recruited who *either* had a previously implanted cardiac rhythm management device with atrial, RV and His bundle leads *or* attended for a clinically indicated EP study including VT stim or VT ablation *or* for cardiac rhythm management device implantation. Using beat-by-beat blood pressure monitoring and acquisition, as previously described, they underwent a pacing protocol designed to determine the contributions to harm of potential differing mechanisms. The

effects of different heart rates, atrio-ventricular (AV) synchrony and bi-ventricular (VV) synchrony were tested.

5.1.2.2 Part 2 Novel Pacing Interventions during VT to improve haemodynamics

23 patients with LV systolic dysfunction were recruited who were attending for clinically indicated VT stimulation or VT ablation procedures. VT was observed in 11 patients (either spontaneously or induced via electrophysiological manoeuvres) the effects of isolated atrial and isolated His bundle pacing therapies were studied using beat-by-beat blood pressure. Those in whom VT was not induced (n=12) underwent my simulated VT mechanism protocol and were only included in Part 1.

5.1.3 Results

5.1.3.1 Part 1

As might be expected, as the rate of asynchronous ventricular pacing (simulated VT) increased acute haemodynamic function declined. The mean percentage decrease in systolic blood pressure from the baseline state at 80 bpm was 15.5%, expanding to 44.4% at 190 bpm ($p<0.0001$). The addition of isolated atrial synchrony to simulated VT improved blood pressure by 10.7% at 125 bpm ($p=0.06$) and by 1.5% at 160 bpm ($p=0.5$). Greater improvements in haemodynamics were seen with the restoration of isolated biventricular synchrony through the addition of His bundle pacing. Blood pressure improved by 13.9% at 125 bpm ($p=0.0002$) and by 9.4% at 160 bpm ($p=0.024$). The combined addition of both atrial synchrony and biventricular synchrony through the addition of dual chamber atrial synchronous His bundle pacing improved blood pressure even more: by 15.4% at 125 bpm ($p=0.0009$) and by 34.9% at 160 bpm ($p=0.0002$).

5.1.3.2 Part 2

Clinical VT was seen in 11 patients however in one patient, before any pacing therapies were tested the VT degenerated into VF requiring defibrillation. Therefore 10 patients

underwent pacing interventions. The first 6 patients underwent the original protocol (A), which was designed only to improve haemodynamic function during VT. Unexpectedly 2 of these patients had VT termination during the protocol. The protocol was therefore modified (B) to increase the ability to detect whether it was the pacing, or merely the passage of time, that terminated the VT. The last 4 patients underwent protocol B.

The mean VT rate in the ten patients was 143 ± 21 bpm. In the 6 patients who underwent protocol A (His bundle pacing), blood pressure increased by 12.9 (CI 11.6 – 14.1) mmHg ($p < 0.0001$). All patients undergoing protocol B experienced VT termination with His bundle pacing.

5.1.4 Conclusions

This Chapter has delineated the contributions of AV and VV synchrony to the harmful effects of VT. It has then demonstrated that during actual VT that asynchronous His bundle pacing can significantly improve cardiac function supporting the patient during VT. Furthermore, it has allowed for the discovery that His bundle pacing seems to be able to terminate ventricular tachycardia.

These results suggest that quite apart from the potential for His bundle pacing in bradycardia, it also provides a novel approach that allows VT to be better tolerated *or even terminated*.

5.2 Introduction

Ventricular tachycardia (VT) frequently causes haemodynamic harm. The haemodynamic effects of VT are variable between patients and even within the same patient. The adverse haemodynamic effect is not solely due to heart rate, since the same heart rate during sinus rhythm, SVT, and VT can cause widely different haemodynamic effects.

Understanding the mechanism by which VT causes harm may enable the development of therapies that can stabilise the patient during VT and perhaps even allow termination of VT without delivering painful shocks.

5.2.1 Potential mechanisms by which VT causes haemodynamic impairment

The haemodynamic effect of VT depends on a complex interplay between a multitude of physiological changes that occur both within the heart and within the wider circulatory system. Within this chapter I limit myself to the cardiac rather than the vascular mechanisms.

5.2.1.1 Heart rate increment

Heart rate itself is a powerful mechanism through which VT impairs cardiac function. Raised heart rates occurring during VT, particularly in patients with impaired ventricular function, are known to result in reductions in cardiac function. (Steinbach et al. 1994; Samet 1973; Hamer et al. 1984) However, the observation that supraventricular or sinus tachycardias, even when they occur at similar rates to VT, do not tend to have such adverse consequences in haemodynamic function would suggest that heart rate alone is not wholly responsible for the decline in cardiac function.

Excluding afterload, a reduction in cardiac output results from a further two factors. A reduction in diastolic filling (“preload”), and a reduction in contractility.

5.2.1.2 Loss of atrial contribution to ventricular preload

At *normal* heart rates, appropriately timed atrial contraction contributes approximately 30% to normal diastolic ventricular filling. (Steinbach et al. 1994) During VT the loss of atrial contribution to ventricular filling may have significant adverse consequences on cardiac function. (Steinbach et al. 1994; Maloney et al. 1992; Hamer et al. 1985; Kosowsky et al. 1968)

Reduced diastolic filling times

High ventricular rates and rapid cycle lengths can lead to shortened diastolic filling times and subsequent incomplete ventricular filling.

Incomplete ventricular relaxation

Incomplete ventricular relaxation may occur between rapid beats. This can lead to an effective reduction in diastolic compliance and hence further reduces ventricular filling.

VT causes AV dyssynchrony

VT characteristically involves the loss of atrio-ventricular synchrony. This dissociation will further reduce filling as the atria will not necessarily contribute to ventricular filling and may even contract against closed atrio-ventricular valves during ventricular contraction.

Reflex activation of baroreceptors

Furthermore, there may be a negative impact of poorly timed atrial contractions and subsequent cannon 'a' waves which can rebound off closed AV valves which may initiate atrial stretch baroreceptors causing subsequent vasodilatation and worsening of hypotension.

5.2.1.3 *Reduced Contractility*

Loss of Ventricular Synchrony and Dyssynchronous Ventricular activation

VT typically results in abnormal and dyssynchronous ventricular activation patterns, which may also contribute to the impairment in cardiac function. (Steinbach et al. 1994; Gilmore et al. 1963; Badke et al. 1980; Lima et al. 1983) The characteristic wide QRS complexes in VT are a manifestation of this electrical dyssynchrony. The broad QRS pattern may represent an inefficient contractile sequence and could lead to reduction in stroke volume. This inefficient contractile sequence may be exaggerated by the effects of progressive ischaemic dysfunction that occurs with progressive VT duration that could lead to further deteriorations in cardiac function.

What is unclear is *to what extent* the different components above affect the haemodynamic state. This question is not merely of theoretical interest but might be of practical value. In a patient in VT, there are two reasons why one might wish to improve haemodynamics while they remain in VT. First, one may be delaying a shock to give an opportunity for symptomatically and prognostically beneficial spontaneous termination. In this scenario at least improving haemodynamics gives the patient more comfort and prolongs the window of opportunity for spontaneous termination. Second, whilst performing VT ablation in the electrophysiology catheter laboratory, it is diagnostically and therapeutically desirable for the patient to remain in VT but providing better haemodynamics again improves patient comfort and allows more detailed mapping and intricate ablation to be performed.

5.2.2 Current Approaches for Device Based Management of VT

Current implantable cardiac rhythm management device-based therapies for VT are well established and include Anti-Tachycardia Pacing (ATP) and defibrillation.

Defibrillation, although acutely lifesaving when delivered appropriately, is painful and causes both pathological and psychological harm to patients. Worse still, as discussed elsewhere in Chapters 1 and 6, defibrillation when delivered either appropriately or inappropriately is associated with worse longer-term outcomes for patients, including increased mortality rates. (Proietti et al. 2015; Scott et al. 2014)

It is already known that pacing based manoeuvres can offer potentially beneficial interventions in VT mainly through attempts to provide *painless* termination of rhythm disturbances. Anti-Tachycardia Pacing aims to terminate VT by delivering an opportunistically timed paced beat so that it interacts with a re-entry VT circuit and extinguishes the antidromic limb by the arrival of the paced stimulus making the antidromic limb of the circuit refractory. Furthermore, this paced stimulus is optimally timed so that its arrival does not *reset and advance* the orthodromic limb through the paced stimulus arriving at a time point when the tissues are still refractory from the tail of the tachycardia circuit. Figure 5-1

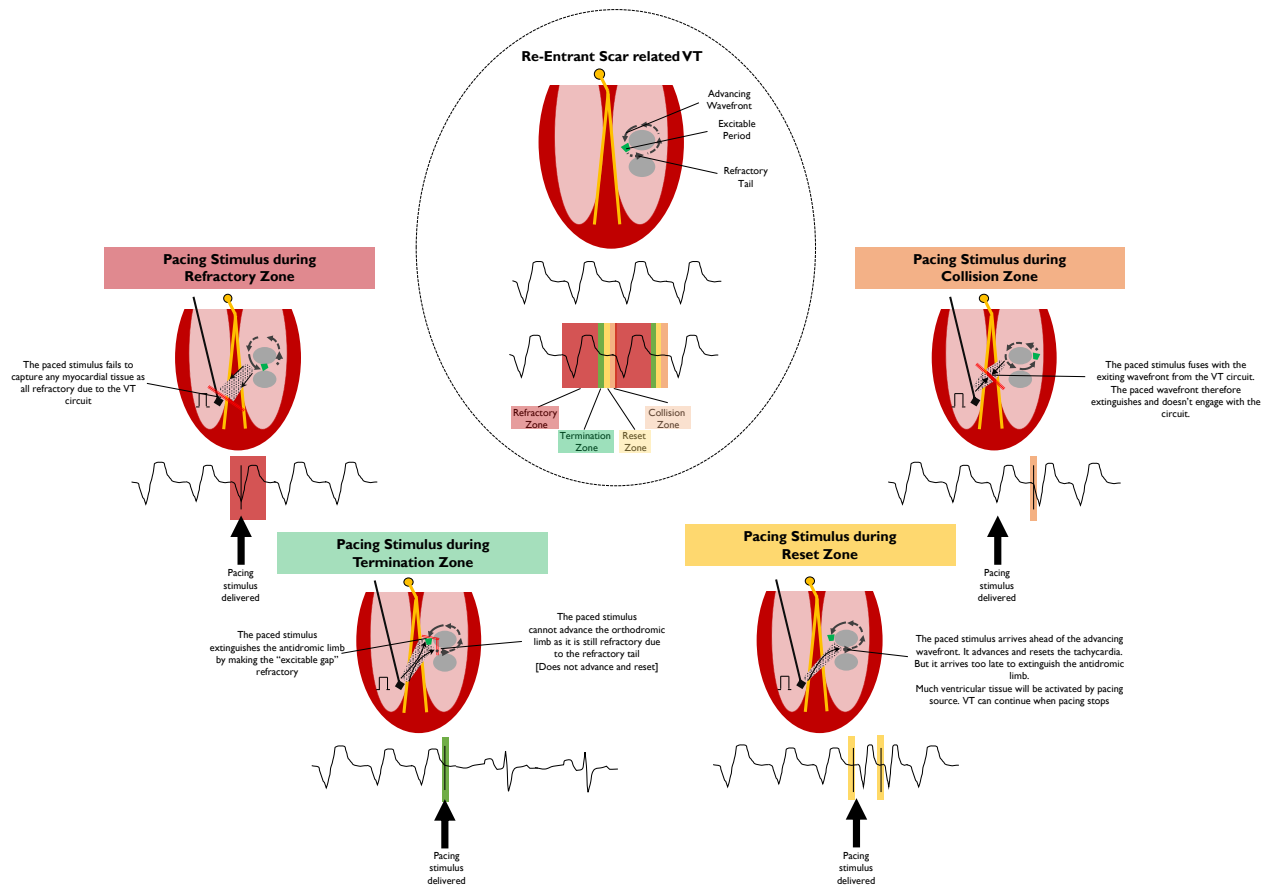


Figure 5-1 The principles underlying Pacing termination of re-entry arrhythmias

This figure highlights how paced beats can interact with a re-entrant VT. The Central element of the figure shows a re-entrant circuit around an area of scar.

The re-entrant arrhythmia has an advancing wavefront, which advances into an excitable period or gap and which follows on from a refractory tail.

Pacing stimuli delivered can have 4 different interactions with the re-entrant circuit depending on the phase of the circuit when the pacing stimulus is delivered.

If a pacing stimulus is delivered during the *Refractory zone*; the pacing stimulus will not interact with the VT circuit as the myocardial tissue between the pacing

site and the VT circuit will already be refractory due to activation spreading out from the VT site.

If a pacing stimulus is delivered during the *Termination zone*; the pacing stimulus will be timed so that it arrives at the VT circuit and be able to block and “extinguish” the advancing antidromic wavefront as it will make the “excitable gap” refractory. Furthermore, the pacing stimulus cannot advance the orthodromic limb as this tissue remains refractory from the tail of the VT circuit. As such an appropriately timed pacing stimulus can terminate a re-entrant VT.

If a pacing stimulus is delivered during the *Reset zone*; the pacing stimulus arrives ahead of the advancing wavefront and so advances and resets the VT circuit. However, it arrives too late to extinguish the antidromic limb. The VT will likely continue when the pacing stimuli cease.

If a pacing stimulus is delivered during the *Collision zone*; the pacing stimulus and the exiting wavefront of the VT collide in the myocardium such that the resultant QRS morphology represents a fusion between the VT and the paced activation. The paced stimulus does not arrive at the re-entrant circuit and therefore does not affect the re-entry properties in any way.

However, in clinical practice, multiple paced stimuli are required to maximise the likelihood that one of the beats arrives with such optimal timing to be at the “*termination zone*”. (Josephson et al. 2014) Such protocols of sequences of stimuli are the basis of modern ATP.

Because the pacing site (frequently RV) for ATP is often distant from the site of the VT re-entrant circuit (frequently LV), there are multiple layers of cells for the paced impulses to travel across before reaching the re-entrant circuit of the VT. ATP can only successfully engage with a VT re-entrant circuit if the paced impulse arrives at each intervening cell layer (between pacing site and the VT circuit) without hitting a refractory area that will block the impulse travelling to the VT circuit. Pacing at faster rates than the VT cycle length can help to “*peel back refractoriness*” so that the stimulus can progress and reach the VT circuit and engage with it (Koneru et al. 2011) (Figure 5-2).

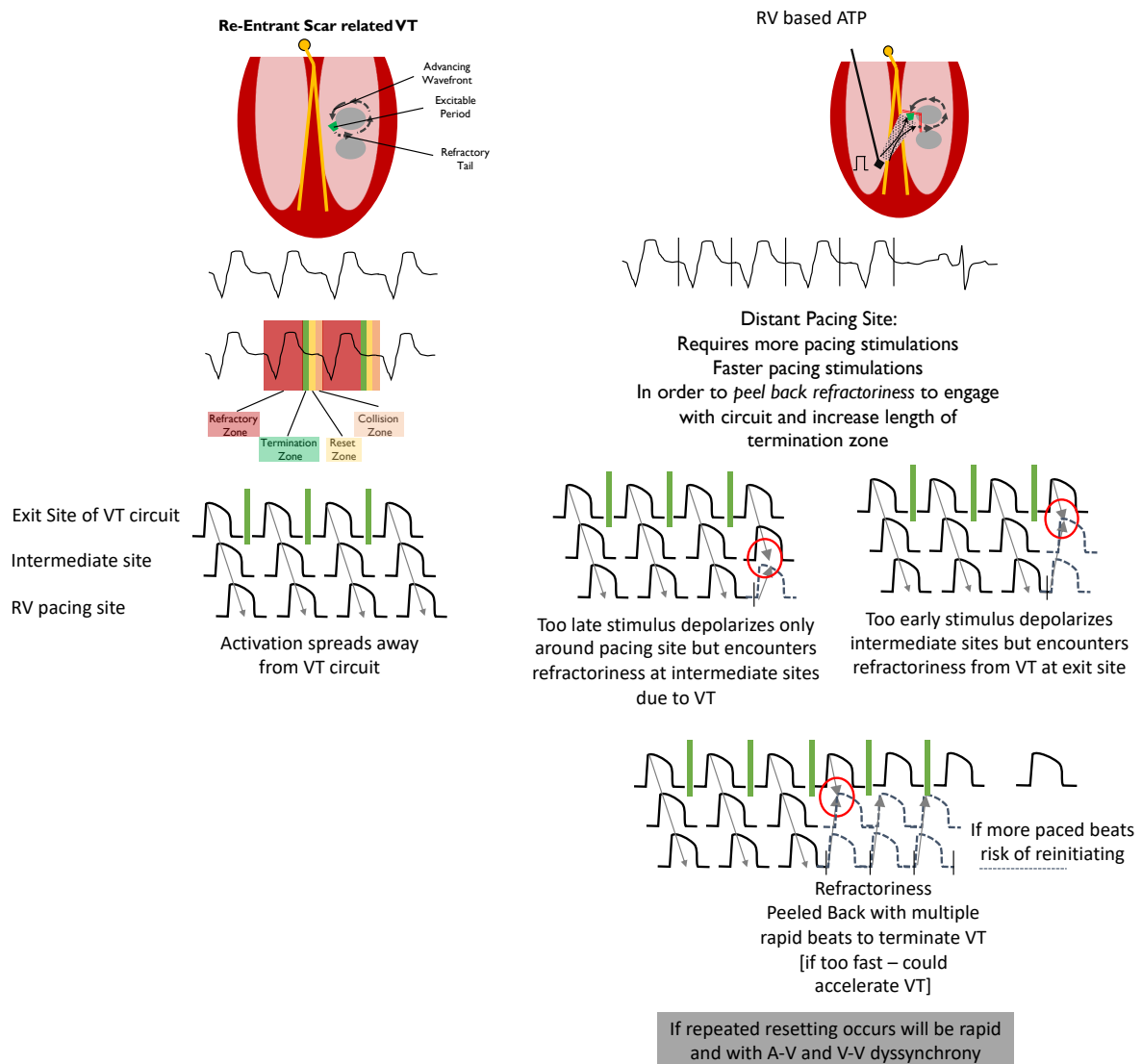


Figure 5-2 Principles of "Peeling Back Refractoriness" for successful VT termination

Often for a pacing stimulus from a distant site (i.e RV) to successfully arrive and interact with a VT site multiple, rapid beats are required to allow the pacing stimulus to travel to the circuit and not to be stopped by refractory cells in the intermediate tissue between the pacing stimulus and the VT.

Unfortunately, ATP is not always successful at terminating VT. This failure rate may be increasing in the modern era as we seek to delay delivery of therapy in the hope of spontaneous rhythm termination. This then appears to make VT less responsive to termination with ATP. (Arenal et al. 2016) Furthermore, ATP may also cause rhythm acceleration and deterioration into ventricular fibrillation in around 4-8% of ICD recipients, (Schukro et al. 2013; Grimm et al. 1993) this is one of the disadvantages of more rapid stimulus delivery in the attempt to *peel back refractoriness* to engage with the VT circuit.

If traditional RV ATP arrives at a VT circuit at a time where it entrains the VT circuit but cannot terminate it, this may unfortunately result in a more rapid ventricular rate (due to the rate of the stimulation) and unfortunately is likely to be without both atrio-ventricular synchrony and bi-ventricular synchrony.

Both ATP and shock therapies can be harmful. MADIT RIT and ADVANCE III have shown that delaying therapies (to give more opportunity for spontaneous VT termination) and therefore reducing therapies improves outcomes as well as minimising symptoms. (Moss et al. 2012; Gasparini et al. 2013) Of course, the scope to delay therapies is limited by the impaired haemodynamics in VT which can lead to discomfort and even syncope. Any therapy that assists haemodynamics during VT could offer greater scope to delay ATP and shock therapies safely, thereby opening an avenue for further improvements in outcomes.

5.2.3 Pacing interventions to improve cardiac haemodynamics

The concept of utilising atrial pacing interventions to improve haemodynamics during VT was first explored in the 1980s (Hamer et al. 1985; Fisher et al. 1982) and more recently revisited in 2011 (Piccini et al. 2011) but has not become mainstream.

Hamer et al demonstrated in 8 patients that atrial pacing at 60-73% of the tachycardia cycle length led to an immediate and significant increase in mean systolic BP from 96 ± 22

to 126 ± 18 mmHg in patients with impaired left ventricular systolic function (EF <35%). They saw resolution of pulsus alternans and improvement in stroke volume. These improvements they hypothesized could have resulted from (1) augmentation of ventricular filling by mandating an atrial contribution to ventricular filling and (2) mandating forward flow across the mitral valve that could provide a barrier to mitral regurgitation thus reducing the amount of blood loss at end diastole and therefore again improving ventricular filling and subsequent available stroke volume. The increased ventricular filling by Frank-Starling mechanisms could then result in subsequent increases in stroke volume.

Complications of rapid atrial pacing were, however, noted in the study by Hamer and colleagues and included (1) induction of atrial arrhythmias in 25% of cases and (2) deleterious haemodynamic effects if the atrial pacing was not optimally timed.

Lima and colleagues explored potential mechanisms for deterioration in cardiac function during VT by assessing echocardiographic markers and pressure volume loops. (Lima et al. 1983) They found significant differences in the contributions of haemodynamic harm in those patients with impaired left ventricular function (<40%) compared to those with better ventricular function. In those with less severely affected ventricular function it appeared that diastolic filling was the main reason for reduced cardiac output but the harmful effect of ventricular dyssynchrony was far more important in those with more severely impaired ventricular function. The characteristic wide QRS complex of VT is a manifestation of this electrical dyssynchrony. It is possible that pacing from the His bundle (albeit at a faster heart rate which may have negative effects) may improve upon the ventricular dyssynchrony and bring about improvements in haemodynamics.

5.2.4 Applicability of a potential new therapy

If successfully delivered there would be several advantages. By preserving cardiac output, the negative impact VT has on cardiac function due to reduced coronary perfusion could be minimized and by preserving cerebral perfusion, episodes of syncope or pre-syncope may be avoided. As a result of this, it would be possible to delay conventional ATP or defibrillation therapy even further than is currently carried out in clinical practice. This may allow more time for spontaneous termination of rhythm disturbances.

Furthermore, a mode that permits improvements in haemodynamics may potentially allow for mapping and ablation of haemodynamically unstable VTs which previously would not have been suitable for targeted ablation rather just ablation of substrate or such ablations may only be conducted with the utilisation of mechanical support devices. (These adjunct devices are not without risk to the patient and also may impair catheter manoeuvrability and thus ablation success despite mitigating the haemodynamic challenges.)

This Chapter has two aims.

Part 1: To evaluate the harm attributable to, and hence the potential benefit through treatment of the various mechanistic components of VT. These will be tested through a protocol of experiments in which the various elements of VT are systematically removed. To be able to achieve this comprehensive analysis *simulated VT* using RV apical pacing was utilised.

Part 2: To explore the feasibility and assess the actual benefit of pacing therapies to target these harmful (and potentially modifiable) components in patients during *actual VT*, arising spontaneously or by induction.

In part 1, the relative contribution of:

- Heart rate
- Loss of AV synchrony
- Loss of VV synchrony

during *simulated* VT will be evaluated.

In part 2, the potential benefit achieved through:

- Re-introduction of AV synchrony during VT
- Re-introduction of VV synchrony during VT (through His bundle pacing)
- The ability of His bundle pacing during VT to terminate VT

Will be tested. Part 2, in contrast to Part 1, is conducted in patients during *actual* VT.

5.3 Methods

5.3.1 Patient Population

5.3.1.1 *Part 1 – Determining the mechanisms of haemodynamic harm during simulated VT.*

24 patients were recruited with left ventricular systolic dysfunction ($EF < 40\%$) who either:

- had a cardiac rhythm management device implanted with three leads permanently positioned within the right atrium, right ventricle and the His bundle position, or
- were attending for a clinically indicated invasive procedure to the cardiac catheter lab where electrophysiology catheters could be temporarily positioned within the right atrium, right ventricle and at the His bundle position. These procedures included VT stimulation or VT ablation.

Patients were ineligible if they had atrial fibrillation or were unable to give informed consent.

5.3.1.2 *Part 2- Investigating novel pacing interventions during actual VT*

11 patients in actual VT were studied. 9 were induced VT episodes from 23 patients with LV systolic dysfunction ($EF < 40$) who attended for clinically indicated VT ablation or VT stimulation procedures. The other 2 of these 23 patients had spontaneously occurring VT episodes within the cardiac catheter laboratory. The remaining 12 went into part 1 above.

Patients gave prior written informed consent for this study which was approved by the local Research Ethics Committee (London – Central 16/LO/0339).

5.3.2 Pacing and Haemodynamic Experiment

5.3.2.1 *Measurements*

Patients had continuous monitoring of beat-by-beat blood pressure. Where invasive monitoring was not clinically indicated, non-invasive monitoring was performed using a

Finometer (Finapres Nova, Finapres Medical Systems, NL). Patients also had continuous ECG monitoring (Fukuda Denshi 7100, Fukuda Denshi, Japan). For those patients undergoing EP studies, quadripolar electrophysiology catheters were positioned in the high right atrium and right ventricular apex. For the His pacing protocol an EP catheter was positioned at the His bundle. Either Selective or Non-Selective His bundle capture was accepted in this study.

5.3.2.2 Part 1 – Determining the mechanisms of haemodynamic harm during simulated VT.

The pacing protocol was performed in either the cardiac catheter lab or in the cardiac rhythm management follow up clinic.

Pacing Protocol

The aim of this part of the study was to assess the relative contribution that each of the stated mechanistic components contributes to the haemodynamic response seen during VT so that we may predict the potential benefit of correcting the individual components. These experiments were conducted within the artificial construct of simulated VT to enable accurate quantification. Whilst artificial, this serves to enhance the mechanistic understanding before Part 2 in which these therapies during actual VT were tested. Patients underwent the pacing protocol to help delineate the relative haemodynamic effect of:

1. Heart Rate
2. Atrio-ventricular synchrony
3. Bi-ventricular synchrony
4. Combined Atrio-ventricular synchrony and Bi-ventricular synchrony

The pacing protocol included:

Simulated VT

This was achieved by asynchronous isolated ventricular activation at various heart rates.

This resembled VT in that there was neither atrio-ventricular (AV) nor bi-ventricular (VV) synchrony.

1. Simulated VT by asynchronous pacing from the right ventricle at 80bpm
2. Simulated VT by asynchronous pacing from the right ventricle at 125bpm
3. Simulated VT by asynchronous pacing from the right ventricle at 160bpm
4. Simulated VT by asynchronous pacing from the right ventricle at 190bpm

Restoration of AV synchrony alone

1. Synchronous dual chamber atrial and right ventricular pacing at 125 bpm (AV delay 140ms)
2. Synchronous dual chamber atrial and right ventricular pacing was additionally performed at 160bpm (AV delay 140ms) in some individuals

Restoration of Bi-ventricular synchrony alone

1. His bundle pacing was performed at 125bpm
2. His bundle pacing was additionally performed at 160bpm in some individuals

Restoration of both AV and biventricular synchrony

1. Synchronous dual chamber atrial and His bundle pacing was performed at 125bpm (AV delay 100ms)
2. Synchronous dual chamber atrial and His bundle pacing was performed at 160bpm (AV delay 100ms) in some individuals

This shorter programmed AV delay was selected in order to actually deliver an AV delay more similar to the 140ms as used previously. The programmed 100ms here allows the intrinsic H-V time ~40ms to be added on so as to contribute to the actual AV delay (HV time is the time taken for the activation wavefront to travel down the His Purkinje system before ventricular breakout).

Each patient underwent the pacing-created scenarios at least three times, in a computer-generated random order.

For assessment of the effect of simulated VT, the patient was left in their underlying rhythm for 30 seconds, then the pacing scenario was initiated. The patient was then returned to their intrinsic baseline rhythm for at least thirty seconds before the next pacing-created scenario was tested. An example of a recording from a single pacing scenario is shown in Figure 5-3.

For assessment of the other pacing scenarios, the patient was left in their underlying rhythm for 30 seconds, then asynchronous RV pacing was initiated either at 125 bpm or 160bpm and then the pacing mode changed to determine the effect of the tested component on haemodynamic response.

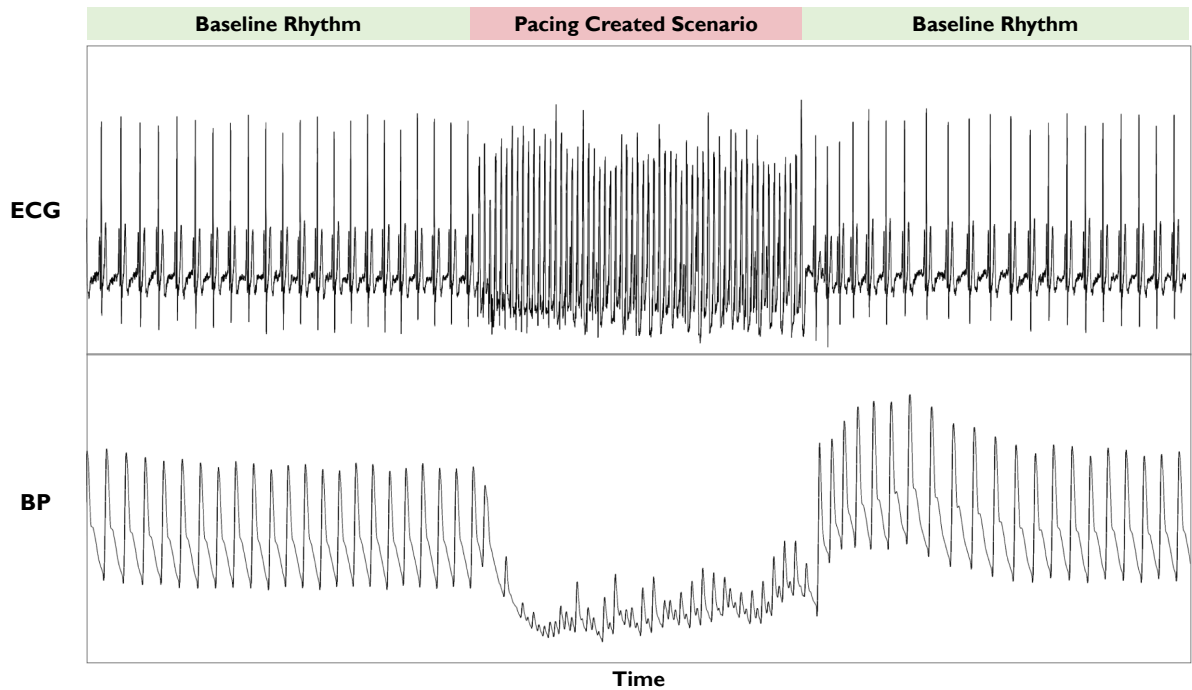


Figure 5-3 Example of a pacing created scenario

In this Figure, the ECG and beat-by-beat BP can be seen at rest with the patient's intrinsic activation. The pacing-created scenario (simulated VT, 190bpm) is then started, and the effects on ECG and BP are seen. The pacing scenario is then stopped and the patient returns to baseline. Note that this process was repeated for each patient, and for each pacing scenario, at least 3 times in a random order.

5.3.2.3 *Part 2 – Assessment of pacing interventions to maximize cardiac function during clinical VT*

Part 2 aimed to assess the actual benefit derived through the correction of atrio-ventricular and biventricular synchrony during actual VT whether occurring spontaneously or being induced as part of an electrophysiology study.

Pacing Protocol

Two patients experienced spontaneous VT. In other patients VT was induced using standard VT induction approaches with a ventricular drive train and shorter coupled S2 and S3 beats as required.

Only patients who experienced spontaneous VT or induced VT after pace stimulation, were included in this part of the study.

The protocol aimed to allow ~ 15 seconds of actual VT prior to testing the pacing interventions described below. Pacing interventions were delivered at ~5 bpm above the clinical VT rate. Where possible a minimum of three alternations were made between clinical VT and the tested pacing intervention.

The experimental pacing interventions which we aimed to test included:

1. Attempted restoration of AV synchrony through the addition of Atrial pacing at ~ 5 bpm above the VT rate
2. Attempted restoration of VV synchrony through the addition of His-bundle pacing at ~ 5 bpm above the VT rate

Because of clinical time pressures it was not possible to try every pacing protocol in each patient. After the first few patients, it was noted that there was sometimes unexpected termination with His bundle pacing, and therefore the protocol was adapted to specifically test for this.

The relative change in acute haemodynamic function relative to VT was measured, for each of the performed interventions. During VT the stimulus timing in relation to the VT cycle length and the preceding ventricular beat was measured to attempt to determine the ideal timing of stimuli to interact with the VT.

5.3.3 Data and statistical analysis

5.3.3.1 Part 1

The impact of simulated VT rate

To assess the impact of the rate of VT on the haemodynamic harm for each patient at each rate the harms as the percentage drop in systolic blood pressure as compared to the patient's sinus rhythm rate was calculated. Group differences were assessed using ANOVA and Tukey's post-hoc test when appropriate.

The potential benefit that might be achieved through restoration of AV and VV synchrony

The importance of AV and VV synchrony during VT was assessed as the potential benefit that might be achieved through their restoration as compared to the simulated VT at the same heart rate. Calculations were made at 125 bpm and 160 bpm separately. The percentage increase in systolic blood pressure with the restoration of both AV and VV synchrony or just AV synchrony or just VV synchrony as compared to the simulated VT without AV or VV synchrony was quantified. Group differences were assessed using ANOVA and Tukey's post-hoc test when appropriate.

5.3.3.2 Part 2

To assess the impact of the pacing intervention on haemodynamics during VT the absolute change in systolic blood pressure was calculated between the VT state and the pacing intervention. Each patient had one or more interventions performed. For each patient the mean change with a particular pacing approach was calculated. The mean

across all patients was then calculated. The t-test was used to determine if the change was significantly different from zero. The t-test was used because blood pressure values are typically approximately normally distributed and by the Central Limit Theorem, changes in blood pressure are therefore even more normally distributed.

5.4 Results

5.4.1 Part 1

5.4.1.1 Patient Population

In this part, 24 patients were recruited (including 12 patients initially included in the Part 2 cohort). The characteristics are reported in Table 5-1. In summary the mean age was 68 ± 9 years and the mean EF was $32 \pm 7\%$.

Table 5-1 Characteristics of the 24 patients included in Part 1	
Male	19 (79%)
Age (years)	68 ± 9
LV Ejection Fraction (%)	32 ± 7
Ischemic Aetiology of Ventricular impairment	13 (54%)
History of Diabetes	6 (25%)
NYHA class	2.3 ± 0.5
BNP (ng/l)	568 ± 909
Resting systolic Blood Pressure (mmHg)	119 ± 15
Resting Heart Rate (bpm)	62 ± 7
QRS duration (ms)	113 ± 23
Protocol performed with temporarily placed electrophysiology catheters	8 (33%)
Values presented are either Mean $\pm$ Standard Deviation or N (%)	

Example traces showing the haemodynamic effects of changes in pacing mode are shown in Figure 5-4 and Figure 5-5.

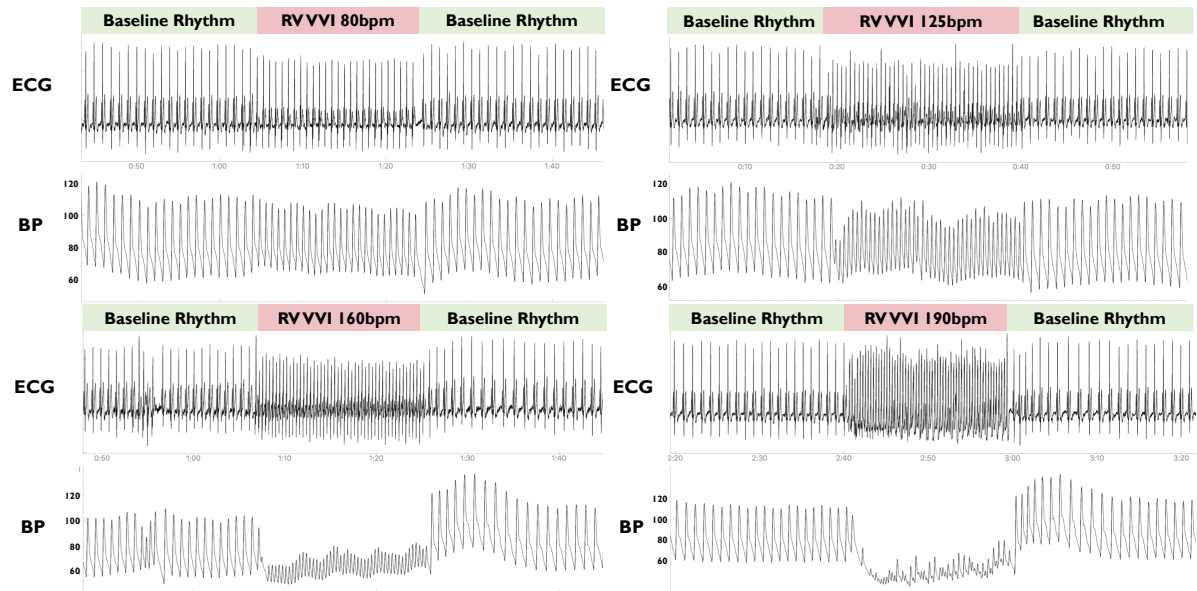


Figure 5-4 Example traces showing the assessment of change in simulated VT rate

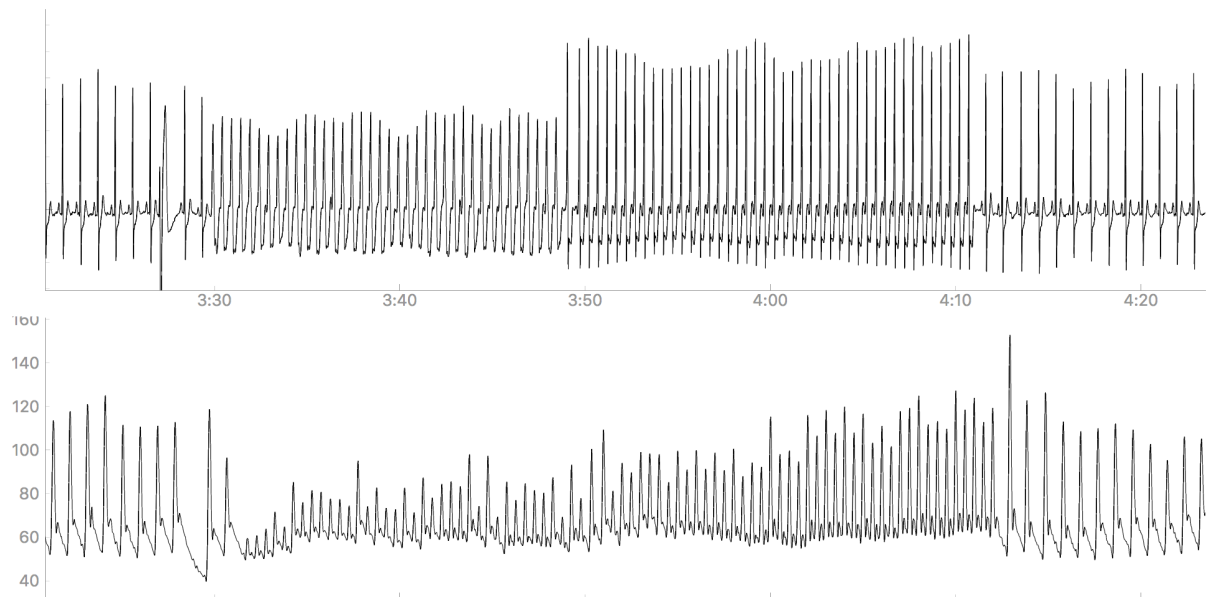


Figure 5-5 Example trace showing the mechanistic effect of transitioning from asynchronous VVI pacing at 125 bpm to delivering bi-ventricular synchrony with the addition of His bundle pacing at the same rate

5.4.1.2 Impact of VT rate on Haemodynamics

The impact of rate on VT haemodynamics was simulated by apical right ventricular pacing at increasing rates in VVI mode. As the rate of asynchronous pacing increased there was a significant and increasing fall in haemodynamics, Figure 5-6. The mean percentage decrease in systolic blood pressure from the baseline state at 80 bpm was 15.5%, at 125 bpm was 18.5%, at 160 bpm 34.5% and at 190 bpm 44.4%. (ANOVA $p < 0.0001$ for difference between groups)

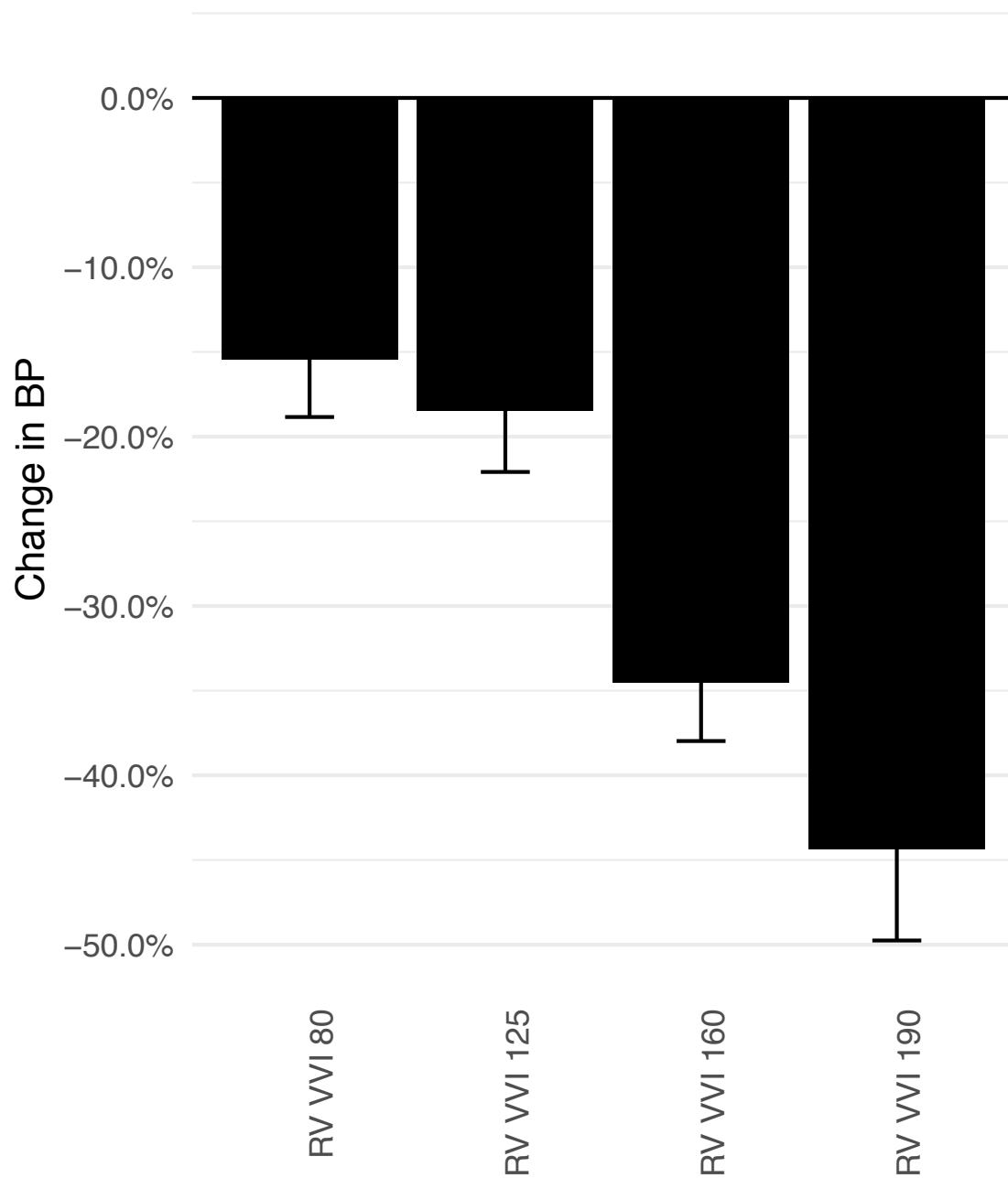


Figure 5-6 Impact of VT rate on Haemodynamics

As the rate of simulated VT increased so did the haemodynamic harm. This was indicated by larger percentage reductions in systolic blood pressure from the baseline reference state with the higher simulated VT rates.

5.4.1.3 Potential benefit through restoration of Atrio-ventricular synchrony

Compared with simulated VT (without atrio-ventricular or biventricular synchrony) the addition of isolated atrial synchrony through the addition of synchronous atrial pacing showed only a non-significant trend to improve blood pressure by 10.7% at 125 bpm ($p=0.06$) and by 1.5% at 160 bpm ($p=0.5$), Figure 5-7 and Figure 5-8.

5.4.1.4 Potential benefit through restoration of bi-ventricular synchrony

Compared with simulated VT (without atrio-ventricular or biventricular synchrony) the addition of isolated biventricular synchrony through the addition of His bundle pacing significantly improved blood pressure by 13.9% at 125 bpm ($p=0.0002$) and by 9.4% at 160 bpm ($p=0.024$), Figure 5-7 and Figure 5-8.

5.4.1.5 Potential benefit through restoration of both Atrio-ventricular and bi-ventricular synchrony

Compared with simulated VT (without atrio-ventricular or biventricular synchrony) the addition of both atrial synchrony and biventricular synchrony through the addition of dual chamber atrial synchronous His bundle pacing significantly improved blood pressure by 15.4% at 125 bpm ($p=0.0009$) and by 34.9% at 160 bpm ($p=0.0002$), Figure 5-7 and Figure 5-8.

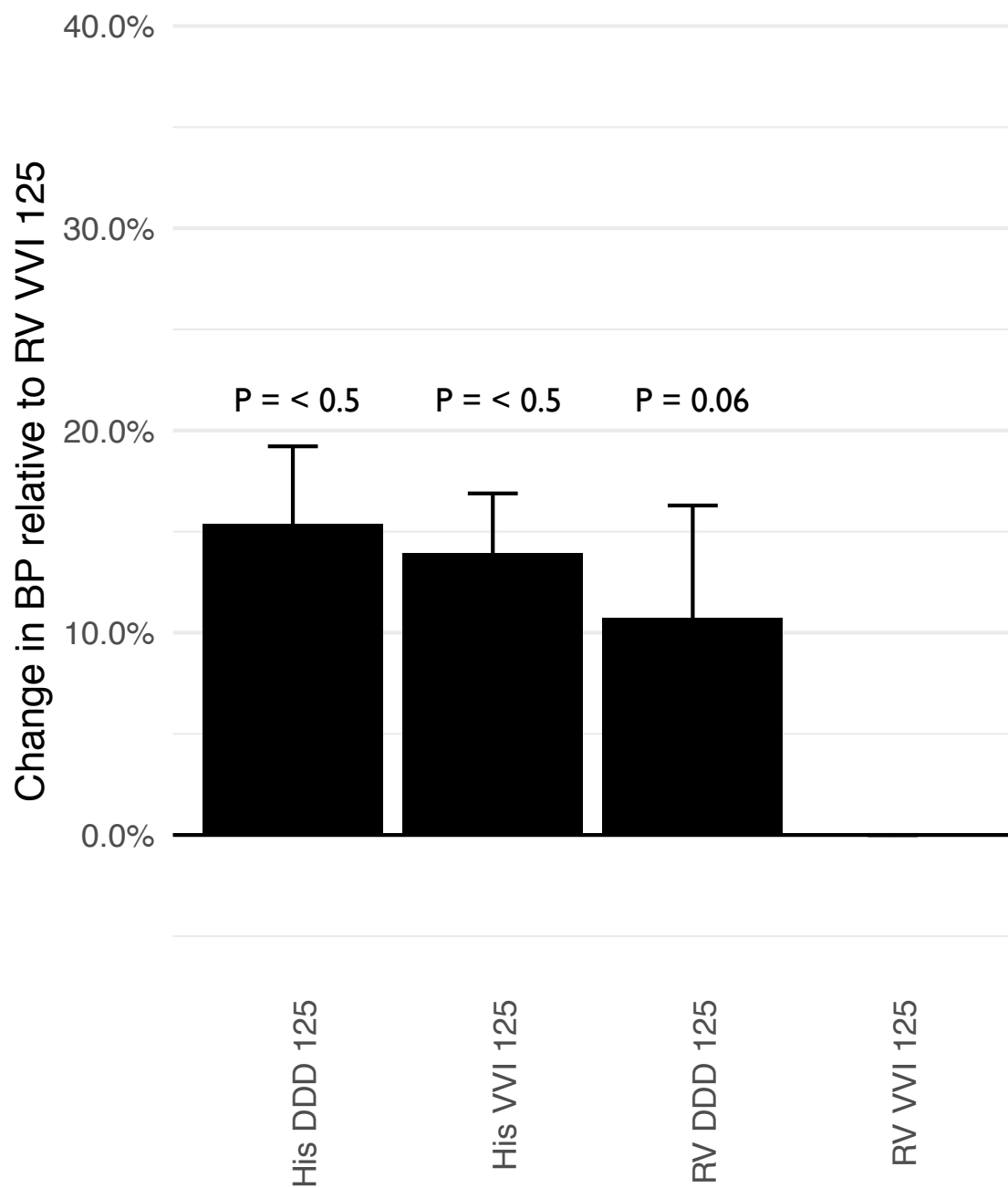


Figure 5-7 Impact of the various mechanisms of harm in VT at 125bpm

At 125bpm the addition of isolated atrial synchrony (RV DDD 125) to simulated VT (RV VVI 125) increased systolic blood pressure by 10.7%. The addition of isolated bi-ventricular pacing (His VVI 125) increased systolic blood pressure by

13.9%. The addition of atrial synchrony and bi-ventricular synchrony (His DDD 125) increased systolic blood pressure the most by 15.4%.

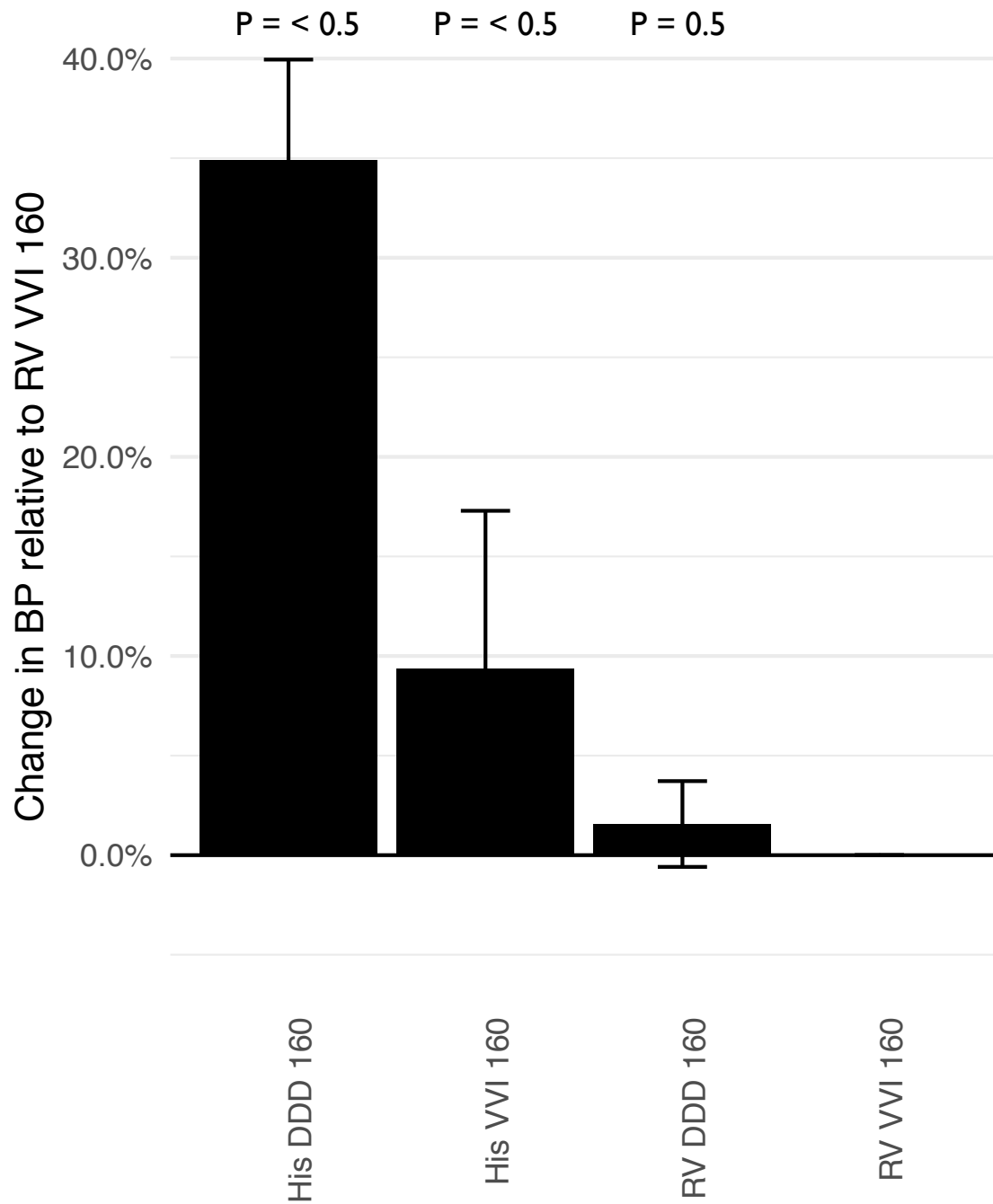


Figure 5-8 Impact of the various mechanisms of harm in VT at 160bpm

At 160bpm the addition of isolated atrial synchrony (RV DDD 160) to simulated VT (RV VVI 160) increased systolic blood pressure by 1.5%. The addition of isolated bi-ventricular pacing (His VVI 160) increased systolic blood pressure by

9.4%. The addition of atrial synchrony and bi-ventricular synchrony (His DDD 160) increased systolic blood pressure the most by 34.9%.

5.4.2 Part 2

5.4.2.1 Patient Population

In this part, 23 patients were recruited. Spontaneous or induced VT occurred in 11 patients and these patients continued in this study protocol (Patient flow chart shown in Figure 5-9). Their mean age was 71 ± 10 years and mean EF was $27 \pm 6\%$. Other characteristics of these 11 patients are reported in Table 5-2.

The mean VT rate of included patients was 143 ± 21 beats per minute (range 95 to 173). All included patients had evidence of monomorphic VT. Patients had high resolution substrate mapping that delineated the likely arrhythmogenic substrate during stable sinus and/or paced rhythms. This methodological approach identified scar in all patients and led to the assumption that all included VTs were scar related VT with re-entry as the mechanism. In each case exit sites and channels were identified which could be representative of an isthmus during VT. Furthermore, all but one case was acutely non-inducible following substrate ablation.

8 patients had scar related to ischemic cardiomyopathy and 3 related to DCM. Scar responsible for the VT in all patients in this study came from the left ventricle. From the patients with DCM, 2 patients had scar on the basal posterior wall and 1 at the mitral annulus. From the patients with ischemic cardiomyopathy scar responsible for the VT was located at the inferior septum in 1 patient, the septum in 2 patients, anteriorly in 3 patients and at the apex in 2 patients.

No patients had apparent evidence to suggest bundle-branch re-entry as the mechanism of the VT as His potentials were not seen to be related to the ventricular activation during induction of VT.

Table 5-2 Characteristics of the 11 patients included in Part 2	
Male	10 (83%)
Age (years)	71 ± 10
LV Ejection Fraction (%)	27 ± 6
Ischemic Aetiology of Ventricular impairment	8 (66%)
History of Diabetes	2 (17%)
NYHA class	2.4 ± 0.5
BNP (ng/l)	551 ± 287
QRS duration (ms)	111 ± 15
Values presented are either Mean ± Standard Deviation or N (%)	

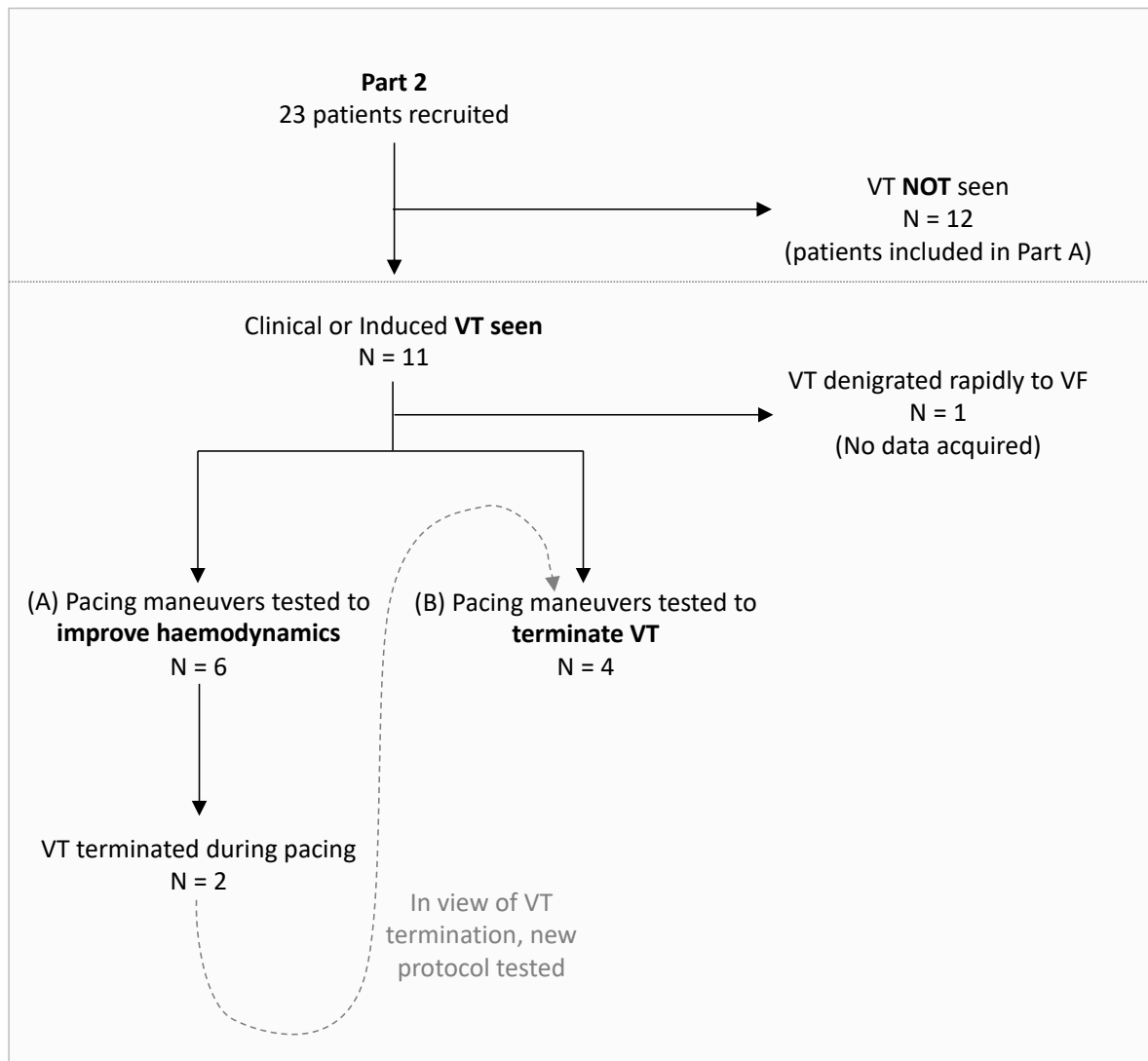


Figure 5-9 Patient Flow Chart for Part 2

6 patients were involved in Protocol (A), in view of VT termination seen with His bundle pacing, a new protocol, (B) was tested to better assess cause and effect

One of the 11 patients in whom VT was induced required defibrillation because the induced VT degenerated into VF before any pacing therapies could be performed.

In 6 of these 11 patients, pacing interventions including His bundle pacing and Atrial Pacing were performed with the aim of improving haemodynamics.

5.4.2.2 Effect of His bundle pacing in VT

The first 6 patients underwent protocol A. This was His bundle pacing 5 bpm above the VT rate, which turned out to be 95-97% of the tachycardia cycle length. In all 6 cases haemodynamics improved, by an average of 12.9 mmHg (95% CI 11.6 to 14.1 mmHg) ($p < 0.0001$, Figure 5-10.) An example trace is shown in

Figure 5-11. In these patients the mean pacing stimulus to QRS onset was 45 ± 18 ms, in keeping with ventricular activation via the His Purkinje system. Typically, this time interval was shorter at the outset of pacing, and then increased to this level once the VT circuit became entrained.

In 2 of these 6 patients, during the pacing experiments, it was observed that the VT terminated (Figure 5-12 and Figure 5-13). Because of the large potential therapeutic value of such an effect, and the inability to be confident from the existing protocol whether it was the pacing or simply the passage of time that terminated the VT, the protocol was changed.

The new protocol, B, made it easier to reason about cause and effect. Instead of multiple different pacing interventions with haemodynamic measurements, protocol B involved a single intervention with a short burst (8-15 beats) of His bundle pacing at 91% of the tachycardia cycle length. 91% of the Tachycardia Cycle Length was chosen based on my clinical experience of a patient with a permanent His lead in situ who had presented in VT to the hospital and in whom manually delivered ATP at this interval (with the aim of being less aggressive than traditional RV ATP [88%]) had successfully terminated the

ventricular arrhythmia. In the final case, I planned to precede this attempt with single sensed extras.

In all 4 out of 4 patients undergoing protocol B, the first His bundle pacing attempts terminated the VT (Examples are shown in Figure 5-14 and Figure 5-15)

In 3 patients this first pacing was a burst. In the final patient, this was the single sensed extra (Figure 5-16) and the Burst pacing was therefore not performed. In that final patient, the VT of 125 bpm was terminated by the single sensed extra delivered at 76% of the tachycardia cycle length. The VT spontaneously reinitiated a few seconds later, and single and coupled sensed extras were tried again. The QRS following the sensed extras were variously modified, indicating some interaction with the VT circuit but the VT did not terminate on any of these later occasions. We still do not know why only the first sensed extra terminated the VT.

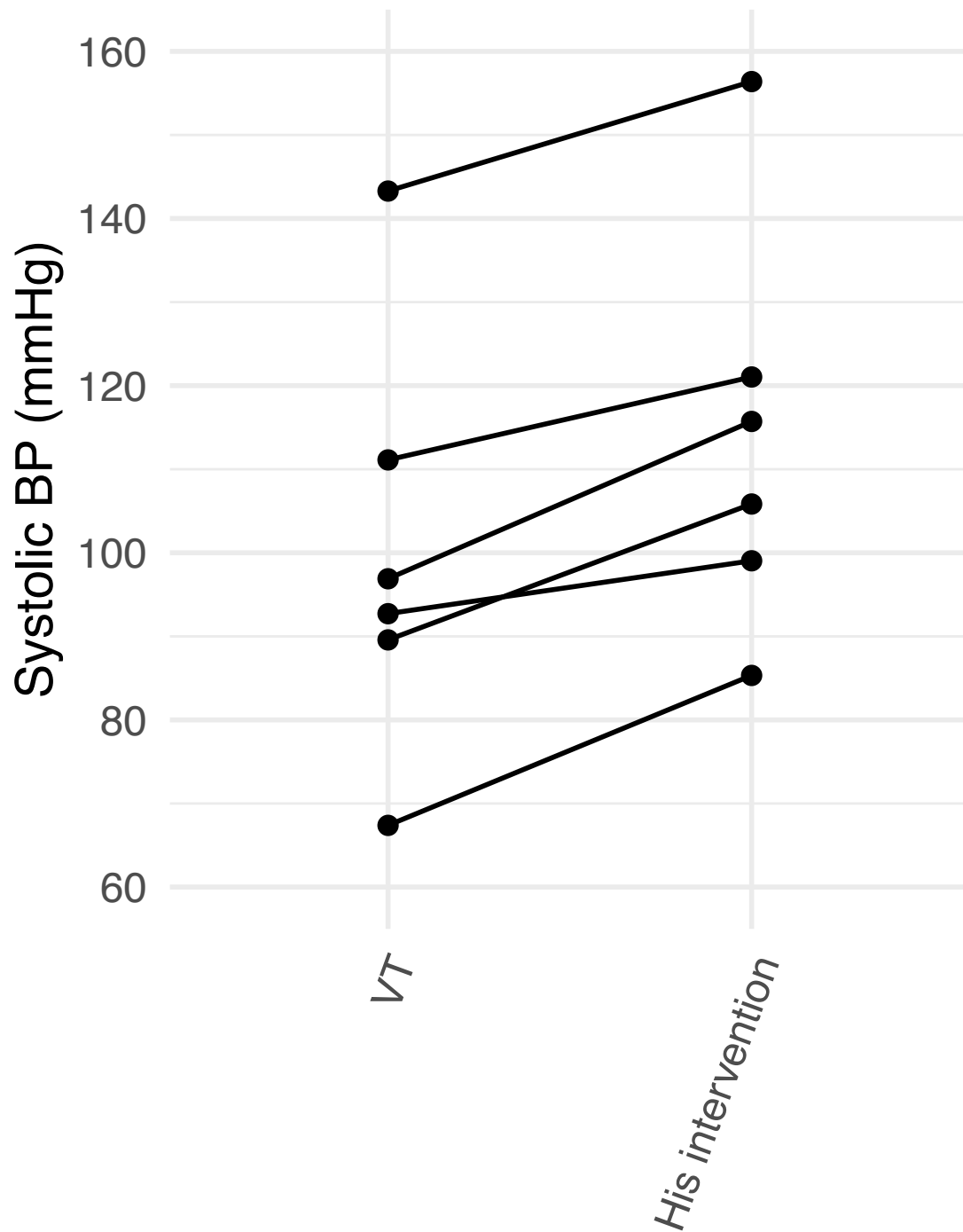


Figure 5-10 Effect of His bundle pacing on acute haemodynamics during VT

On average His bundle pacing improved systolic blood pressure by 12.9 mmHg (95% CI 11.6 to 14.1 mmHg) ($p < 0.0001$)

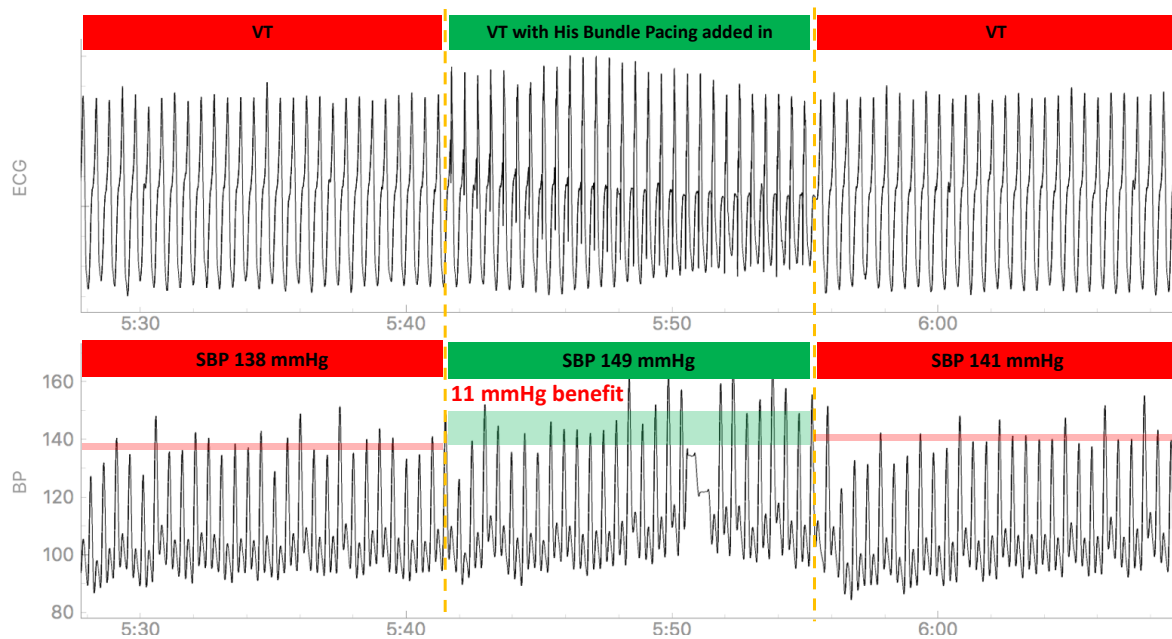


Figure 5-11 An example trace showing His bundle pacing during VT and an improvement in systolic blood pressure

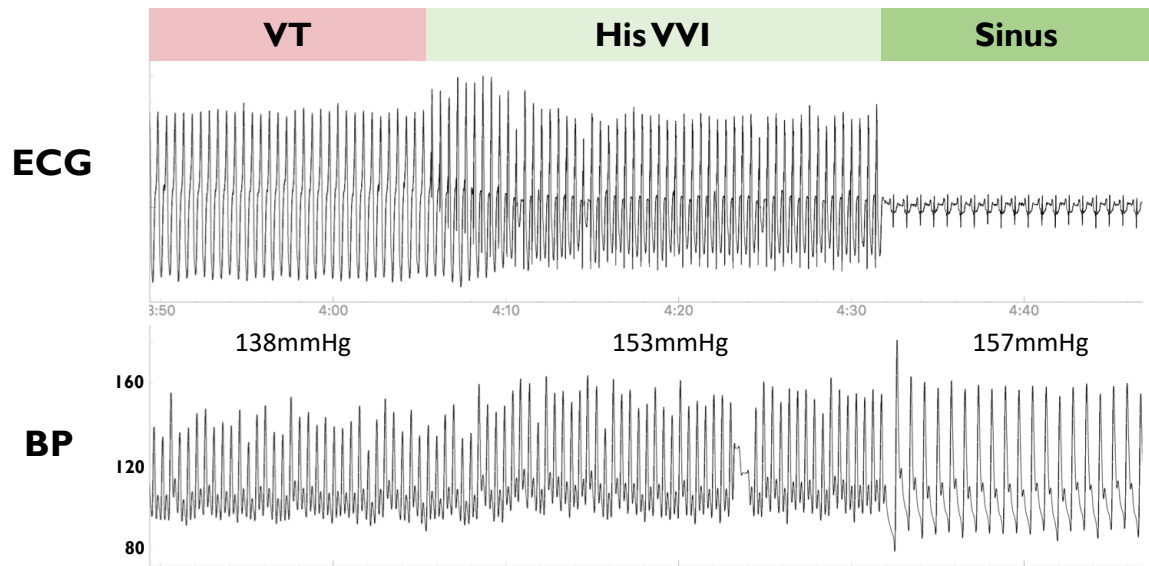


Figure 5-12 Example trace showing His bundle pacing during VT

In addition to an improvement in systolic blood pressure termination of VT was noted.

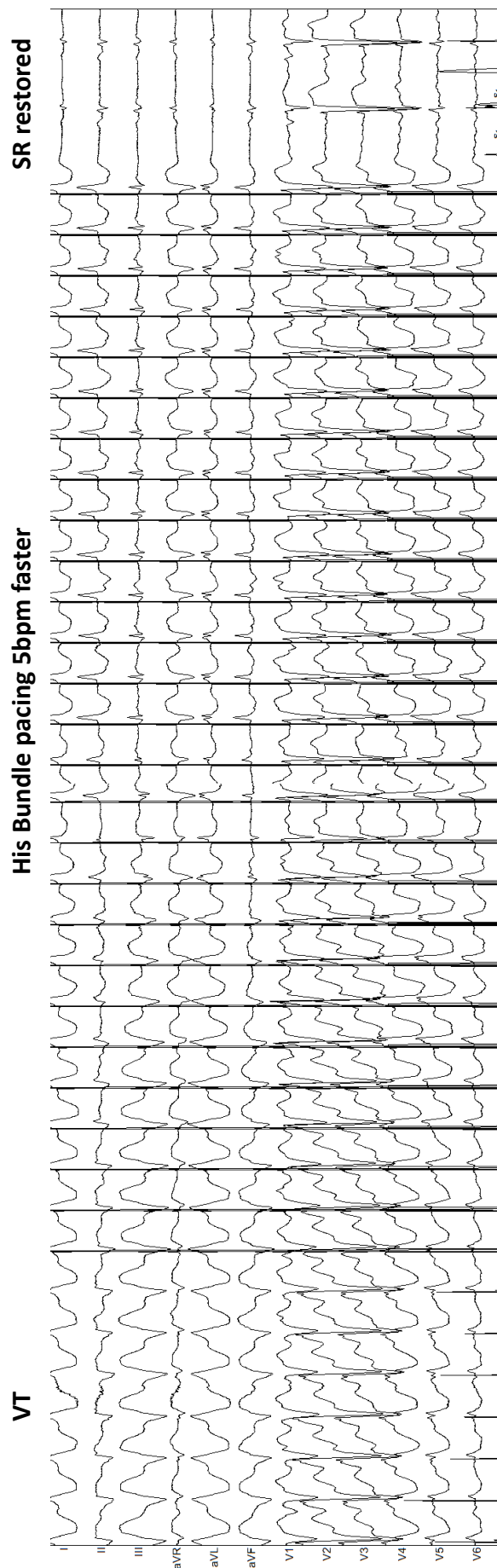


Figure 5-13 Example trace showing His bundle pacing during VT

An example trace showing His bundle pacing during VT which resulted in termination of VT

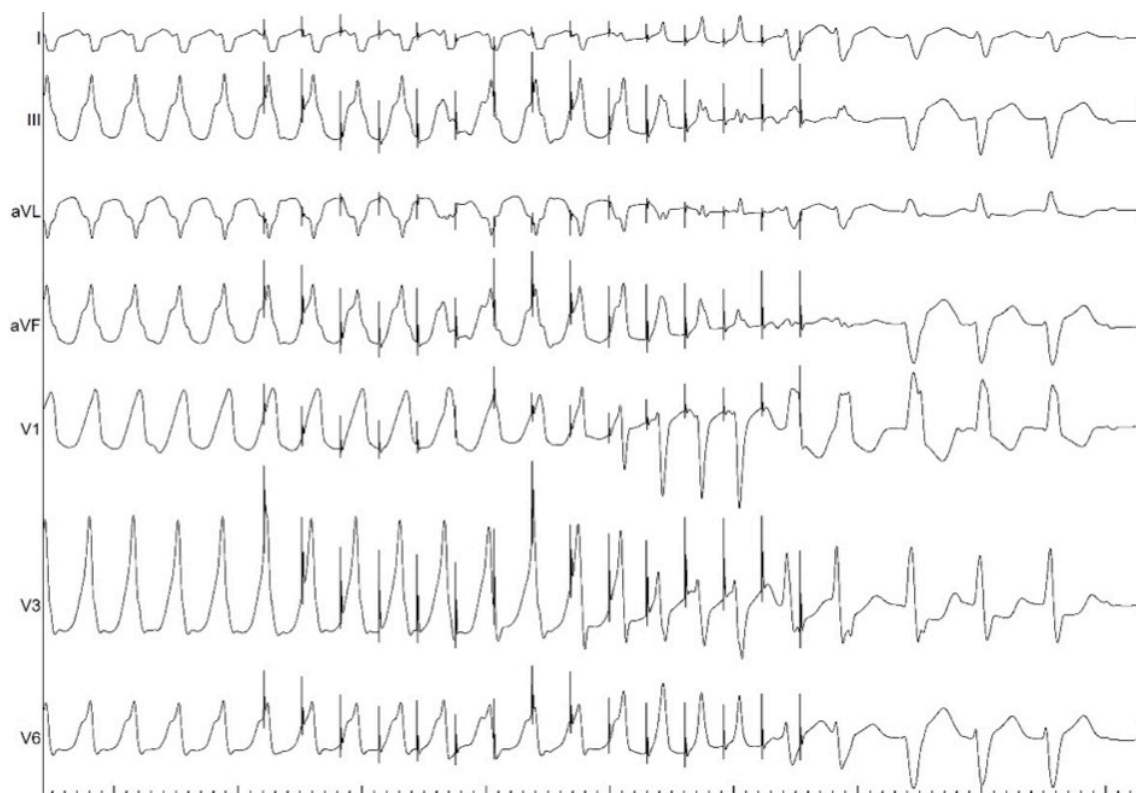


Figure 5-14 Example trace showing termination of VT with 15 beats of His bundle pacing delivered at 91% of the Tachycardia Cycle Length

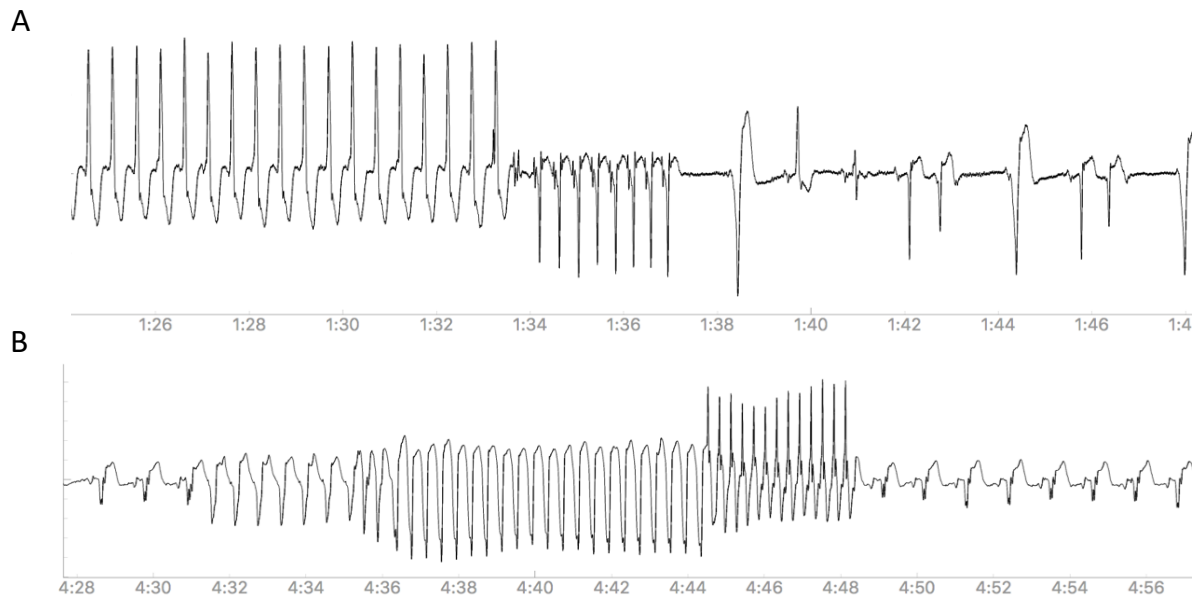


Figure 5-15 Example traces of His bundle pacing terminating VT from two patients, patient A and patient B

A – A spontaneously occurring VT was terminated with 10 beats of His bundle pacing at 91% of the tachycardia cycle length

B – VT is induced (4:31 to ~4:35) in this trace and then terminated with 13 beats of His bundle pacing at 91% of the tachycardia cycle length

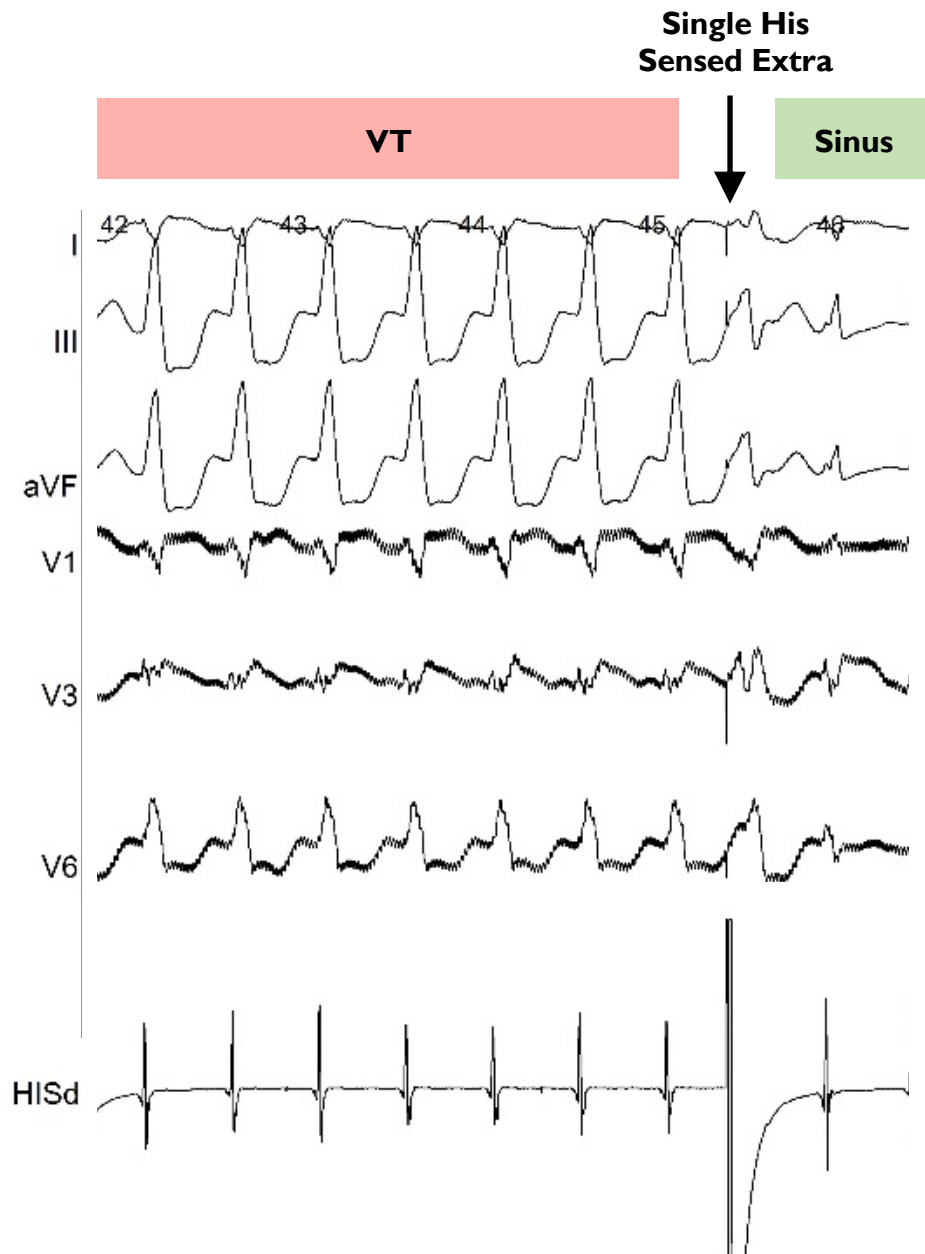


Figure 5-16 Utilisation of a single sensed His paced extra to terminate VT

5.4.2.3 *Effect of Atrial pacing in VT*

3 of these patients also underwent atrial pacing at 5 bpm above the VT rate. Acute haemodynamic function improved, on average by 12.4 mmHg (95% CI 10.4 to 14.5 mmHg) ($p < 0.0001$) as shown in Figure 5-17. Example traces are shown in Figure 5-18 and Figure 5-19, including an example of atrial pacing entraining the VT.

Because the VT rate was different to the pacing rate, the timing of the atrial stimulus in relation to the QRS varied from beat to beat. There was a range of AV relationships during the pacing intervention. In Figure 5-20 the relationship between the AV delay and the resulting blood pressure was plotted.

When the atrial stimulus arrives with, or shortly before, or shortly after the QRS complex myocardial contraction is undesirable with the AV ring being pulled in both directions by atrial and ventricular muscle. On the whole this can be considered to be more akin to a situation of very short AV delay than it is to very long AV delay. Therefore, we measured the time interval between each VT beat and the nearest pacing stimulus regardless of their order in time. Where the relationship was V before A this was represented as a “negative AV delay”. An alternative view however is that this should be considered a large “positive AV delay” with a preceding atrial signal. To allow for this alternative view an alternative x axis labelling for “negative” values of my AV delay measure is also presented.

In the first patient, there was an increment in blood pressure when the AV delay was between 40 and 169 ms but a decrement when it was outside this range (either shorter or much longer).

In the second patient, this zone of benefit was AV delays between 70 and 189 ms.

In the last patient, the pacing entrained the VT so that there was not a wide range of AV delays. The graph shows the zone of benefit included AV delays of between 170 and 209.

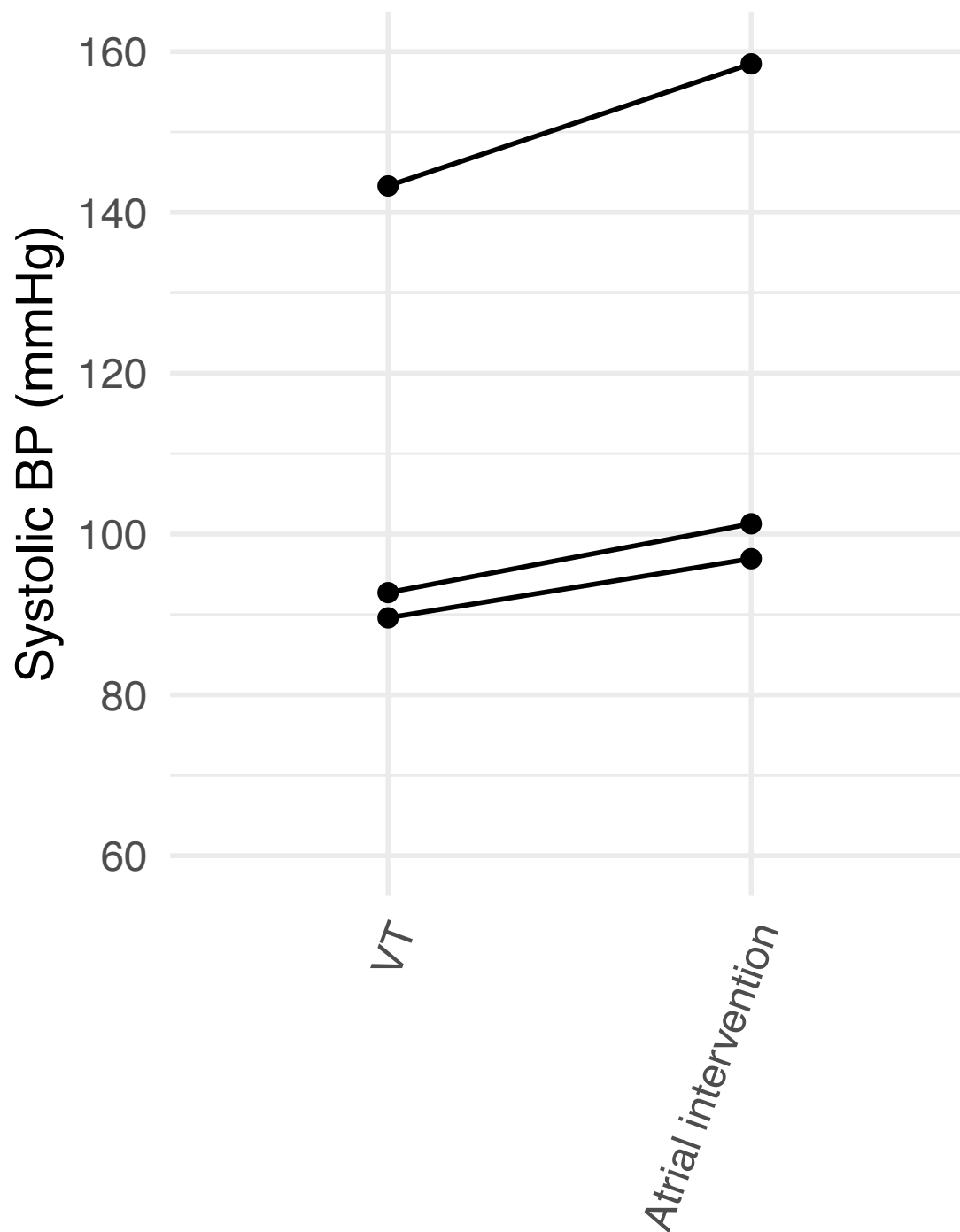


Figure 5-17 Effect of isolated Atrial pacing on acute haemodynamics during VT

On average atrial pacing improved systolic blood pressure by 12.4 mmHg (95% CI 10.4 to 14.5 mmHg) ($p < 0.0001$)

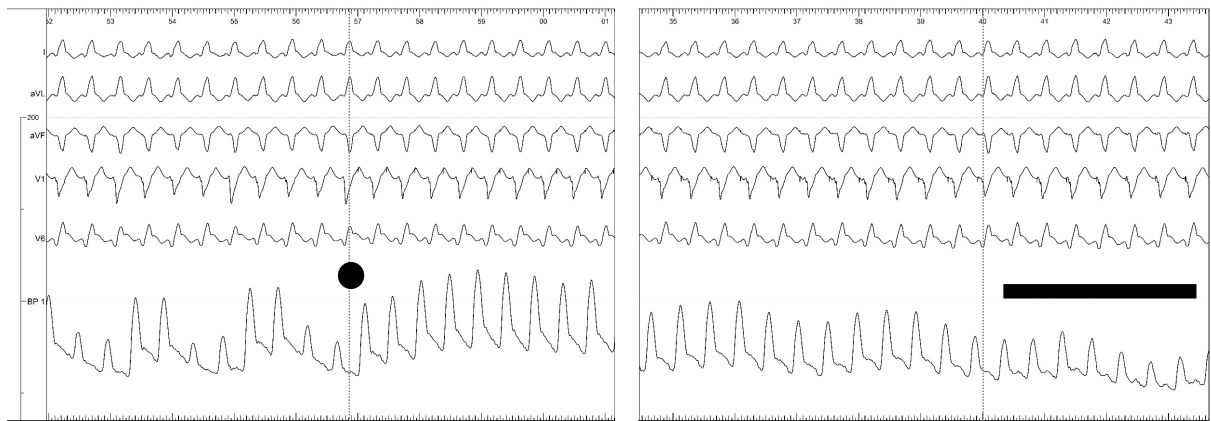


Figure 5-18 Example trace showing the effect of atrial pacing on VT

This example of atrial pacing during VT shows the haemodynamic improvements associated with well-timed atrial pacing. (Onset of atrial pacing is marked by black circle). However due to the phasic relationship between the pacing and the VT, when the atrial pacing occurred either such that it occurred just before or just after the QRS [not an appropriate AV delay] it resulted in deterioration in haemodynamic function (black rectangle).

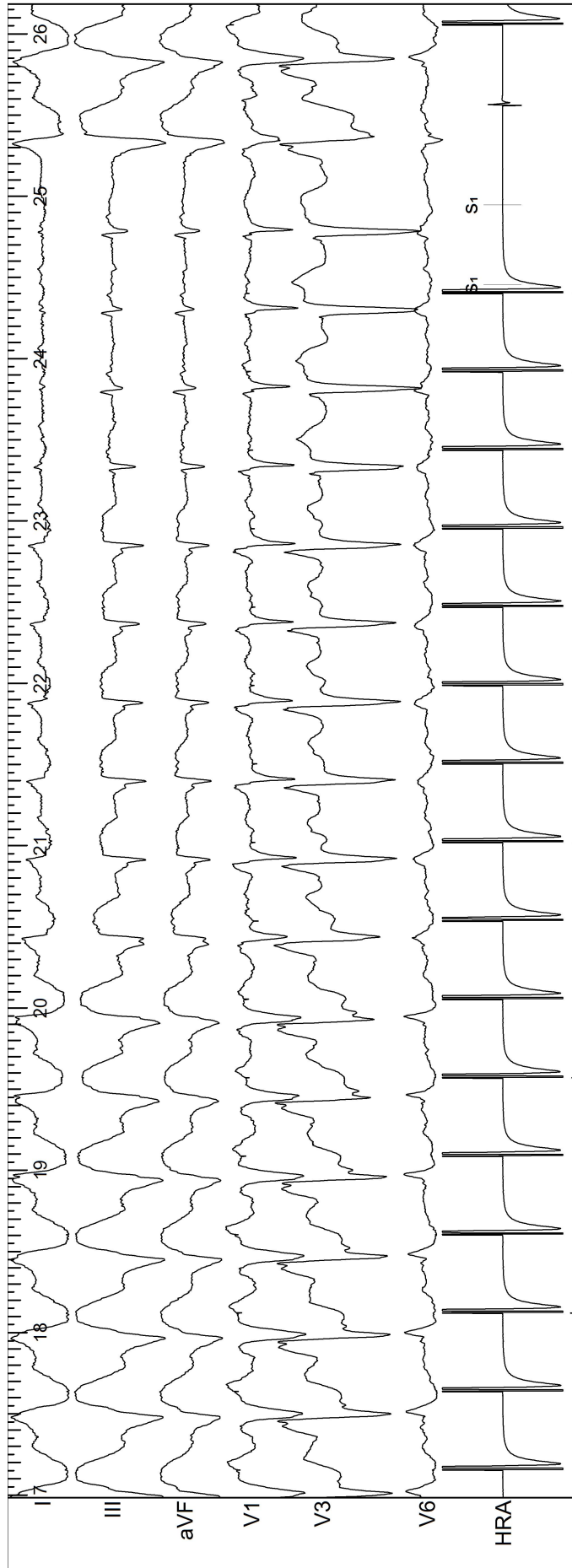


Figure 5-19 An example trace showing atrial pacing during VT

An example trace showing atrial pacing during VT, atrial pacing in this example resulted in entrainment of the VT and improved haemodynamics.

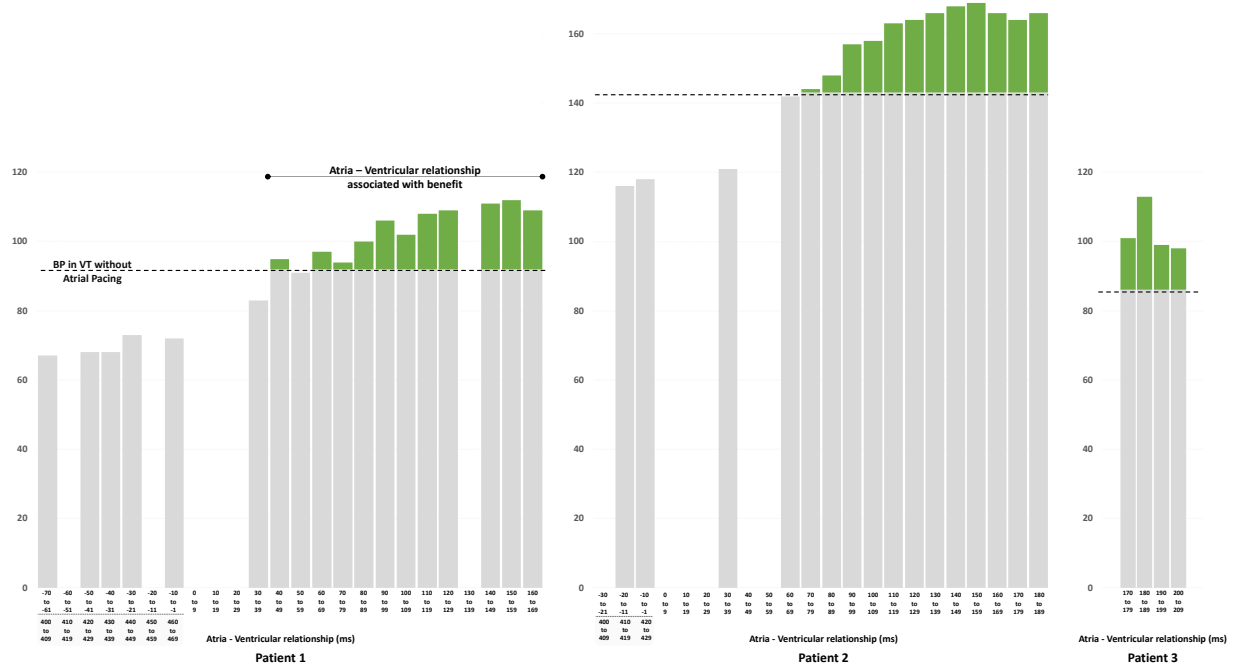


Figure 5-20 Effect of AV relationship on haemodynamics in VT

This graph shows the relationship between the derived AV delay from atrial pacing during VT and the resulting blood pressure.

The Atria -Ventricular relationship is the time interval between a VT beat and the nearest atrial pacing stimulus regardless of their order in time. If the ventricular signal occurred before the atrial signal this was considered a negative AV delay. This could also be interpreted as a very long AV delay relative to the preceding atrial paced beat, as such both possible interpretations have been included on the x axis.

Blood pressure increases above that recorded during VT with atrial pacing only when the atrial pacing is appropriately timed, too short or too long an AV can be harmful to blood pressure response.

5.5 Discussion

VT causes variable amounts of haemodynamic harm in patients. Cardiac contributors to harm can be:

- (1) the high **rate** itself, because this shortens diastolic filling time,
- (2) dyssynchrony of contraction of the **ventricular** walls, and
- (3) miscoordination between **atria** and ventricles.

This Chapter has attempted to separate the contributions that these make to haemodynamic harm in patients with severe left ventricular dysfunction. It has then attempted to rectify them separately, during both simulated VT and actual VT.

As VT rate increases, so does the haemodynamic harm. It might be tempting to think that high rate itself is in itself harmful, but this is not so. Sinus tachycardia itself does not reduce blood pressure. Atrial pacing at elevated rates also raises rather than lowers systolic blood pressure: the Bowditch Effect or Treppe Phenomenon. (Noble 1988)

VT often causes markedly worse haemodynamics and we must therefore turn to the **ventricular** dyssynchrony and the **atrio**-ventricular dyssynchrony to look for large contributors to this decline.

5.5.1 Impact of correcting **atrio**-ventricular timing

Restoring atrio-ventricular timing alone (and not ventricular synchrony) did not statistically significantly improve haemodynamics during simulated VT, but did improve it during actual VT. Even during the actual VT, the timing of the atrial stimulus was key. There was a window of AV relationship that produced an increment in haemodynamics. Outside this window there were deleterious responses, which could be considered similar to the physiology of AVNRT.

If this were to be clinically applied an algorithm that times the atrial pacing to precede the ventricular sensed event would be recommended. This would require the system to

monitor ventricular cycle length and for this cycle length to be reasonably regular, so that the timing of the next ventricular activation can be predicted from the previous one.

5.5.2 Impact of improving **ventricular** synchrony

During simulated VT, improving bi-ventricular synchrony (using His bundle pacing) statistically significantly improved haemodynamics both at 125bpm and at 160bpm. This appears to be the first demonstration of this phenomenon in VT.

5.5.2.1 Novel findings of His pacing in actual VT

During actual VT, restoring bi-ventricular synchrony had two effects:

Firstly, in all cases, it significantly improved haemodynamics. This was despite the increased heart rate arising from the pacing being slightly above the original VT rate.

Secondly, His bundle pacing showed an ability to terminate VT. This appears to be the first report of this. Two mechanisms for this effect can be proposed.

Termination Mechanism Hypothesis 1. Blocking in the diastolic pathway

The pacing stimulus may achieve termination of re-entry VT in a manner similar to that of ATP delivery from the RV. However, there are a number of potential advantages of pacing at the His bundle rather than an RV site.

- (1) The stimulus begins closer to the VT circuit (since this is usually in the LV) which is an advantage in entering the excitable gap
- (2) The stimulus propagates more quickly throughout the whole myocardium because it rapidly enters the conduction system: in a sense, His pacing can be “electrically close” to the VT circuit even if there is a considerable anatomical distance.

Because of these differences in timing and location it is conceivable that fewer paced beats at less aggressive heart rates (with subsequent reduced risk of VT acceleration) may

be all that is needed to “peel back refractoriness” and achieve VT termination. Furthermore, the data we have on the effects of His bundle pacing haemodynamics during VT suggest that, even if termination is not immediately achieved, the haemodynamic effects are unlikely to be deleterious in this situation.

Termination Mechanism Hypothesis 2. Blocking at the Exit site

His pacing can rapidly activate the entire ventricular mass and may, while the VT wavefront is mired in the slow diastolic pathway, render all the exit sites refractory to activation and thus achieve termination in this manner.

5.5.3 Future Testing and Application

The work in this chapter suggests two potential treatment approaches to VT.

The first aims to improve VT haemodynamics. This may have two advantages:

1. It may enable safe and adequate mapping of previously felt unstable VT during a VT ablation as can maintain adequate haemodynamic function.
2. It may allow adequate haemodynamics during VT in a patient with an implanted cardiac rhythm management device who experiences clinical VT. The maintenance of haemodynamics would permit more time for the VT to terminate spontaneously without the need for aggressive and potentially harmful interventions. The exact pacing stimulus timing to optimise the interaction with a VT circuit needs further work to determine at what pacing interval it is most likely to enable isolated entrainment of the VT.

The second treatment approach aims to terminate VT more safely and efficaciously than conventional RV ATP. More work is needed across a wider range of patients to determine the mechanism through which VT termination is achieved and therefore when the His paced stimulus or stimuli should be delivered in relation to the ventricular tachycardia.

The utility of His bundle pacing for VT management via an implantable cardiac rhythm management device may well be enhanced further by information provided by dynamic feedback on haemodynamic state by an adequate haemodynamic sensor within the ICD itself.

5.5.4 Limitations

In similarity to much of the initial work of RV based ATP (Almendral et al. 1986), the rates of the VT in this study were lower than that which is currently set to be treated by primary prevention devices. That being said the principles from the earlier studies of RV based ATP did extrapolate to faster rates but whether this will be the case for His bundle pacing during VT will need testing. It is possible that due to the refactoriness of the His Purkinjee system that this approach may not provide rapid conduction system capture which is the potential mechanism for benefit in those with more rapid VTs.

In this study subjects did not receive RV pacing or even biventricular pacing as a comparator for the effects of His bundle pacing during VT. It is possible that the positive effects observed with His bundle pacing may be replicated by these other methods, but this is unlikely due to inherent ventricular dyssynchrony that can arise from these approaches and the harm this can cause as demonstrated above. That being said it will be invaluable in the future to compare the efficacy of His bundle pacing based treatments for VT with the current standard of care to determine that both safety and efficacy are superior.

Not all subjects underwent the same protocol during the clinical VT. However, this was to minimize risk to patients. It was clinically important that patients did not spend excessive periods in VT that could have resulted in prolonged periods of global hypoperfusion.

5.6 Conclusions

Data from this Chapter has delineated the contributions of AV and VV synchrony to the harmful effects of VT. Furthermore, it has then demonstrated that during clinical VT that asynchronous His bundle pacing can significantly improve cardiac function supporting the patient during VT. Furthermore, for the first time we have documented that His bundle pacing can terminate ventricular tachycardia.

These results suggest that not only may His bundle pacing provide for a paradigm shift in bradycardia therapeutics but also provides a novel approach that allows VT to be better tolerated *or even terminated*.

- 6 Development of the Electro-Mechanical coupling algorithm and Quantification of Electro-Mechanical coupling to prevent inappropriate Implantable Cardioverter Defibrillator shocks

6.1 Abstract

6.1.1 Background

Inappropriate ICD therapies remain a clinically important problem associated with morbidity and mortality.

Tissue perfusion biomarkers, such as laser Doppler, to assist automated diagnosis of VF, suffer the vulnerability of sometimes mistaking artefact and random noise for perfusion, which could lead to shocks being inappropriately withheld. In this chapter the development of the Electro-Mechanical coupling algorithm which I devised and patented with my supervisors is explained. It is tested against conventional approaches for processing biological signals to discriminate between ventricular fibrillation (VF) and common causes of inappropriate therapies.

6.1.2 Methods

I, together with my supervisors, developed a novel processing algorithm that combines electrogram data and laser Doppler perfusion data, as a method for assessing circulatory status.

50 patients undergoing VF induction during ICD implantation were then recruited. From each patient, non-invasive laser Doppler and continuous electrograms, during both sinus-rhythm and VF were recorded. For each patient two additional scenarios that may lead to inappropriate shocks: ventricular-lead fracture and T-wave oversensing were simulated.

The laser Doppler signal was analysed using two traditional approaches and the newly proposed approach. The tested approaches are:

- (i) Running Mean

- (ii) Oscillatory Height
- (iii) The novel quantification of Electro-Mechanical coupling which gates laser Doppler against electrograms.

Additionally the algorithms were tested during exercise induced sinus tachycardia.

6.1.3 Results

Only the novel Electro-mechanical coupling algorithm distinguished a clear perfusion cut-off between sinus rhythm and VF (sensitivity and specificity 100%). Sensitivity and specificity remained 100% during simulated lead fracture and electrogram oversensing. (AUC: Running Mean 0.91, Oscillatory Height 0.86, Electro-Mechanical Coupling 1.00). Sinus tachycardia did not cause false positives.

6.1.4 Conclusions

Quantifying the coupling between electrical and perfusion signals increases reliability of discrimination between VF and artefacts that ICDs may interpret as VF. Incorporating such methods into future ICDs may safely permit reductions of inappropriate shocks.

6.2 Introduction

Forty percent of ICD shocks in clinical practice are inappropriate (Theuns et al. 2018; Turakhia et al. 2017), i.e. delivered in the absence of a ventricular arrhythmia. These cause unpleasant symptoms, increase healthcare costs (Bhavnani et al. 2014; Turakhia et al. 2017; Borne et al. 2013) and are associated with increased mortality (Proietti et al. 2015; Borne et al. 2013; Li et al. 2016). Despite increasingly sophisticated electrogram analysis algorithms, it has not been possible to reduce the rate of inappropriate shocks below ~3% per year, even in carefully recruited, attentively managed clinical trial patients (Gasparini et al. 2013; Moss et al. 2012). Rates appear to be even higher in clinical practice, affecting up to 41% of ICD recipients. (Watanabe et al. 2017)

Several situations can be misinterpreted as extreme high rates requiring a shock. T wave oversensing can increase apparent heart rate by up to two-fold. Right ventricular lead fracture can produce electrical noise artefacts detected as high rates. Electromagnetic interference can similarly be mis-detected as a high heart rate. Occasionally sinus tachycardia occurring during exercise can also lead to inappropriate therapies particularly in patients with a sub-cutaneous ICD. (Daubert et al. 2008; van Rees et al. 2011)

If more than a small fraction of shocks are inappropriate, there is scope for improvement. The development of new electrogram based algorithms has allowed inappropriate therapy rates for subcutaneous ICDs to be lowered to the same ~40% at which transvenous ICDs have plateaued (Theuns et al. 2018; Turakhia et al. 2017). Therefore, for all types of implantable defibrillator, there remains a major opportunity to reduce inappropriate therapies in order to make ICDs safer and more acceptable to people at risk of sudden cardiac death.

A potential method for improving upon purely electrical based detection is the addition of information on haemodynamic status. Ventricular fibrillation inevitably causes

hemodynamic collapse and therefore the presence of good cardiac output eliminates the possibility of VF even if the EGM based electrical measures suggest this. However, if an acute haemodynamic measure is to be incorporated into the ICD diagnostic algorithm it is essential that it provides both a rapid and extremely reliable assessment of haemodynamic status. This is of key importance to make sure therapies are (1) not inappropriately withheld and (2) to avoid delays in the delivery of lifesaving therapies for true VF.

6.2.1 Neither steady state (Running Mean) level nor Oscillatory Height has proved reliable

Regardless of the haemodynamic marker chosen, reliability of decision making is limited by the common theme of how to process the numerical signal to arrive at a diagnostic classification. There have been two approaches investigated for processing haemodynamic markers for this purpose: the Running Mean approach and the Oscillatory Height method.

In the Running Mean approach, an average value for the marker over several seconds is compared to an average taken from a recent reference time, commonly immediately previously (Compton et al. 2012). This requires continuous monitoring, which impairs battery longevity. A subtler limitation is that changes in posture, spontaneous biological variation and movement artefact can lead to changes in the signal that have no clinical meaning but can be difficult to distinguish from changes caused by arrhythmia. Figure 6-1 shows laser Doppler recordings from a subject during stable conditions but demonstrates the presence of baseline variability.

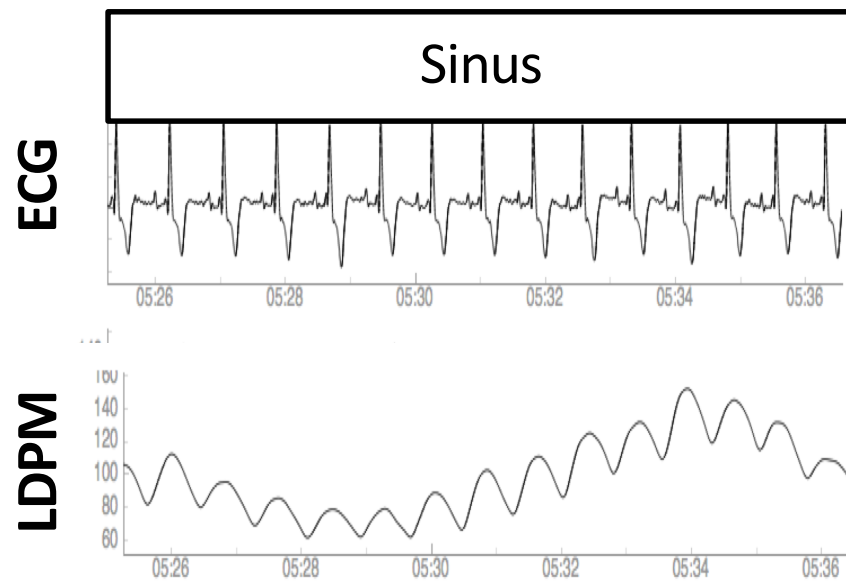


Figure 6-1 Baseline variability of LDPM signals

This example laser Doppler trace obtained from a subject during stable conditions demonstrates the frequently observed baseline variability of the trace.

The second approach is the Oscillatory Height approach which quantifies the amplitude of peak-to-trough variation in the haemodynamic signal, as this reduces or eliminates the problem of gradual baseline drift that plagues the Running Mean approach. (Nabutovsky et al. 2012; Turcott and Pavsek 2008; Turcott and Pavsek 2010) However, in patients there are always small movements and disturbances whose frequency and amplitude can overlap those elicited by cardiac function and therefore cannot be reliably removed using standard filtering of the haemodynamic signal alone. As a result, although carefully designed animal experiments showed good discrimination, (Nabutovsky et al. 2012; Turcott and Pavsek 2008; Turcott and Pavsek 2010) imperfect rapid reliability in humans has prevented clinical application. Figure 6-2 shows an example recording where using the Oscillatory Height method could cause erroneous results.

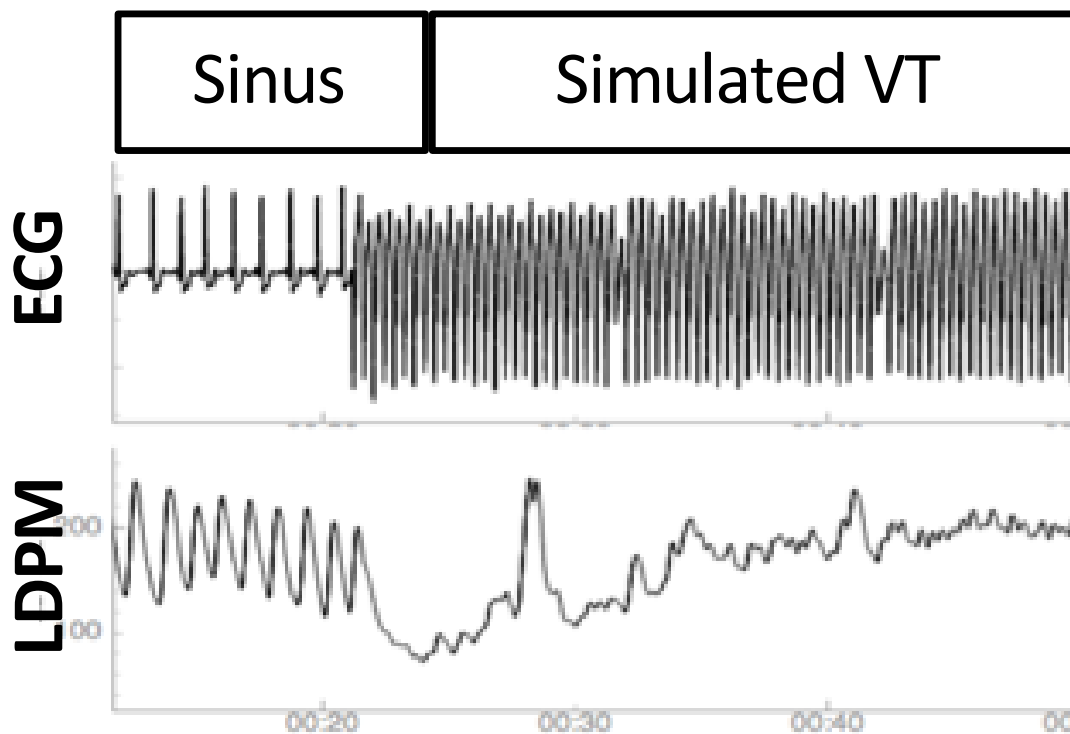


Figure 6-2 Oscillatory Height measurements are subject to artefact

This trace shows an example transition from sinus rhythm to a rapid paced asynchronous ventricular rhythm. There are a number of large oscillations that are observed during the simulated VT these are likely to occur due to artefact rather than reflecting short lived improvements in haemodynamic state.

Electro-Mechanical Coordination as the signal

This Chapter describes our derivation and investigation of a new way to process perfusion signals in order to deliver a reliable assessment of haemodynamic status when the apparent electrogram heart rate is in the VF zone. This method combines simultaneous electrogram and haemodynamic measures to confirm whether observed haemodynamic pulsatility is consistent with the apparent electrical rhythm at that instant.

Specifically, the novel algorithm in combination with laser Doppler perfusion signals is tested to determine whether it can reliably assess haemodynamic status, during VF and during sinus rhythm even in the presence of double counting, simulated lead fracture and sinus tachycardia. The reliability of this novel algorithm is then compared to the previously described Running Mean approach and Oscillatory Height approach.

6.3 Methods

6.3.1.1 Study Population

Patients undergoing clinically planned VF induction during clinically indicated ICD implantation were recruited. VF was induced under general anaesthesia for subcutaneous ICDs and under intravenous sedation for trans-venous ICDs, using a 50-Hz burst or a drive train and T-wave synchronised shock.

6.3.1.2 Measurements

Patients had continuous monitoring of beat-by-beat blood pressure. Where invasive monitoring was not clinically indicated, this was done non-invasively (Finapres Nova, Finapres Medical Systems, NL). Patients had two laser Doppler sensors (Periflux 5000, Perimed, Sweden) positioned non-invasively on the skin, one on the index finger of the hand contralateral to the implant and the other on the chest wall. (Figure 6-3) Patients also had continuous ECG monitoring (Fukuda Denshi 7100, Fukuda Denshi, Japan).

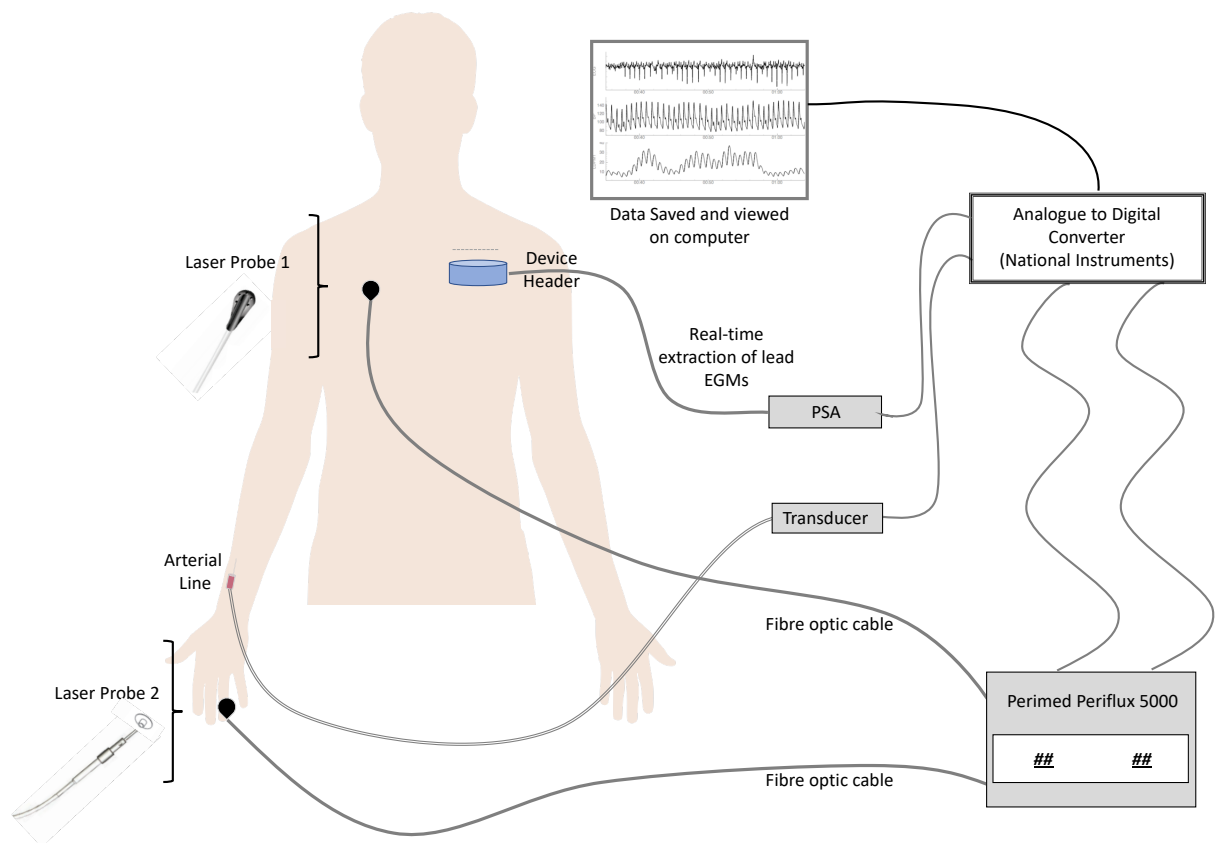


Figure 6-3 Methodological approach for data acquisition

Shows the position of the laser Doppler probes. Both were placed on the contralateral side to the implanted device; one on the right chest wall and one on the finger. Signals travel via a fibre optic cable to the Perimed Periflux 5000 device. From here they are converted from analogue to digital signals together with inputs from the ICD and blood pressure. They are then displayed and saved on a PC for analysis.

Where possible, the electrogram from the ICD lead and the device marker channel via the Pace-Sense Analyser were acquired simultaneously. In the remaining participants, the surface ECG was used as a substitute for the ICD lead signal.

Recording began at least one minute before VF induction and continued until at least 1 minute after returning to sinus. Data were acquired at 1000 Hz using an analogue to digital card (National Instruments Texas) and Labview (National Instruments). Signals were then analysed offline using automated custom software (Python Foundation, USA).

6.3.1.3 Sampling Windows

To ensure that results could not be unintentionally manipulated through our selection of the time window during which the algorithm ran. For each VF episode, therefore a series of overlapping six-second time windows were analysed, starting from the onset of VF and stepping forward by one second at a time until the end of the period of VF. (Figure 6-4) Similarly, it was pre-defined that the sinus rhythm analysis windows would be the same number of overlapping six second windows, but from immediately before VF induction and working backwards. This meant that for each episode there were multiple (at least 4) individual measurements during VF and the same number during sinus rhythm. All measurements were included in the analysis.

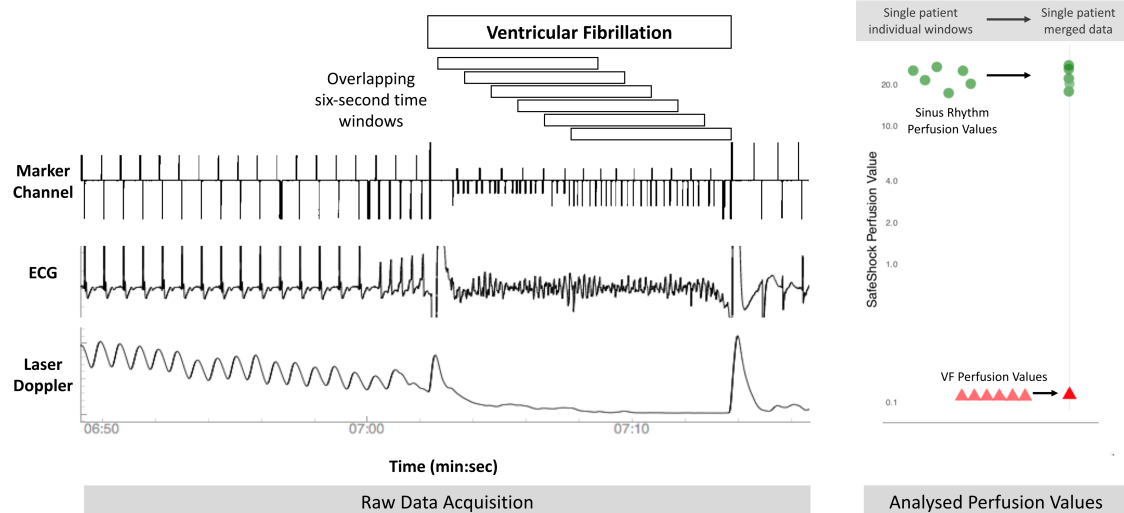


Figure 6-4 Data Sampling windows

Left: For each VF episode, overlapping 6-second time windows were analysed. (The same number of sinus rhythm windows were analysed from immediately before VF induction.)

Right: For each window, a perfusion value was calculated (green circles for sinus rhythm, red triangles for VF).

6.3.2 Choice of Hemodynamic Sensor

Beat-by beat cardiac output or blood pressure might be seen as ideal methods for assessing clinical status. However, long term monitoring of systemic arterial blood pressure or cardiac output is not straight forward because intra-arterial devices can be difficult to implant, risk thrombosis, require separate power and need to communicate with the ICD.

An alternative is to assess perfusion. Methods for this include photoplethysmography (PPG), near infrared spectroscopy (NIRS) and laser Doppler perfusion monitoring. These methods rely on various properties of reflected light rather than on a pressure sensor inside the blood stream. Some have previously been investigated as an approach for augmenting ICD discrimination (Compton et al. 2012; Nabutovsky et al. 2012; Turcott and Pavek 2008; Turcott and Pavek 2010).

6.3.2.1 *Laser Doppler Perfusion Monitoring*

Laser Doppler quantifies flow from the change in wavelength of a laser signal reflected back from moving red blood cells (Salgado et al. 2014). Pulsatility of blood flow is then detected.(Bonner et al. 1981; Rajan et al. 2009; Leahy et al. 1999)

6.3.3 Datasets for four conditions per patient

For each patient recordings were made during sinus rhythm and VF. The electrogram recorded during sinus rhythm was also transformed to simulate lead fracture and double counting.

To simulate lead fracture, in each patient the ventricular signal was substituted with an EGM from a clinical lead fracture. The algorithm was then supplied with the atrial lead's sensed electrical data or, if this was unavailable, the original ventricular lead data but shifted backward by an appropriate AV delay(120ms).

To simulate double-counting, an extra sensed R-wave was synthesized between the truly detected R-waves at 33% of the R-R interval. During processing with the novel algorithm, the new approach can form multiple hypothesis about which R-waves are true or false and test them against the perfusion signal.

6.3.4 Sinus Tachycardia data set

To test misdetection of sinus tachycardia, heart rates in the 180-200bpm range were required. This required a different group of subjects. 12 healthy volunteers were recruited, who exercised on a treadmill to a peak heart rate that averaged 184bpm. ECG, laser Doppler and non-invasive beat-by-beat blood pressure were recorded.

6.4 Analytical algorithm

The novel electro-mechanical coupling algorithm I derived with my colleague and supervisors has now been patented by our University. (Keene n.d.)

The algorithm was developed from pilot data collected during VF induction testing, during rapid ventricular pacing to simulate VT and from patients presenting to the hospital with clinically occurring spontaneous arrhythmias.

Firstly, reviewing the raw data revealed problems that would be associated with using a running mean approach for analysing the LDPM signals as large phasic changes in the mean value were noted even during a steady state. In Figure 6-5 we show how, during a simulated VT, which caused a fall in blood pressure, there was only minimal change in the mean LDPM signal until 10 seconds into the episode. Moreover, when the change finally appeared it was a rise in mean signal rather than a fall.

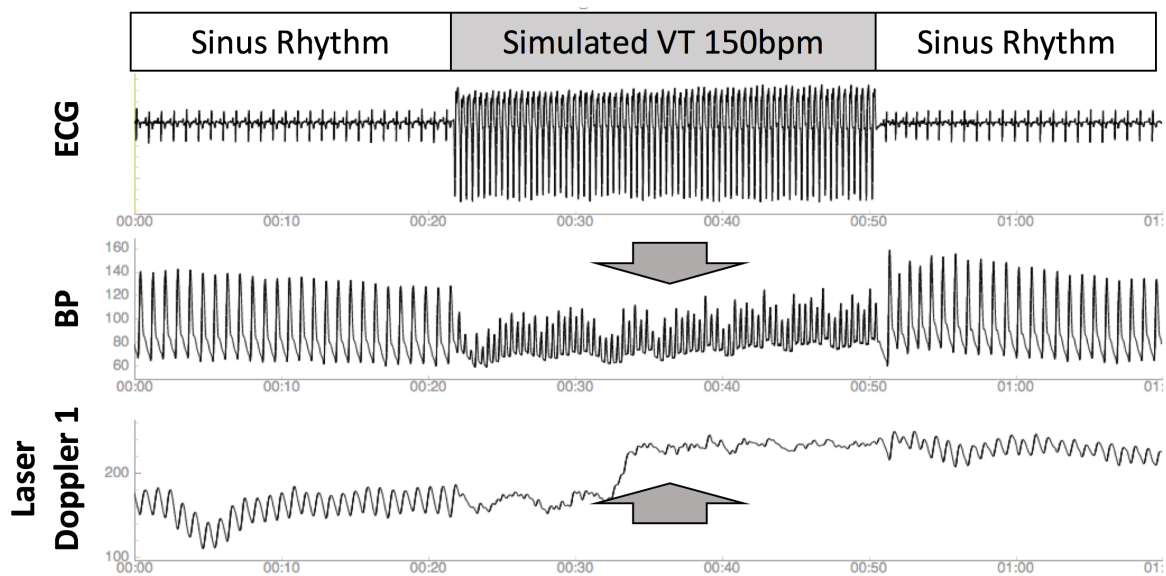


Figure 6-5 Issues with a Running Mean based assessment

This figure demonstrates an example of a simulated VT at 150bpm. With the initiation of the simulated arrhythmia there is no apparent change in the running mean of the laser Doppler signal for the first 10 seconds despite a fall in blood pressure. After this point despite a now stable albeit lower than baseline blood pressure the laser Doppler trace is seen to paradoxically rise.

It was consistently observed, however, that when the signal is sampled at a high enough frequency (1000hz), oscillations are seen in the signal in phase with the cardiac contraction. Furthermore, a clear reduction in the amplitude of these oscillations was seen during periods of haemodynamic impairment for example in VT (Figure 6-6) and in VF (Figure 6-7).

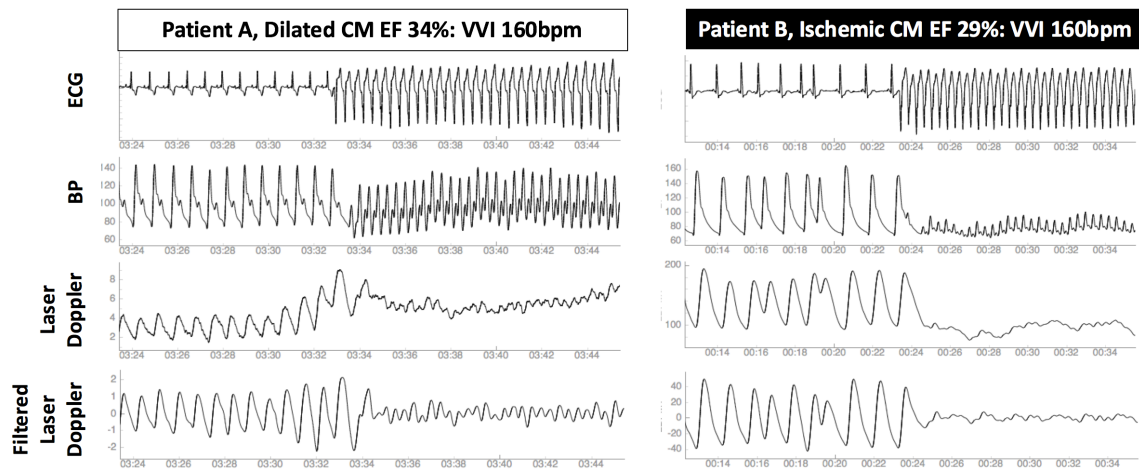


Figure 6-6 The importance of Oscillatory Height to signal interpretation

This figure shows data from two patients undergoing transitions to a simulated ventricular tachycardia from sinus rhythm with a modest (patient A) and a large fall (patient B) in blood pressure. Patient A demonstrates that despite the drop in BP the mean unfiltered laser Doppler signal rises, this is corrected for with a filtered signal. It is apparent though that the oscillatory amplitude is reduced during periods of haemodynamic insult. In patient B where there is an even greater fall in blood pressure observed it is clear to see that again the oscillatory amplitude falls and the fall in oscillatory height appears to be greater here where there is a larger fall in blood pressure than in patient A.

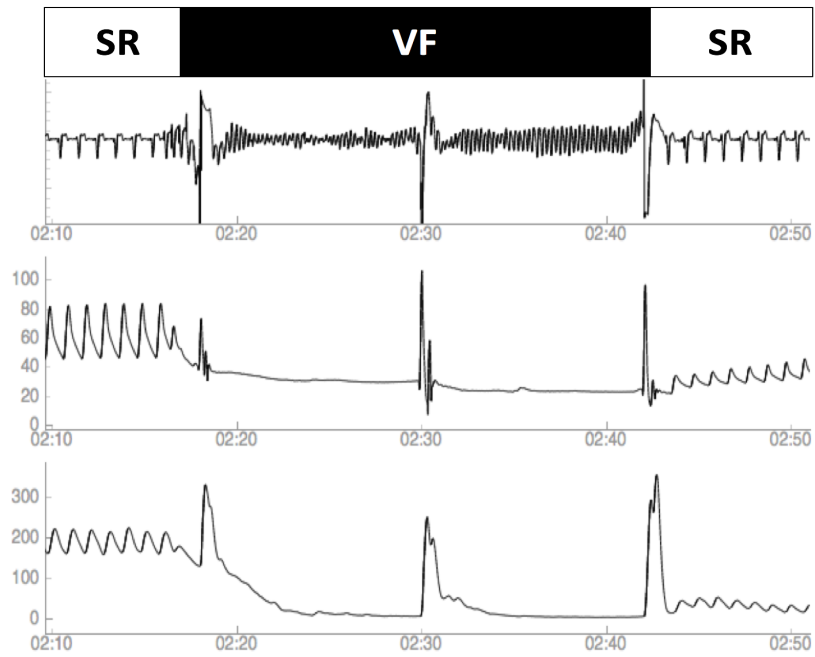


Figure 6-7 Fall in signal Oscillatory Height during VF

This figure shows an example of VF induction at time of device implant. There is a significant drop in blood pressure as expected and a corresponding reduction in synchronous oscillations of the laser Doppler signals demonstrating again that oscillatory height relates to haemodynamic state

We therefore developed an analytical strategy based on the relative amplitude of these oscillations to the mean signal.

We perform band pass filtering (0.05hz to 20hz) to remove electrical noise and phasic changes associated with ventilation. The signal is then segmented based on the R-R interval of the ECG over a 6 second window. These segments are then ensembled to produce a consensus signal. The oscillatory height (expressed as a percentage of the mean value) is then used as our marker of perfusion. This approach is detailed in Figure 6-8 and Figure 6-9. This method is known as the Electro-Mechanical Coupling algorithm.

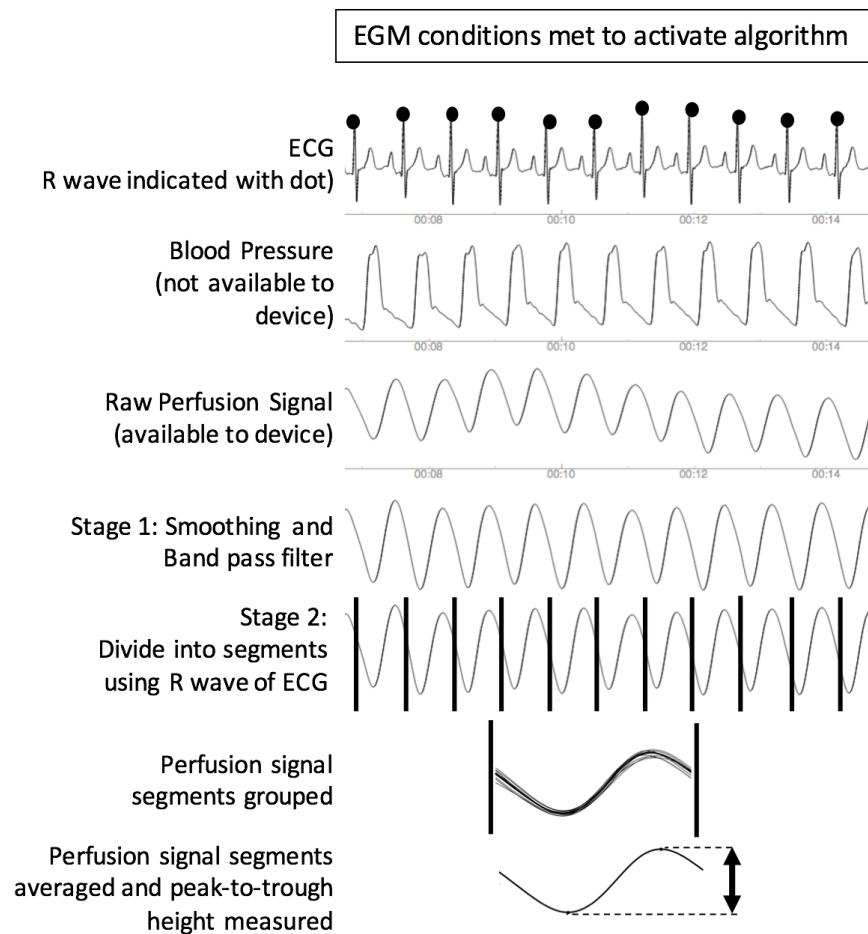


Figure 6-8 The Electro - Mechanical Coupling Algorithm

This Figure demonstrates the Electro-Mechanical Coupling algorithm for haemodynamic signal interpretation. The key to the method is that false fluctuations on the physiological sensor “do not align with the heart beat”. The Electro-Mechanical coupling algorithm can take any physiological measure of perfusion be it pressure or flow or anything in between. It segments the data using the electrogram, into chunks of one single heart beat, (the device can check the perfusion signal with the detected heart rate from multiple leads to mitigate against RV lead issues for example lead fractures) it then aligns the data and then

signal averages across multiple beats. This can be done efficiently in the time domain and without requiring Fourier transformations. The end result is a signal that shows a large result when the fluctuations are genuinely in time with the electrogram and shows a small fluctuation when the fluctuations are biological or technical artefacts and do not line up with the electrogram or when there are no fluctuations as very poor perfusion is detected

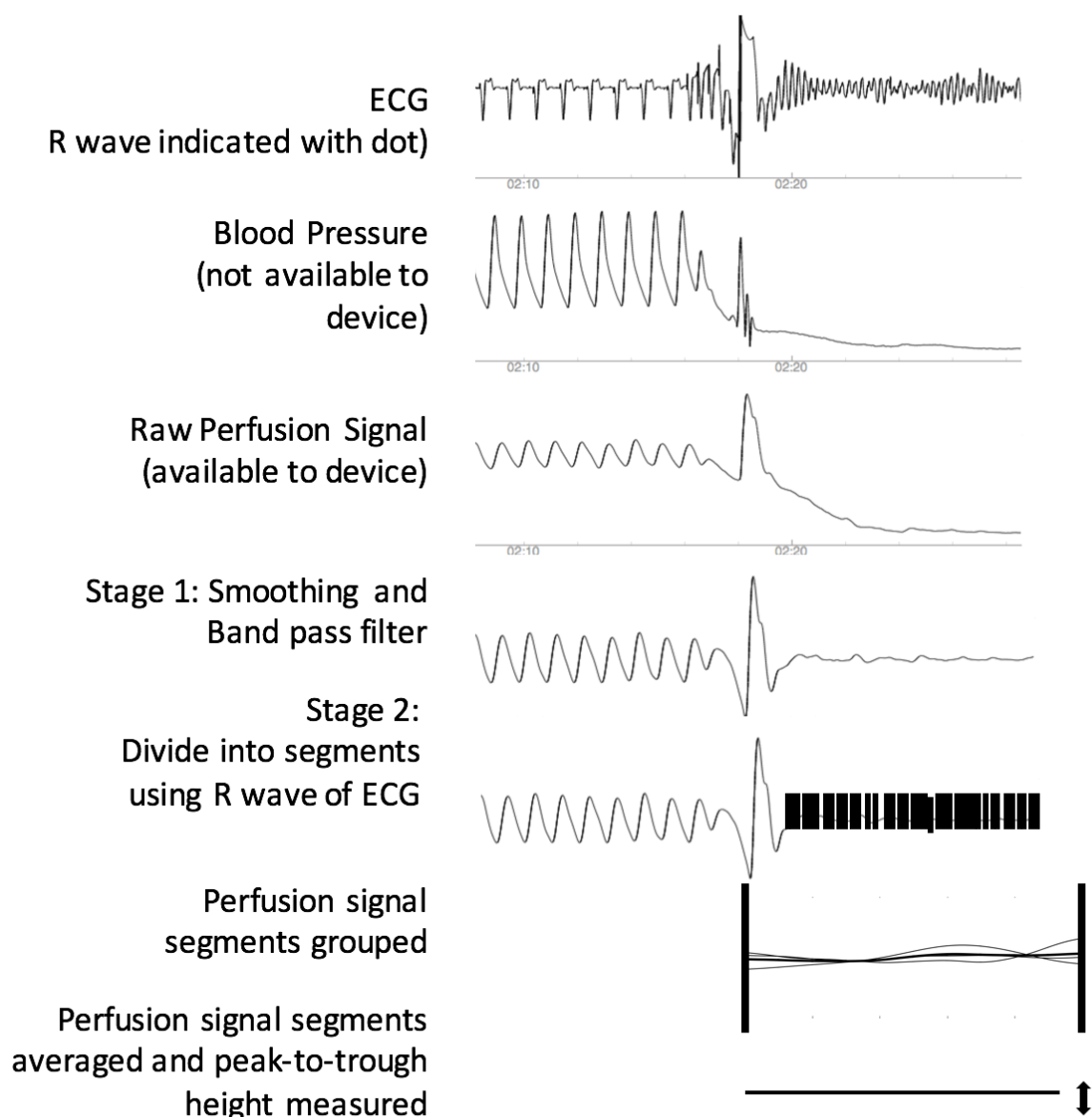


Figure 6-9 The Electro - Mechanical Coupling Algorithm during VF

This Figure demonstrates the Electro-Mechanical Coupling algorithm approach again, this example demonstrates that in VF very minimal fluctuations are observed when there is poor perfusion in contrast to the sinus rhythm example shown above

As already mentioned there are two previously described techniques for analysing optical sensors that may be used in implantable cardiac rhythm management devices. The first approach involves quantifying the mean of a signal over a time window, or, using the average peak to peak height of the signal (Oscillatory Height) without considering synchrony with the ECG. We analysed our pilot data using these two methods in addition to our novel algorithm so we could consider their relative advantages and disadvantages. Two examples of their disadvantages are highlighted in Figure 6-10 and Figure 6-11.

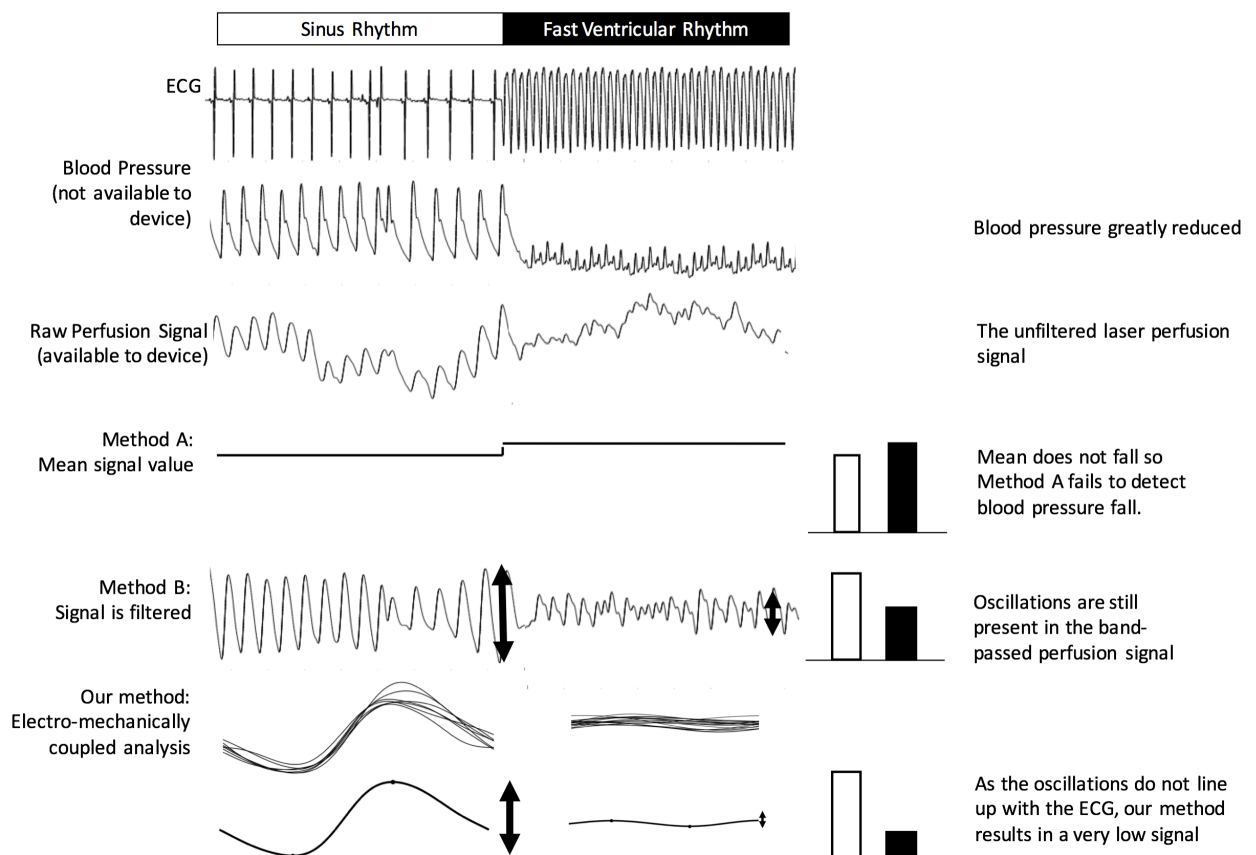


Figure 6-10 Analytical Algorithms Issues (1)

An example of ventricular pacing simulating VT inducing a large drop in BP. The raw perfusion signal shows the mean signal has risen, thus using a running mean approach would not detect the fall in BP and decline in haemodynamic state. The oscillatory-height based method shows large oscillations in sinus rhythm and smaller ones during VT. The oscillatory height appears to have dropped by almost a half. The oscillatory height method thus appears to work here. However, the drop in oscillatory height may not fully reflect the haemodynamic state as the Electro-Mechanical coupling algorithm detects an almost ten fold drop in the measured signal, a very clear signal of gross reduction in perfusion more akin to the BP reduction observed.

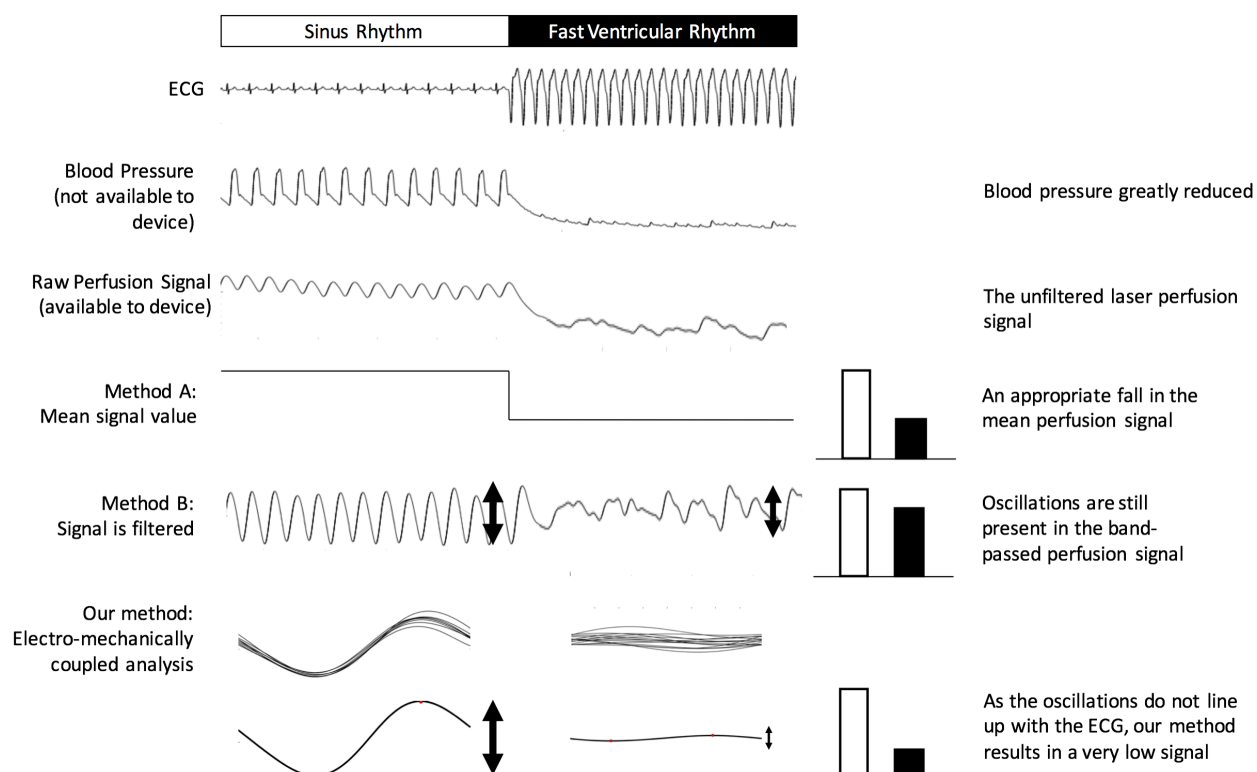


Figure 6-11 Analytical Algorithms Issues (2)

Here is another example of fast ventricular pacing simulating VT. The BP falls and so does the mean perfusion signal. It shows a halving of the signal. However, the oscillatory height approach fails to detect the dramatic drop that is present in the BP. That is because the fluctuations that it is measuring are not in keeping with the heart rate. The Electro-Mechanical Coupling method though does accurately detect the dramatic drop in BP as it discounts the observed fluctuations in the signal as they are not related to the heart rate.

In view of the reliance placed by our Electro-Mechanical Coupling algorithm on gating based on the ECG we obtained pilot during atrial fibrillation to assess if this would cause issue for the algorithm. From the limited data we collated, it was apparent that as long as the R wave detector utilised for ECG gating was successful in detecting the QRS complexes during atrial fibrillation, our algorithm will still work. Figure 6-12

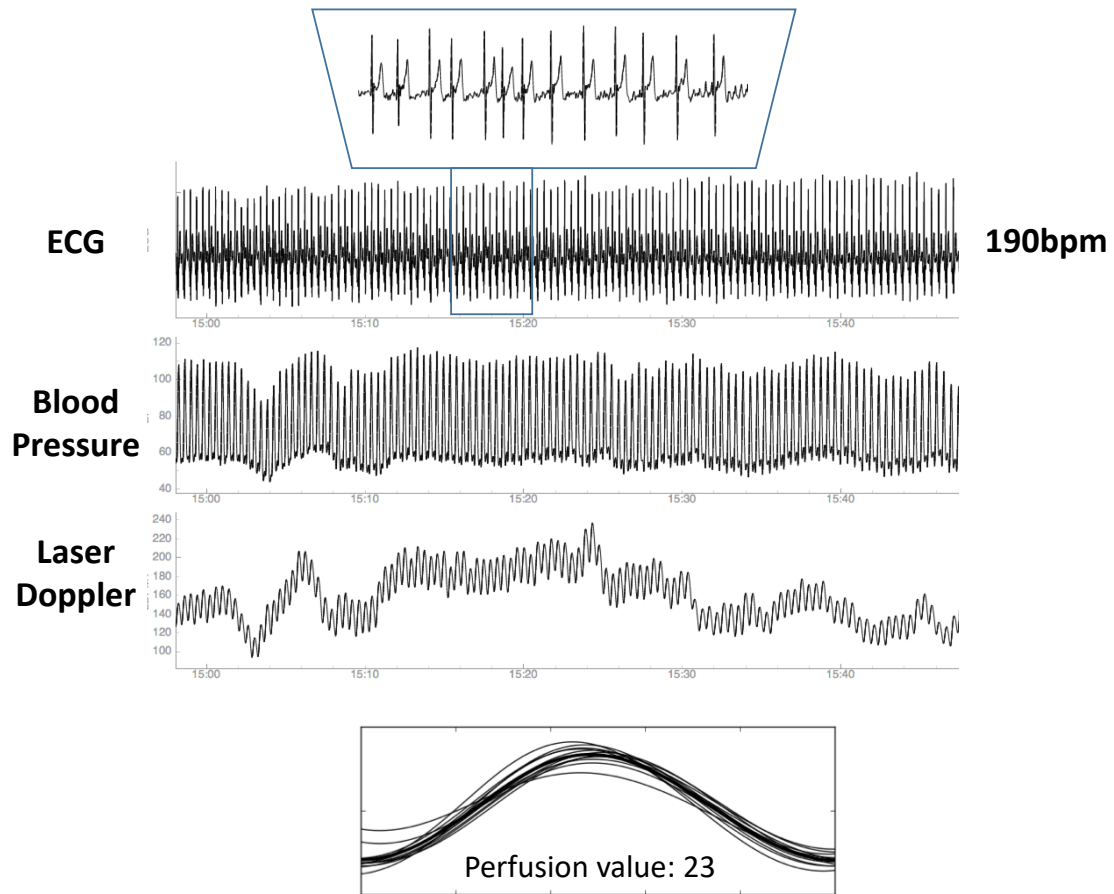


Figure 6-12 Example of the Electro - Mechanical Coupling algorithm in AF

This example demonstrates that the algorithm appears resistant to issues that Atrial Fibrillation may cause. It also serves as a reminder that not all rapid heart rates are associated with haemodynamic harm and that is clearly seen in this example with adequate Blood Pressure response seen which is matched by the Electro-Mechanical Coupling score.

The Electro-Mechanical Coupling analytical approach begins with three simultaneous analyses of the laser Doppler data, each with a different gating. The primary gating is with the ventricular lead, the secondary is with an alternate lead or vector, and the tertiary is with a synthetic signal designed to deal with over-counting. The synthetic signal is created from the original EGM data from which our analytical approach generates multiple hypotheses as to which of the observed R-R intervals are true and testing them against the perfusion signal. If satisfactory perfusion is detected due to derived electro-mechanical synchrony these “true” R waves then form the synthetic signal.

It is currently designed to be used as a confirmatory step after traditional EGM discriminators have potentially identified a ventricular arrhythmia. The algorithm though has been designed not to add any additional time to this current process as this could potentially risk patient harm which of course is undesirable. It is envisaged that the laser Doppler assessment would only need to be activated once the traditional EGM algorithms have started to detect suspected VF. If there is sufficient pulsatility (exceeding a global threshold which does not need personalizing to the patient) with the primary gating, the algorithm reports this and halts. If there is not sufficient pulsatility, the algorithm tests for the possibility of disruption by noise (by trying the secondary gating) or disruption by oversensing (by trying the tertiary gating). If the secondary or tertiary gatings reveal satisfactory pulsatility, the algorithm reports this, otherwise it reports insufficient pulsatility. Although these tests have been described in sequence, they are actually conducted simultaneously. Figure 6-13

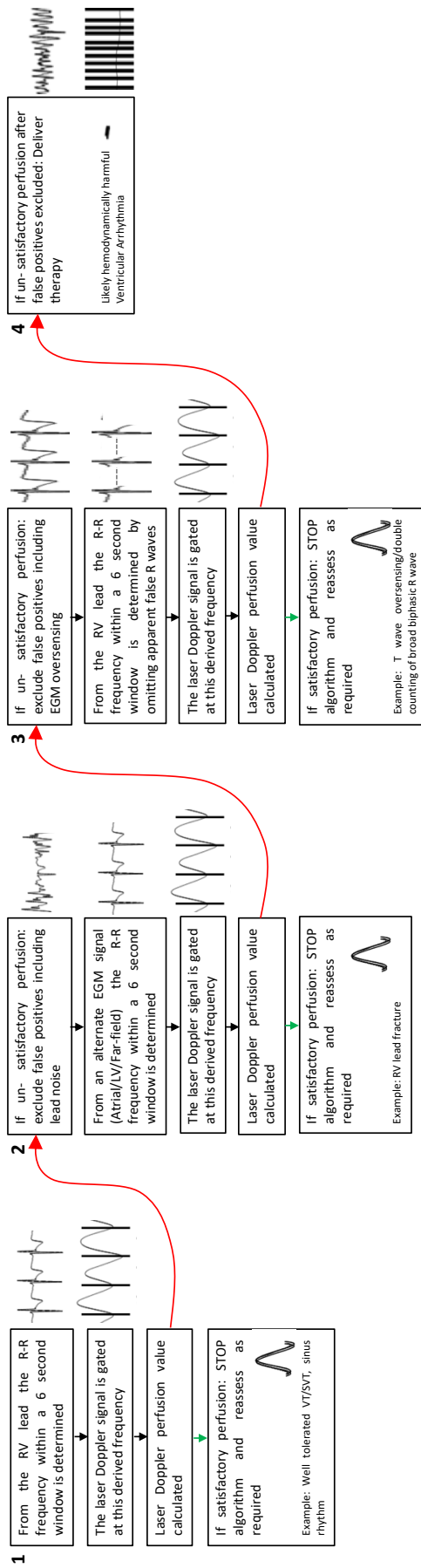


Figure 6-13 The Electro - Mechanical Coupling analytical approach

Three simultaneous analyses of the laser Doppler data are performed. For ease of understanding here we consider them as if they occur in turn. 1) Gating of the laser Doppler signal is performed based on the R-R interval from the RV defibrillator lead. If satisfactory perfusion is noted the algorithm stops. 2) Gating of the laser Doppler trace is performed based on an alternate EGM signal (atrial / LV lead / from an electrode positioned within the generator itself) to mitigate against potential lead fracture of the RV lead. If satisfactory perfusion is noted the algorithm stops. 3) Gating of the laser Doppler signal is performed based on generating multiple hypotheses as to which of the observed R-R intervals are true and testing them against the perfusion signal. This is to mitigate against potential oversensing of cardiac electrical signals. If satisfactory perfusion is noted the algorithm stops. 4) If unsatisfactory perfusion remains after exclusion of false positives the algorithm determines that haemodynamic harm is occurring and in keeping with the EGM based algorithm and would recommend therapy delivery.

If traditional EGM algorithms continue to suspect VF, the laser Doppler quantification can be repeated as often as required. Additionally, the laser Doppler assessment can detect lead fracture from the difference between the results of primary and secondary gating. This could be used to alert the patient's medical team.

In this chapter, the algorithm is analysed in its three component parts. (1) The primary gating, (2) secondary gating with an alternate *electrode* (to deal with lead fracture), and (3) tertiary gating with an alternate *EGM interpretation* (for oversensing).

The perfusion data is also analysed using two previously described algorithms. The first calculates the Running Mean of the perfusion data over the analytical window.

(Compton et al. 2012) The second calculates the mean peak-to-trough height after passing a band-pass filter over the analytical window (the Oscillatory Height method). (Turcott and Pavek 2008; Turcott and Pavek 2010; Nabutovsky et al. 2012) No absolute cut-offs have been described for these previously published methods.

Quantification of Electro-Mechanical coupling, the Running Mean algorithm and the Oscillatory Height algorithm were tested for their ability to distinguish between VF and the situations that could mimic VF.

6.4.1 Statistical analysis

Pilot testing had indicated the Electro-Mechanical coupling perfusion value, which runs on a scale from 0 to 100, always has values less than 2 during VF and always has values above 2 during sinus rhythm. For this study, therefore a threshold of 2 was used.

Sensitivities and specificities were calculated using appropriate methods. The perfusion data was processed using Python (Python Foundation, USA) and statistical analyses were performed on R version 3.0.2 (R Project, Austria)

6.4.2 Study Conduct

Patients gave prior written informed consent for this study which was approved by the local Research Ethics Committee (London – Dulwich, 14/LO/2158).

6.5 Results

6.5.1 Patient population

50 patients were recruited (Table 6-1), 19 were having implants for secondary prevention of ventricular arrhythmias, and 31 for primary prevention. 35 were trans-venous and 15 sub-cutaneous. 24 patients had left ventricular impairment due to ischaemic heart disease. The mean age was 61.6 (SD 15.5) years, and the mean left ventricular ejection fraction 39% (SD 14.3). Induction was by 50Hz burst in half the patients and drive train and T wave shock in the others.

Table 6-1 Patient Demographics and Device Characteristics	
Age (mean±sd)	61.6 (±15.5)
Sex	
Male	37 (74%)
Female	13 (26%)
Ethnicity	
Caucasian	31 (62%)
Asian	12 (24%)
Afro-Caribbean	7 (14%)
Left Ventricular Ejection Fraction (mean±sd)	39% (±14.3)
Rhythm	
Sinus	48 (96%)
Atrial Fibrillation	2 (4%)
Prevention	
Primary	31 (62%)
Secondary	19 (38%)
Indication	
LVSD with IHD	24 (48%)
LVSD without IHD	10 (20%)
HCM	5 (10%)
Brugada	2 (4%)
Sarcoid	1 (2%)
Amyloid	1 (2%)
Idiopathic VF	2 (4%)
AR+/LVC	5 (10%)
ICD Type	
Trans-venous	35 (70%)
Single Chamber	2 (4%)
Dual Chamber	7 (14%)
CRT-D	26 (52%)
Sub-cutaneous	15 (30%)
Induction method	
R-on-T	25 (50%)
50Hz	25 (50%)
LVSD; Left ventricular systolic dysfunction. IHD; Ischemic Heart Disease. HCM; Hypertrophic Cardiomyopathy. AR+/LVC; Arrhythmogenic Right / Left Ventricular Cardiomyopathy.	

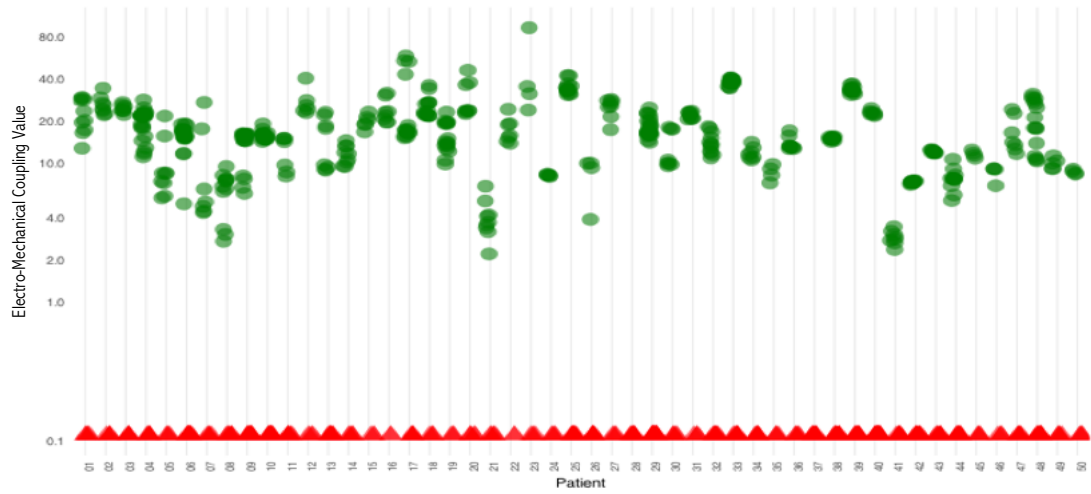
6.5.2 Test 1: Confirming onset of VF using continuous Doppler measurement

A rudimentary test of discriminative power for the three processing algorithms (Running Mean, Oscillatory Height and Quantification of Electro-Mechanical coupling) is to assess the ability to correctly detect the change from sinus rhythm to VF, on VF induction, assuming a continuous stream of Doppler data is being acquired. This test can be considered rudimentary because it assumes there is sufficient energy to perform continuous Doppler measurements so that the algorithms always have an immediately preceding segment of normal rhythm against which to compare the suspected VF.

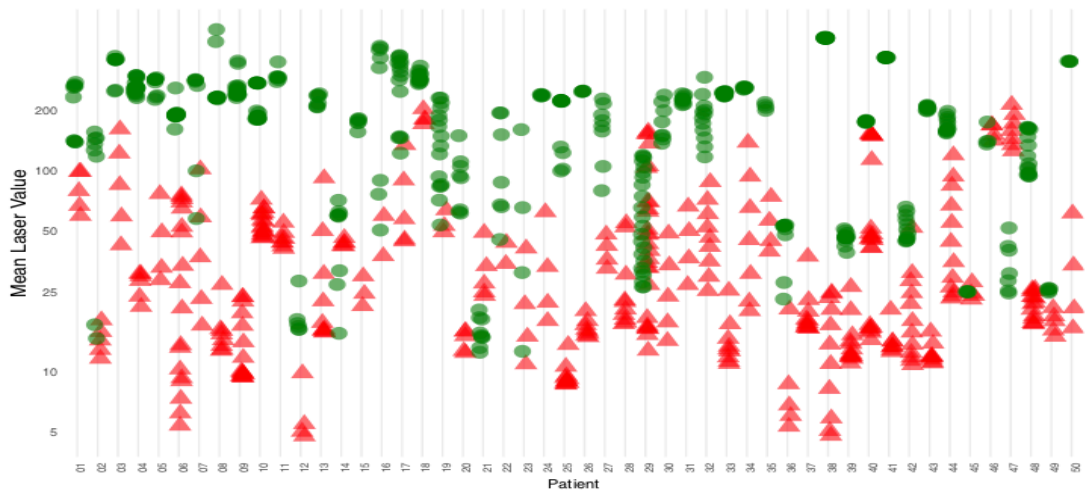
For each patient the algorithms have the data from four or more overlapping windows of VF and the same number of immediately preceding windows of sinus rhythm. In this section of the analysis, for an algorithm to be counted as successful on a patient, it is only required for there to be no overlap between the values in VF and those in sinus on that patient. This mimics a mode of implementation where there is continuous laser Doppler measurement so that when the algorithm is triggered, there is always an immediately prior reference. This way, the threshold is individualized not only to the patient but also to the particular episode of suspected VF since the immediately preceding normal rhythm is available for reference.

Running Mean was successful in this analysis in 76% of patients (38/50). Oscillatory Height was successful in 48% (24/50) which was significantly lower ($p=0.004$). Electro-Mechanical Coupling was successful in 100% (50/50) which was significantly higher than both Running Mean ($p=0.0002$) and Oscillatory Height ($p<0.0001$). Figure 6-14

A The Electro-Mechanical Coupling Method



B Running Mean Method



C Oscillatory Height Method

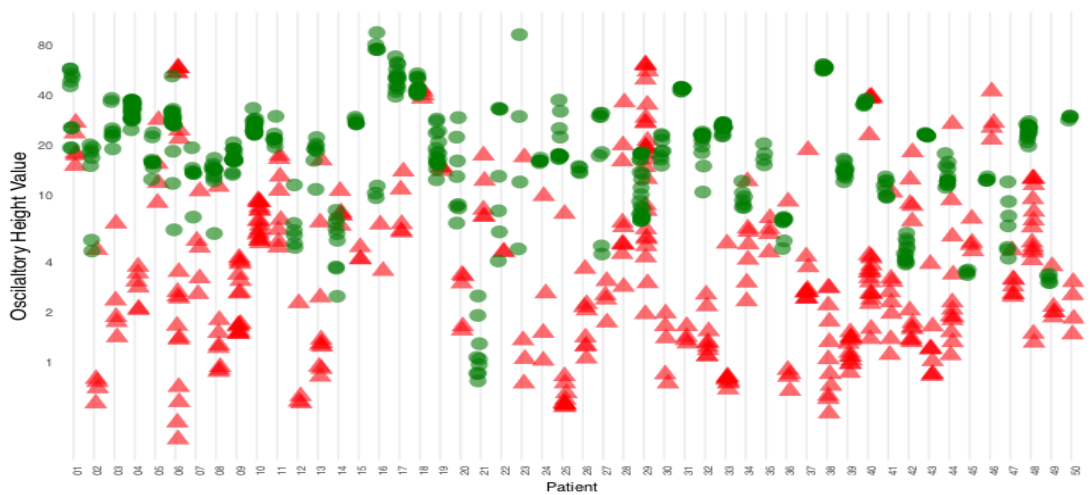


Figure 6-14 Discriminative capability of laser Doppler to differentiate sinus rhythm from VF

Perfusion values as green circles (sinus rhythm windows) and red triangles (VF windows)

A The Electro-Mechanical coupling method shows 100% discrimination for each patient between the two states. No sinus rhythm window of any patient scored <2 .

B Running Mean method, failing to discriminate in 12 patients

C Oscillatory Height method, failing in 26 patients.

6.5.3 Test 2: Confirming onset of VF without continuous Doppler measurement

In practice it would be preferable that the laser would only be switched on when required, to conserve the device's battery life. This means the algorithm is initiated only to confirm an EGM suspicion of VF; there would therefore be no available recording of the immediately preceding normal rhythm for comparison. Therefore, the algorithm would work most effectively if there was a complete separation between all the values in sinus rhythm (in all patients) and all the values in VF (in all patients), so that a common discriminatory threshold could be used.

The full spectrum of potentially discriminatory thresholds was tested. Each window of VF was treated individually, yielding 393 VF windows from the 50 patients. Similarly, each of the 393 sinus rhythm windows was treated individually. For every possible discriminatory threshold, a sensitivity and specificity were calculated across all of these windows and plotted on a ROC curve.

Running Mean provided an area under curve of 0.91. Oscillatory Height provided an area under curve of 0.86 which was significantly lower ($p < 0.0001$). The Electro-Mechanical Coupling algorithm provided an area under curve of 1.00 which was significantly higher than both Running Mean ($p < 0.0001$) and Oscillatory Height ($p < 0.0001$). Figure 6-15

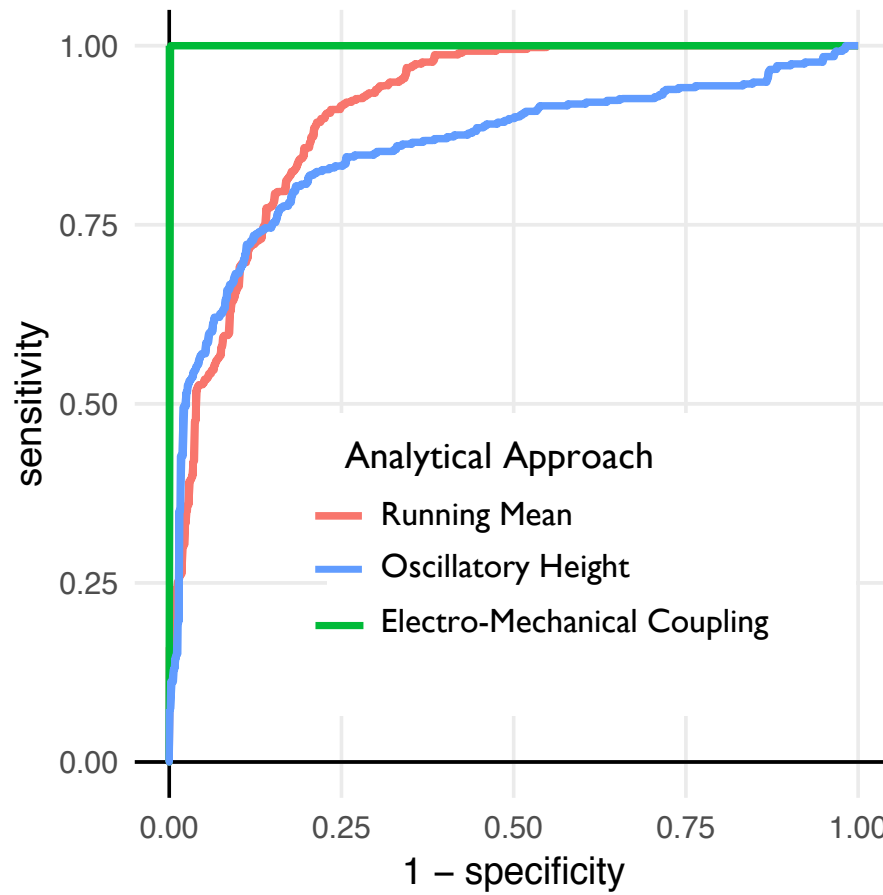


Figure 6-15 Receiver Operator Characteristics for the different analytical methods

ROC curves for Running Mean, Oscillatory Height and Electro-Mechanical coupling analytical methods. The AUCs are 0.91, 0.86 and 1.00 respectively.

Examples of where the Running Mean and Oscillatory Height methods fail are shown in Figure 6-16.

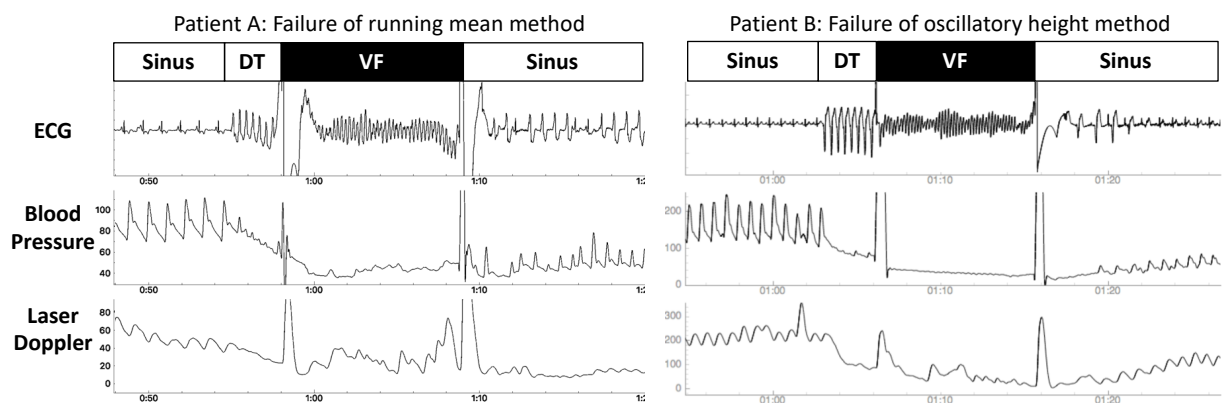


Figure 6-16 Examples of Failure of Oscillatory Height and Running Mean

Patient A. The Running Mean method fails in this patient as the laser Doppler signal does not significantly fall during VF.

Patient B. The Oscillatory Height method fails in this patient as there are still oscillations during the period of VF.

6.5.4 Test 3: Correct handling of ventricular lead fracture

When the ventricular lead develops a fracture, artefacts can occur at a frequency which falls in the VF zone. Even the presence of a normal rate in an alternate lead (i.e. the atrium) does not provide adequate reassurance, since VF can co-exist with normal atrial activity. The Electro-Mechanical coupling approach includes a specific test of haemodynamic pulsatility in synchrony with an alternate lead (or an alternate EGM source for example a sensor located in the generator), so that it can distinguish between fracture of the ventricular lead (in which situation there will be preserved haemodynamic pulsatility in synchrony with the alternate EGM) and VF (where there will not, even if there is normal atrial activity).

In this test, the electrogram signal from a fractured lead was imposed in place of the true ventricular lead signal during sinus rhythm. Each of the three algorithms was then triggered and tested whether they categorized the situation as VF or not. This was conducted with the data from each of the 50 patients.

For each algorithm the threshold derived from the sinus rhythm and VF data in Test 2, Figure 6-17 was applied.

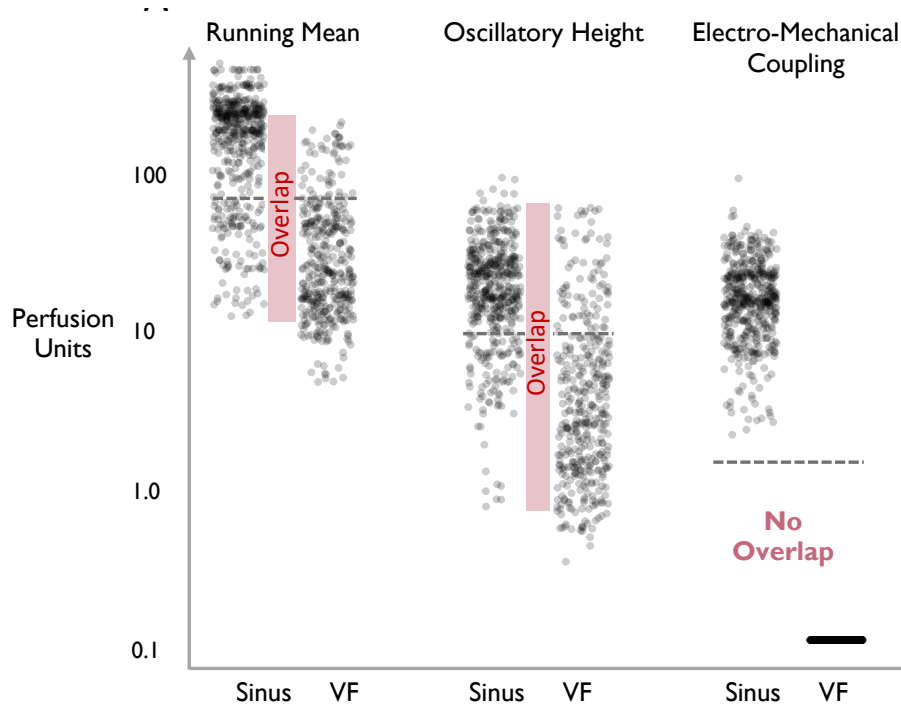


Figure 6-17 Cut off thresholds for the analytical approaches

Horizontal grey dotted lines indicate thresholds for each analytical mode, chosen to maximize the sum of sensitivity and specificity. The Running Mean and Oscillatory Height had substantial overlap between sinus rhythm and VF perfusion data.

The threshold was chosen to maximize the sum of sensitivity and specificity. In practice, Electro-Mechanical coupling showed such a large separation between the VF and sinus rhythm data in Test 2, such that any threshold between 0.1 and 2 perfusion units provided optimal results (sensitivity and specificity both 100%). I therefore used the value of 2 perfusion units derived from previous pilot experiments, as the Electro-Mechanical Coupling threshold in Test 3.

Running Mean (threshold 80 perfusion units) correctly categorized the lead fracture windows in 52% (26/50) and Oscillatory Height (threshold 10 perfusion units) in 62% (31/50). Electro-Mechanical Coupling correctly categorized the lead fracture windows in 100% (50/50) which was significantly higher than both Running Mean ($p < 0.0001$) and Oscillatory Height ($p < 0.0001$)

6.5.5 Test 4: Correct handling of Electrogram Double-counting.

Devices are susceptible, despite blanking algorithms to picking up extra parts of the cardiac cycle beyond the intended activation, for example the T-wave, and thereby overestimating the heart rate by up to two-fold. The Electro-Mechanical Coupling algorithm tests for this possibility by quantifying the pulsatility not only with a full-set of the suspected R-waves but also with sub-sets that make allowances for electrogram double-counting. If it finds satisfactory pulsatility in association with one or more of these subsets, it can advise that this is not VF.

In Test 4, each algorithm was given laser Doppler data from sinus rhythm but paired with a modified version of the corresponding electrical data. The modification implemented T wave double counting.

Running Mean (threshold 80 perfusion units) correctly categorized the double counting windows in 52% (26/50) and Oscillatory Height (threshold 10 perfusion units) in 62% (31/50). SafeShock correctly categorized the double counting windows in 100% (50/50)

which was significantly higher than both Running Mean ($p < 0.0001$) and Oscillatory Height ($p < 0.0001$)

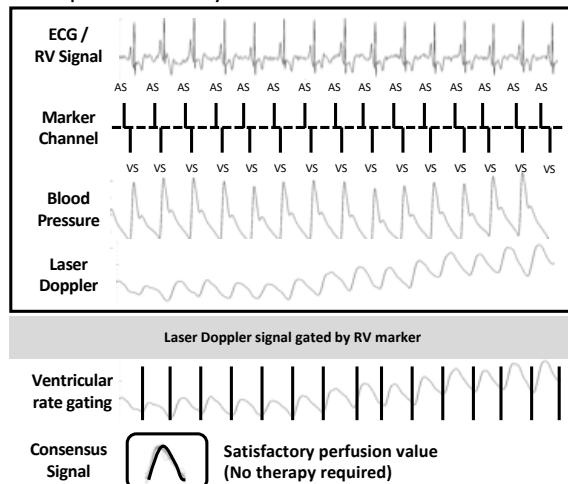
6.5.6 Test 5: Behaviour of algorithms during physical activity

Sometimes, in young fit individuals, sinus tachycardia can reach the rate of the VF zone. Haemodynamic signals can themselves be vulnerable to increased noise during exercise. The ability of the three algorithms to correctly interpret the laser Doppler signals in 12 volunteers exercising to a mean maximum heart rate of 184 bpm (max 201 bpm) was therefore tested.

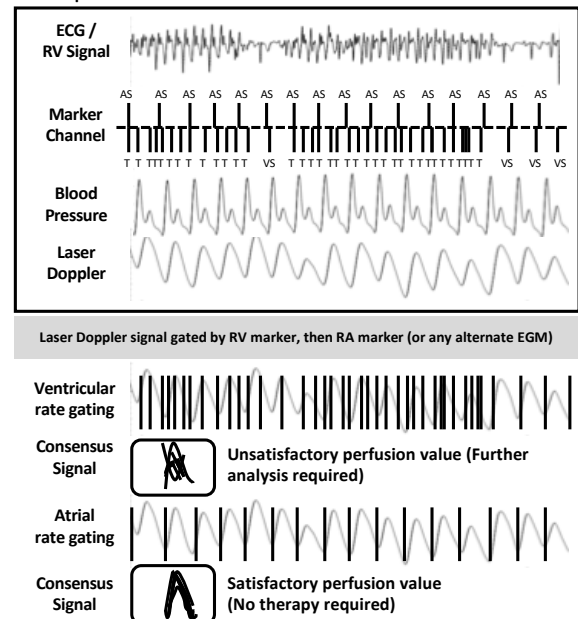
For each individual, six second windows around the peak heart rate were analysed and no electro-mechanical coupling quantification perfusion value was below the cut-off of 2 perfusion units.

Figure 6-18 shows how the Electro-Mechanical algorithm behaves in various situations.

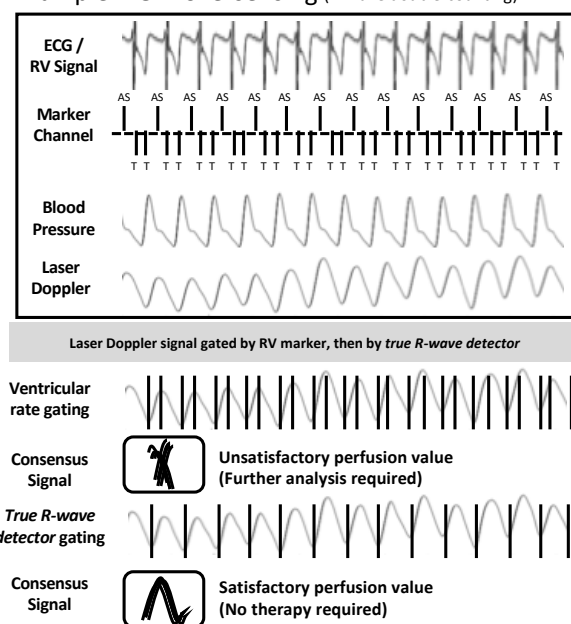
Example: Sinus Rhythm



Example: RV lead fracture



Example: EGM oversensing (T Wave double-counting)



Example: True Ventricular Fibrillation

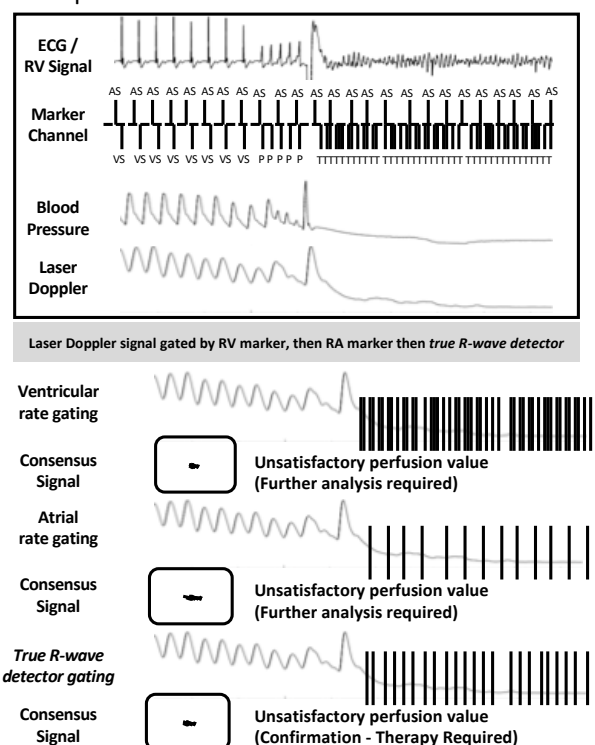


Figure 6-18 The Electro-Mechanical Coupling approach in situations where inappropriate therapies may otherwise result.

Sinus Rhythm: Gating the laser Doppler signal by the R-R interval from RV lead shows a satisfactory consensus perfusion value. A similar situation would occur in other well tolerated rhythm disturbances.

RV lead fracture: Gating the laser Doppler signal by the R-R interval from the fractured RV lead shows an unsatisfactory perfusion value. When gating is performed by an alternate electrical signal (atrial lead in this example) a satisfactory consensus perfusion value is seen.

EGM oversensing: Gating the laser Doppler signal by the R-R interval from the RV lead shows an unsatisfactory perfusion value. Appropriate gating by the algorithm (which simultaneously tests multiple hypotheses as to which are the true R waves) shows a satisfactory consensus perfusion value.

True VF: Gating the laser Doppler signal by R-R intervals detected by the ICD lead, alternate electrical signal and by the multiple hypothesis method each time reveals no satisfactory perfusion.

6.6 Discussion

In this study it was found that laser Doppler perfusion monitoring can reliably distinguish between genuine VF and a variety of situations that can be mistaken by a device for VF. These include ventricular lead fracture, electrogram double-counting and sinus-tachycardia. The key to making the diagnostic separation reliable appears to be the quantification of coupling between electrical and haemodynamic data.

Opportunity and Challenge of haemodynamic monitoring

Although haemodynamic monitoring is potentially an ideal method of augmenting the reliability of electrogram-based event discrimination, the early suggested potential has not yet turned into clinical reality. One possible reason suggested by our data is that small biological fluctuations that continue to occur in the early seconds of VF can be mistaken, in the Running Mean and Oscillatory Height Methods, for meaningful perfusion. (Once VF has persisted for sufficient time, these methods will eventually recognize lack of perfusion, as found by Compton et al.) This study, that incorporates Electro-Mechanical coupling quantification, means a confident automated diagnosis can be reached quickly. Early diagnosis and the avoidance of even modest error rates is valuable for ICD algorithms dealing with VF.

Although laser Doppler is a good marker to measure, the reason for its success in this study was not the choice of marker but the choice of analytical algorithm. Both the Running Mean and the Oscillatory Height methods are attractive in principle but have weaknesses in practice that prevent ICDs relying on them for life or death decisions.

The Running Mean (Compton et al. 2012) method aims to reduce the impact of noise by averaging a number of beats and comparing this to a reference. However, variables such as laser Doppler flow vary enormously between individuals and over time, so there is no global threshold that can be applied uniformly. The only chance for a Running Mean

algorithm with laser Doppler flow would be with continuous monitoring so that dramatic declines can be detected from any baseline level. This study indicates that, even at the power consumption cost of continuous monitoring, and even with the patient kept stationary, there is unfortunately overlap between sinus rhythm and VF.

Oscillatory Height is a more advanced analytical approach which has the advantage of looking for fluctuations which are always present in a pulsatile cardiovascular system. However, many other sources can also produce fluctuations in haemodynamic markers. The influence of some of these sources can be eliminated by filtering, because their frequency is outside the plausible range of heart rate. Unfortunately, many influences lie in the frequency range of plausible heart rates and therefore are a persistent source of misclassification of VF as normal rhythm.

The third approach, quantification of Electro-Mechanical coupling, maximizes the diagnostic information from haemodynamic signals because it automatically focuses on oscillations that are not merely at *a* plausible rate but are at *the* exactly correct rate on a beat-by-beat basis.

Minimization of battery usage

Quantification of electro-mechanical coupling not only provides more reliable separation between sinus rhythm and VF within individual patients (Test 1) but also retains this separation even when all data are pooled across all patients (Test 2). This allows a common threshold to be applied across all these patients without personalisation. This has an important consequence for battery energy usage, namely that the laser Doppler only needs to be switched on from the time that an electrogram is suggestive of VF. This allows the algorithm to have a very low impact on battery longevity.

Potential to reduce inappropriate therapies

With 40% of ICD shocks being inappropriate, better discrimination is clinically very desirable, but only if it can be done safely.

Laser Doppler perfusion monitoring together with quantification of electro-mechanical coupling, allows many false positive EGM based VF detections to be detected which would facilitate shocks to be safely withheld. Sensitivity and specificity were 100% and there was a wide margin of safety, not only within individual patients but also when the data of all patients were merged together i.e. without personalisation. The data in this study is encouraging and provides justification for further prospective testing.

Hemodynamic sensor within an ICD

Laser Doppler sensors have recently been miniaturized to a size that could be incorporated into a future ICD generator design. This study made perfusion measurements from the finger and the chest, on the exterior surface the skin. Previous workers (Compton et al. 2012; Turcott and Pavek 2008; Turcott and Pavek 2010; Nabutovsky et al. 2012) have shown that even after 9 months and with mean capsule thickness of 2.3 ± 1.8 mm (Nabutovsky et al. 2012), high fidelity signals are still acquired. In our laboratory, we have conducted a pilot recording with a laser Doppler sensor placed inside a mature capsule of a patient needing device extraction, and this showed no impairment of signal fidelity. Figure 6-19

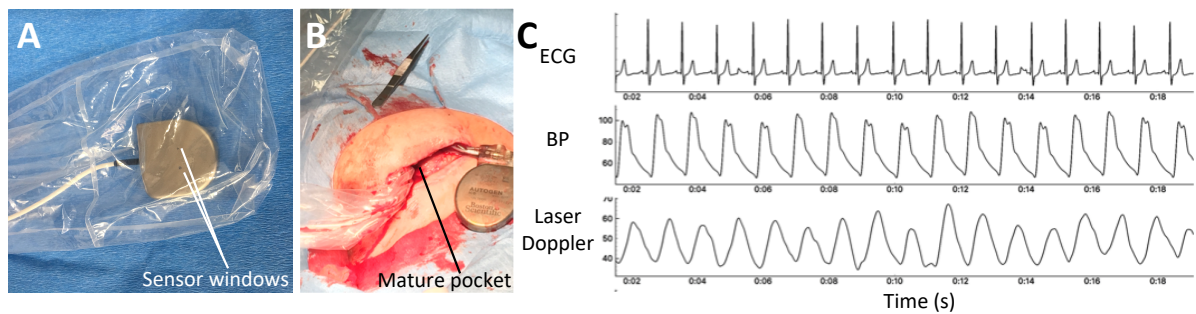


Figure 6-19 Pilot data of signals acquired from mature device pocket.

A: Laser Doppler sensor encased in ICD can with fibre optic cables for data transmission seen extending away from can. Device is placed within sterile sleeve.

B: Laser Doppler device placed within mature pocket.

C: Example data trace showing ECG and BP data (not obtained from can) and simultaneous laser Doppler data occurring in synchronous fashion.

6.6.1 Limitations

This study focused on the VF zone because, if these rates persist, ICDs are generally programmed to deliver a shock. T wave oversensing, lead fracture and electromagnetic interference readily generate rates in the VF zone and thereby cause inappropriate shocks.

This study relied on VF induced under sedation or general anaesthetic rather than spontaneous VF. Patients were lying still, in a controlled environment, and not in the community where most VF and shock events occur. We do not know whether the reliability of the electro-mechanical coupling approach would still be high outside our controlled research environment. However, a higher performance than traditional algorithms was seen, and with a considerable margin of safety. In the present study Laser Doppler recordings were made non-invasively, the Running Mean and Oscillatory Height methods could suffer from artefacts that might be inherent in this approach. Further studies using invasive recordings are now required to confirm whether the promising results for the electromechanical coupling method also apply to invasive perfusion recordings.

A previous study (Compton et al. 2012) using the Running Mean method and near infrared spectroscopy found that with longer detection windows (15 seconds), sensitivity for VF detection was improved. In my study we used only standard-duration clinical ICD VF detection windows. If VF is allowed to continue for sufficient time, eventually almost any method of processing will diagnose it. However, in clinical practice promptness of diagnosis of VF is considered desirable.

In some patients it was not possible to extract and utilise EGM and marker channel data and for them surface ECG data was used instead. Reassuringly, despite this, the performance of the electro-mechanical coupling algorithm remained good.

This study addressed VF and its imitators because there is a binary gold standard: it is always appropriate to shock VF and inappropriate to shock its imitators. It is therefore possible to determine indisputably whether an algorithm is performing correctly in each case. Our laboratory has now embarked on a study of VT and SVT, which are different because it can be less obvious whether device intervention is necessary even if the electrical rhythm is correctly diagnosed. From my pilot data it is apparent that rate alone which is often the gatekeeper in conventional ICD treatment algorithms may not be sufficient to determine whether a therapy is needed and haemodynamic data may be significantly additive. Examples demonstrating this are shown in Figure 6-20.

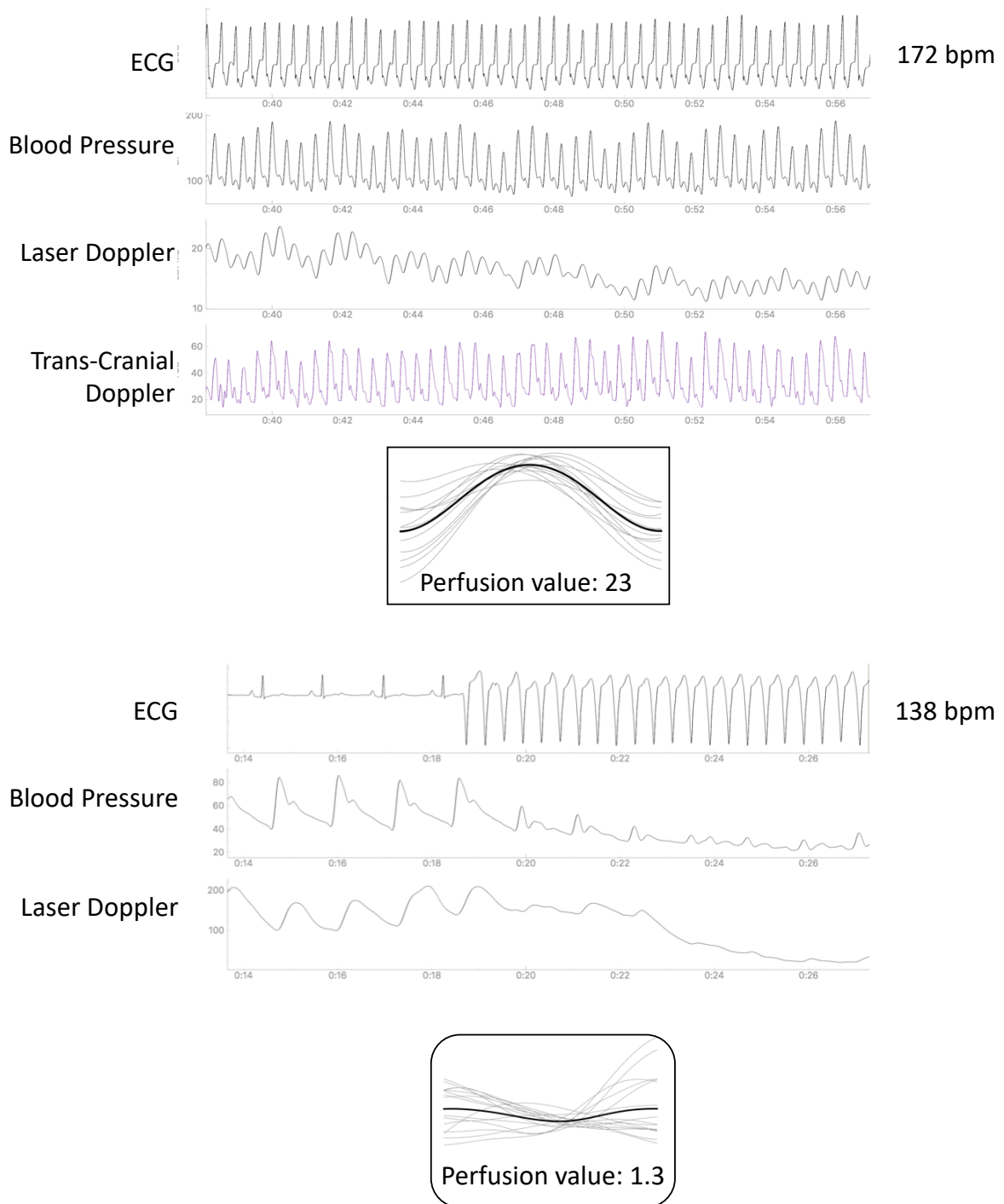


Figure 6-20 Heart Rate alone is not an adequate discriminator for haemodynamic harm

The upper trace is from a patient implanted with a secondary prevention device having had prior VT at 180 bpm. ICD therapies had been disabled in this patient because of recent unnecessary shocks. From the traces it is apparent he tolerates the

present VT well as evidenced by satisfactory BP, satisfactory blood flow to his brain (trans-cranial Doppler) and an Electro-Mechanical coupling perfusion value which is more than satisfactory.

In contrast, the patient in the lower trace has a slower VT but it is associated with poor haemodynamics and a poor Electro-Mechanical coupling perfusion value. This second patient did not receive automatic therapy from the ICD because the rate was below the detection threshold. Using haemodynamics to guide therapy in this situation may allow therapies to be appropriately delivered that are needed to treat this infrequent but potentially fatal scenario of slow VT causing significant haemodynamic compromise.

6.7 Conclusions

Strong electro-mechanical coupling is a reliable discriminator between VF and situations that mimic VF, achieving an AUC of ROC curve of 1.00 (100% sensitivity and 100% specificity).

Because there is such a large margin of safety between the electro-mechanical coupling scores of VF and situations that mimic VF, the discrimination is successful even with no personalisation to the individual patient. This means that a haemodynamic sensor would only need to be switched on during suspected VF. With electro-mechanical coupling quantification, the haemodynamic guidance seems to be reliable enough to be used by an ICD to withhold inappropriate shocks for common VF mimics. Incorporating such methods into future ICDs may permit reductions of inappropriate shocks whilst preserving safety.

7 Synthesis

In this thesis I began by discussing limitations of current cardiac rhythm management device technology and their therapies. I then explored two new strategies for improving these devices.

Firstly, I investigated providing patients with physiological ventricular activation through the means of His bundle pacing.

His bundle pacing has the potential to fundamentally change the way pacing for bradycardia, atrio-ventricular resynchronisation and biventricular resynchronisation can be delivered. Furthermore, I investigated a new role for His bundle pacing in the stabilisation of ventricular arrhythmias. I was intrigued to discover that it has potential to terminate these arrhythmias.

Secondly, I investigated how we can improve ICD therapy algorithms through the use of small implantable haemodynamic sensors. I specifically investigated how, when appropriately interpreted, they can contribute to VF discrimination.

In Chapter 3, I determined the safety and feasibility of His bundle pacing through the development of a 529 patient international, multicentre, retrospective registry. This is the largest registry of His bundle pacing to date. I demonstrated that procedural success is acceptable and feasible and comparable with LV lead placement. Furthermore, I showed that the learning curve (fall in fluoroscopy time and lead capture thresholds) seems to plateau at between 30 to 50 cases.

In Chapter 4, my experiments found that His bundle pacing to correct a prolonged PR interval in those patients with an intermittent pacing indication improves acute haemodynamic function over both pacing avoidance algorithms or traditional dual

chamber right ventricular pacing. Traditionally, patients with a prolonged AV delay but with narrow QRS complex are trapped. With dual chamber RV pacing (or biventricular pacing) although the PR prolongation can be corrected, this is at the cost of creating ventricular dyssynchrony. My data suggests that His bundle pacing provides the optimal solution, allowing the AV delay to be shortened without inducing ventricular dyssynchrony.

This concept of AV delay optimisation but without inducing ventricular dyssynchrony is further being explored in the HOPE-HF randomised controlled trial for which I am a principle investigator. This study, whose rationale is described in the Appendix, is testing the benefit of isolated AV delay optimisation (His bundle pacing) in patients with heart failure and prolonged AV delay but no other indication for pacing.

In Chapter 5, I considered the role of His bundle pacing as a therapy for Ventricular Tachycardia, a condition where ventricular dyssynchrony is a key factor in the haemodynamic consequences. It became apparent that on a mechanistic level ventricular dyssynchrony was important to haemodynamic harm during VT. Furthermore, restoring ventricular synchrony with His pacing improved haemodynamics during VT. Even more excitingly, I appear to have documented the first 6 cases of termination of VT by His bundle pacing. This might be developed into a safer and more efficient approach than conventional ATP.

About 40% of ICD discharges are inappropriate and a further unknown proportion may be unnecessary. One contributor to this sub-optimal situation is that current ICDs cannot assess a patient's haemodynamic state. This ability would be of value to determine

whether therapies are needed during presumed ventricular arrhythmias, or whether therapies can be safely deferred, or whether therapies such as the ones described in Chapter 5 have been successful. I investigate the possibility of this in Chapter 6 using sensors that can be miniaturised and integrated into a device. In this Chapter I derived and patented an automated electro-mechanical coupling algorithm to aid assessment of haemodynamics during ventricular arrhythmias using laser Doppler signals. I tested that it can reliably act as a discriminator between VF and its imitators. In future, devices incorporating such an approach may permit reduction of inappropriate shocks whilst preserving safety.

7.1.1 Future work

His bundle pacing, and the availability of implantable sensors may lead to fundamental changes in our approach to cardiac rhythm management.

7.1.1.1 His bundle pacing for bradycardia and heart failure

Like previously established clinical tools such as biventricular pacing, His bundle pacing would need adequately powered randomised control trials in each of the domains it will be used to validate its utilisation. In the novel domain of providing AV resynchronisation in patients with left ventricular impairment I am part of the study team that has designed, set-up sites, proctored new implanters across the country and followed patients through the HOPE-HF trial. We have now completed recruitment and are awaiting the reported outcomes in approximately one year. Larger trials will be needed for the other domains, such as in the bradycardia treatment domain and cardiac ventricular resynchronisation domain. I am collaborating to secure funding for such trials.

7.1.1.2 His bundle pacing for haemodynamically stabilising and terminating ventricular arrhythmias

I have developed a new strategy for haemodynamically stabilising VT using His bundle pacing. In a small cohort of patients in clinical VT I have demonstrated its potential benefit. Larger studies are needed to further refine the technique and to demonstrate that it does not have undue harms.

Tantalisingly, I believe I have discovered that His bundle pacing can terminate ventricular tachycardias. It has theoretical benefits over traditional ATP methods which through acceleration of the rhythm may worsen haemodynamics and which may also trigger VF. Studies in a larger number of patients are required to fully understand its applicability and limitations.

7.1.1.3 The use of haemodynamic sensors by cardiac rhythm management devices

Cardiac rhythm management devices would greatly benefit from being able to assess the haemodynamic status of a patient. It would allow an additional and unique source for ICD based discriminator algorithms thus reducing the risk of inappropriate shocks. It may also lead to therapies being deferred to allow spontaneous termination if the patient is suitably able to tolerate the arrhythmia. Furthermore, it would also allow dynamic feedback for potential stabilisation therapies. In this thesis I have only tackled the first of these. Future work is required to assess 1) its chronic utility to confirm it is resistant to the effects of capsule formation and 2) to determine whether it can determine the difference between haemodynamically unstable and haemodynamically stable VTs. This is the subject of a current proposed project grant.

8 Published manuscripts from the research period

His bundle pacing, learning curve, procedure characteristics, safety, and feasibility: Insights from a large international observational study.

Keene D, Arnold AD, Jastrzębski M, Burri H, Zweibel S, Crespo E, Chandrasekaran B, Bassi S, Joghetaei N, Swift M, Moskal P, Francis DP, Foley P, Shun-Shin MJ, Whinnett ZI.
J Cardiovasc Electrophysiol. 2019 Oct;30(10):1984-1993.

Quantification of Electromechanical Coupling to Prevent Inappropriate Implantable Cardioverter-Defibrillator Shocks.

Keene D, Shun-Shin MJ, Arnold AD, Howard JP, Lefroy D, Davies DW, Lim PB, Ng FS, Koa-Wing M, Qureshi NA, Linton NWF, Shah JS, Peters NS, Kanagaratnam P, Francis DP, Whinnett ZI.
JACC Clin Electrophysiol. 2019 Jun;5(6):705-715.

Cardiac Rhythm Device Identification Using Neural Networks.

Howard JP, Fisher L, Shun-Shin MJ, Keene D, Arnold AD, Ahmad Y, Cook CM, Moon JC, Manisty CH, Whinnett ZI, Cole GD, Rueckert D, Francis DP.
JACC Clin Electrophysiol. 2019 May;5(5):576-586

How to deliver personalized cardiac resynchronization therapy through the precise measurement of the acute hemodynamic response: Insights from the iSpot trial.

Shun-Shin MJ, Miyazawa AA, Keene D, Sterliński M, Sokal A, Van Heuverswyn F, Rinaldi CA, Cornelussen R, Stegemann B, Francis DP, Whinnett Z.
J Cardiovasc Electrophysiol. 2019 Sep;30(9):1610-1619

His Bundle Pacing: A New Strategy for Physiological Ventricular Activation

Lewis AJM, Foley P, Whinnett Z, Keene D, Chandrasekaran B.
J Am Heart Assoc. 2019 Mar 19;8(6):e010972

Device Programming for His Bundle Pacing.

Burri H, Keene D, Whinnett Z, Zanon F, Vijayaraman P.
Circ Arrhythm Electrophysiol. 2019 Feb;12(2):e006816

Right ventricular pacing for hypertrophic obstructive cardiomyopathy: meta-analysis and meta-regression of clinical trials.

Arnold AD, Howard JP, Chiew K, Kerrigan WJ, de Vere F, Johns HT, Churlilov L, Ahmad Y, Keene D, Shun-Shin MJ, Cole GD, Kanagaratnam P, Sohaib SMA, Varnava A, Francis DP, Whinnett ZI.
Eur Heart J Qual Care Clin Outcomes. 2019 Oct 1;5(4):321-333

His Resynchronization Versus Biventricular Pacing in Patients With Heart Failure and Left Bundle Branch Block.

Arnold AD, Shun-Shin MJ, Keene D, Howard JP, Sohaib SMA, Wright IJ, Cole GD, Qureshi NA, Lefroy DC, Koa-Wing M, Linton NWF, Lim PB, Peters NS, Davies DW, Muthumala A, Tanner M, Ellenbogen KA, Kanagaratnam P, Francis DP, Whinnett ZI.
J Am Coll Cardiol. 2018 Dec 18;72(24):3112-3122

Rationale and design of the randomized multicentre His Optimized Pacing Evaluated for Heart Failure (HOPE-HF) trial.

Keene D, Arnold A, Shun-Shin MJ, Howard JP, Sohaib SA, Moore P, Tanner M, Quereshi N, Muthumala A, Chandresekeran B, Foley P, Leyva F, Adhya S, Falaschetti E, Tsang H, Vijayaraman P, Cleland JGF, Stegemann B, Francis DP, Whinnett ZI.
ESC Heart Fail. 2018 Oct;5(5):965-976

His Bundle Pacing: UK experience and HOPE for the future.

Keene D, Shun-Shin M, Arnold A, Whinnett Z.
Br J Cardiol.. Sept 2018

His Bundle Pacing: A new frontier in the treatment of heart failure.

Ali N, Keene D, Shun-Shin M, Arnold A, Sohaib SM, Whinnett Z.
Arrhythmia and Electrophysiology Review. June 2018

9 Appendix:

Design of a multicentre RCT to test the role of AV optimised His bundle pacing for cardiac resynchronization for heart failure patients with long AV delays and narrow complex QRS

9.1 Abstract

9.1.1 Introduction

In this thesis the problems associated with prolonged PR interval have already been highlighted, this problem is likely to have the greatest clinical impact in those with heart failure. In this chapter I outline the rationale and methods for a randomised trial that is now on-going to test the hypothesis that AV delay optimised His pacing can improve exercise capacity in patients with heart failure with long PR interval but without broad LBBB.

In these patients left ventricular (LV) filling can be improved by shortening atrioventricular delay using His-bundle pacing. His-bundle pacing delivers physiological ventricular activation and has been shown to improve acute haemodynamic function in this group of patients. In the HOPE-HF (His Optimized Pacing Evaluated for Heart Failure) trial, we are investigating whether these acute haemodynamic improvements translate into improvements in exercise capacity and heart failure symptoms.

9.1.2 Methods

This is a multicentre, double-blind, randomized, crossover study aiming to randomize 160 patients with PR prolongation (≥ 200 ms), LV impairment ($EF \leq 40\%$), and either narrow QRS (≤ 140 ms) or right bundle branch block.

All patients receive a cardiac device with leads positioned in the right atrium and the His bundle. Eligible patients also receive a defibrillator lead. Those not eligible for implantable cardioverter defibrillator have a backup pacing lead positioned in an LV branch of the coronary sinus. Patients are allocated in random order to 6 months of (i) haemodynamically optimized dual chamber His-bundle pacing and (ii) backup pacing only, using the non-His ventricular lead. The primary endpoint is change in exercise capacity assessed by peak oxygen uptake. Secondary endpoints include change in

ejection fraction, quality of life scores, B-type natriuretic peptide, daily patient activity levels, and safety and feasibility assessments of His-bundle pacing.

9.1.3 Conclusions

In the Hope-HF study I together with my supervisor aim to determine whether correcting PR prolongation in patients with heart failure and narrow QRS or right bundle branch block using haemodynamically optimized dual chamber His-bundle pacing improves exercise capacity and symptoms. Recruitment was completed at the beginning of 2019 and the study will report in 2020.

9.2 Introduction

In patients with heart failure and a reduced ejection fraction, a prolonged atrioventricular (AV) delay is associated with increased mortality (Stockburger et al. 2016; Kutiyifa et al. 2014; Salden et al. 2017). Pacing is able to reduce a prolonged AV delay, however in patients with a narrow QRS both right ventricular (RV) and biventricular (BiV) pacing can induce additional ventricular dyssynchrony (Ploux et al. 2015). His bundle pacing however avoids this as it activates the ventricles using the intrinsic conduction system.

9.2.1 Prolonged AV delay is pathological in heart failure

Observational studies have found an association between a prolonged PR interval and worse outcomes (Nikolaidou et al. 2017). In ischaemic heart disease, patients with a long PR interval were found to have a 58% higher mortality (Crisel et al. 2011; Nikolaidou et al. 2017). In patients with heart failure, PR prolongation also has an important prognostic impact. For example, in the control arm of MADIT-CRT those patients with a prolonged PR interval had a threefold higher risk of death or heart failure than those whose AV delay was within normal limits (Stockburger et al. 2016).

9.3 Prolonged AV delay can be a target

The concept of providing atrio-ventricular resynchronisation as a therapeutic target in heart failure predates that of ventricular resynchronisation (Breckner et al. 1992; Gibson et al. 1971). Suggestions that a prolonged AV delay in heart failure is not only a prognostic marker but also a therapeutic target, comes from both acute haemodynamic studies and association with benefit found within randomised trials.

Shortening pathologically prolonged PR intervals has the potential to improve cardiac function. PR prolongation impairs LV filling (Nishimura et al. 1995) whilst reducing prolonged PR intervals improves LV filling (Jones et al. 2017). In patients with left bundle branch block optimizing left ventricular filling by shortening AV delay using biventricular pacing acutely improves acute cardiac function, as reflected by changes in LV dp/dt_{max} , stroke volume, coronary artery flow and systolic blood pressure (Kyriacou et al. 2012; Whinnett et al. 2013; Auricchio et al. 1999).

Furthermore, data from large randomised trials of biventricular pacing in patients with left bundle branch block (LBBB), have found that patients with prolonged native PR intervals appear to gain greater benefit from biventricular pacing. (Gervais et al. 2009) In COMPANION, patients with a long PR interval had a 17% greater relative risk reduction in heart failure admissions and death compared with those with a normal PR interval. Similarly, in the MADIT-CRT trial, the prognostic benefits of biventricular pacing appeared somewhat greater for participants with a wide QRS of non-LBBB morphology when the PR interval was prolonged (Kutyifa et al. 2014).

9.3.1 Right Ventricular and Biventricular pacing cause ventricular dyssynchrony in patients with Narrow QRS

Both right ventricular pacing and biventricular pacing can be used to treat a prolonged PR interval. However, both have potential disadvantages.

9.3.1.1 *Right ventricular pacing*

Conventional right ventricular pacing had been used to shorten prolonged PR intervals in small studies with mixed results (Gold et al. 1995; Brecker et al. 1992). However conventional right ventricular pacing prolongs left ventricular activation and therefore causes dyssynchronous ventricular activation which might offset the beneficial effects of

shortening PR interval. It therefore unlikely to be the most efficient method for delivering AV delay optimisation in patients with heart failure.

9.3.1.2 Biventricular pacing

Biventricular pacing might be a better option (Curtis et al. 2013) for delivering AV delay optimisation. Biventricular pacing has transformed the care of patients with reduced left ventricular ejection fraction heart failure, and a prolonged QRS duration (Cleland et al. 2013; Zareba et al. 2011).

The effects of biventricular pacing in patients without QRS prolongation have also been explored (Foley et al. 2011; Ruschitzka et al. 2013), particularly focusing on those with echocardiographic mechanical dyssynchrony, because of the belief that biventricular pacing delivers its benefit mainly through resynchronization of ventricular wall contraction. However, when tested in a bias-resistant manner, the results have not been favourable. Biventricular Pacing has been found to be harmful (the most prominent trial showing an 81% increase in mortality) when applied to this group of patients. (Ruschitzka et al. 2013)

One potential mechanism for harm is that when the native QRS is narrow, biventricular pacing prolongs ventricular activation time and therefore increases ventricular dyssynchrony. (Ploux et al. 2015)

Therefore, even biventricular pacing is an imperfect way to deliver AV delay shortening, since some of the beneficial effects may be offset by the non-physiological ventricular activation.

9.3.1.3 His bundle pacing

His bundle pacing may be a better way to deliver AV delay optimisation in this group of patients. Permanent His bundle pacing allows the ventricles to be activated via the His-Purkinje system. As a result, normal physiological cardiac activation is maintained when

His bundle pacing is applied to people with a narrow QRS duration (Catanzariti et al. 2006). It may even restore normal physiological activation in patients with RBBB or LBBB. (Sharma et al. 2017) Chronic His bundle pacing has been shown to be feasible and safe when used for bradycardia pacing.(Sharma et al. 2015) Figure 9-1

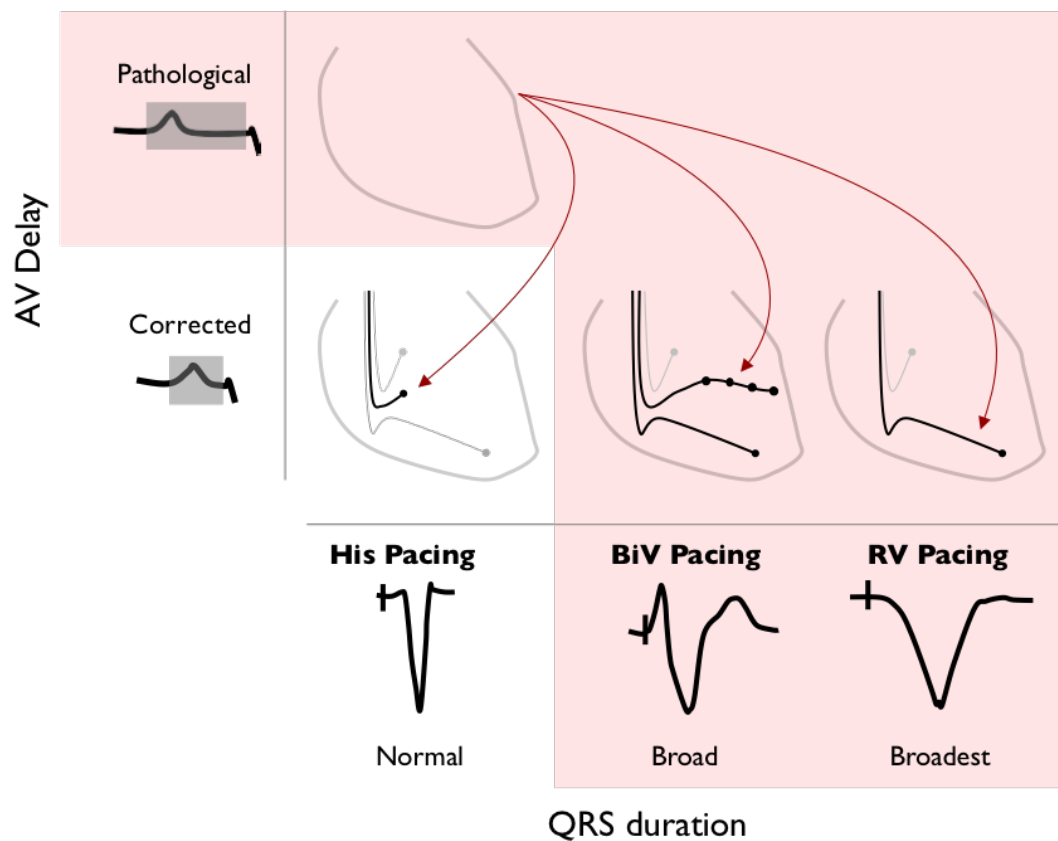


Figure 9-1 Potential pacing methods for Atrioventricular (AV) delay optimisation

His bundle pacing, Biventricular (BiV) pacing and Right Ventricular (RV) pacing are all potential methods for shortening a pathologically long AV delay. His bundle pacing, does not prolong left ventricular activation time, when applied to patients with a narrow QRS duration whereas biventricular pacing and right ventricular pacing do prolong left ventricular activation time.

9.3.2 Evidence that His bundle pacing may be beneficial in heart failure with prolonged AV delay and narrow QRS

In patients with heart failure, a prolonged PR interval and either a narrow QRS or right bundle branch block, AV delay optimisation delivered using His bundle pacing has been shown by our research group previously to improve acute haemodynamic function. (Sohaib et al. 2015) While this is encouraging, longer term outcome data is required before His pacing can be routinely recommended as a method for pacing therapy for heart failure in a group of patients who are not currently targeted for treatment with biventricular pacing.

There is a precedent that haemodynamic changes translate into better patient outcomes. The earliest evidence for benefit from biventricular pacing in patients with heart failure with left bundle branch block was the clear and immediate improvement in haemodynamics seen when pacing was initiated. (Gibson et al. 1971; Cazeau et al. 1996) Medium term physiological studies subsequently, demonstrated a sustained effect with improved exercise capacity compared to controls at up to one year. (Linde et al. 2002) In turn, longer term trials showed reduction in morbidity and mortality. (Cleland et al. 2013)

9.3.3 Aim

The aim of HOPE-HF trial is to test whether the acute haemodynamic effects observed with AV optimised His bundle pacing in patients with heart failure, a long intrinsic PR interval and narrow QRS or right bundle branch block, translate into an improvement in exercise capacity, symptoms and cardiac function.

9.4 Methods

9.4.1 Trial Purpose

The HOPE-HF trial is designed to evaluate the effects of atrio-ventricular optimized His bundle pacing for patients with left ventricular systolic dysfunction and PR prolongation but without left bundle branch block. The primary endpoint is the within-patient difference in exercise capacity with His optimized pacing compared to no pacing in a cross-over trial with 6-month treatment periods. Secondary endpoints are quality of life, echocardiographic measurements, B-type natriuretic protein (BNP) measurements and daily patient activity levels.

9.4.2 Trial Design

HOPE-HF is an investigator-initiated, UK based, multi-centre, blinded, randomised, cross-over trial of permanent AV optimized His-bundle pacing. The planned recruitment is for 160 randomised patients across approximately 20 sites in the UK.

The initial idea for the trial was my supervisors. I was involved in the grant writing process. Furthermore, I completed the ethical application for the study and am a PI for as well as a member of 1) the Trial Management Group, 2) the Trial Steering Committee and 3) the Data Safety Monitoring Board. I have initiated each site involved within the study and have been responsible for the day-to-day running of the trial. This has included patient recruitment, patient device implantation, coordination and conduction of patient follow up visits and management of all serious adverse events.

9.4.2.1 Inclusion and exclusion criteria

Study inclusion and exclusion criteria are shown in Table 9-1.

Table 9-1 HOPE HF Inclusion and Exclusion Criteria

INCLUSION CRITERIA
Age over 18 years
EF $\leq$ 35% or EF 36-40% with BNP $>250\text{pg/ml}$
New York Heart Association (NYHA) class II - IV
Sinus rhythm
PR interval $\geq 200\text{ms}$
QRS duration $\leq 140\text{ms}$ <u>or</u> prolonged QRS duration with typical RBBB morphology
EXCLUSION CRITERIA
Permanent or persistent Atrial Fibrillation (AF)
Paroxysmal AF with history of sustained AF (≥ 24 hours) in the 6 months prior to screening
Patients who are unable to perform cardiopulmonary exercise testing
Lack of capacity to consent
Other serious medical condition with life expectancy of less than 1 year
Pregnancy

In brief, patients with symptomatic systolic heart-failure with an ejection fraction $\leq 40\%$, a PR interval $\geq 200\text{ms}$, and either narrow QRS ($\leq 140\text{ms}$) or right bundle branch block of any duration are eligible. The 140ms QRS threshold arises from a meta-regression of individual patient data from 3782 patients in five trials (Cleland et al. 2013). The evidence for biventricular pacing in patients with a QRS duration less than 140ms is less consistent (Cleland et al. 2013).

An additional requirement for patients with a left ventricular ejection fraction between 36 and 40% is that they must have a documented plasma BNP of $>250\text{pg/mL}$ within the preceding 1 year.

Patients with permanent or persistent atrial fibrillation (AF) are excluded because there is no opportunity for AV delay optimisation. Those with paroxysmal AF (with sustained episodes lasting $>24\text{hours}$) are only eligible once treatment to maintain sinus rhythm has been initiated and they have remained in sinus rhythm for six months.

9.4.3 Intervention

9.4.3.1 *Device implantation procedure*

Permanent His bundle pacing is attempted in all patients.

The trial is a multicentre study with device implantations occurring at a number of different hospitals within the United Kingdom. Implantation procedures are carried out by experienced device implanters who as part of the trial were offered training in His-bundle pacing much of which I personally delivered. The implantation approach has been extensively described in the Methods section of this thesis and the same approach has been advocated for use in this RCT.

If His bundle pacing is unsuccessful then a left ventricular lead is implanted.

The third lead is either a right ventricular defibrillator lead, for patients with an implantable cardioverter defibrillator (ICD) indication, or a left ventricular coronary

sinus lead, for those without an ICD indication. The left ventricular lead was suggested by the funding review committee so that a backup pacing lead is available should it become clinically required and the His pacing lead becomes non-functional or to provide backup pacing when the His lead is programmed off (when in the non-treatment arm). All patients receive a right atrial lead

9.4.3.2 Ventricular activation with His bundle pacing

During His pacing, the theoretical physiological ideal is selective capture of the His-Purkinje system, so that ventricular activation occurs purely via the native conduction system and the resulting QRS is no wider than the native QRS with identical morphology. In patients with RBBB, His pacing may shorten QRS duration due to recruitment of the right bundle branch fascicles.

Non-selective His bundle capture occurs when there is capture of both the His bundle and the surrounding local right ventricular myocardium close to the lead tip. Local ventricular activation occurs while the His wave front is travelling through the His-Purkinje system (prior to myocardial breakout). This results in a pseudo-delta wave on the surface ECG. The majority of ventricular activation occurs rapidly via the His-Purkinje system. Overall QRS duration is prolonged slightly during non-selective capture, as a result of the early local myocardial activation, however, the stimulation to end QRS time is not prolonged compared to the His to end of QRS time and reassuringly left ventricular activation time and pattern are not prolonged with non-selective His capture (Arnold et al. 2016). In the HOPE HF trial, the aim is to achieve His bundle capture without prolongation of left ventricular activation time. Therefore, we accept either selective or non-selective capture. His capture is confirmed using previously documented criteria (Vijayaraman, Dandamudi, Zanon, et al. 2017) and summarized in Table 9-2 and illustrated in Figure 9-2.

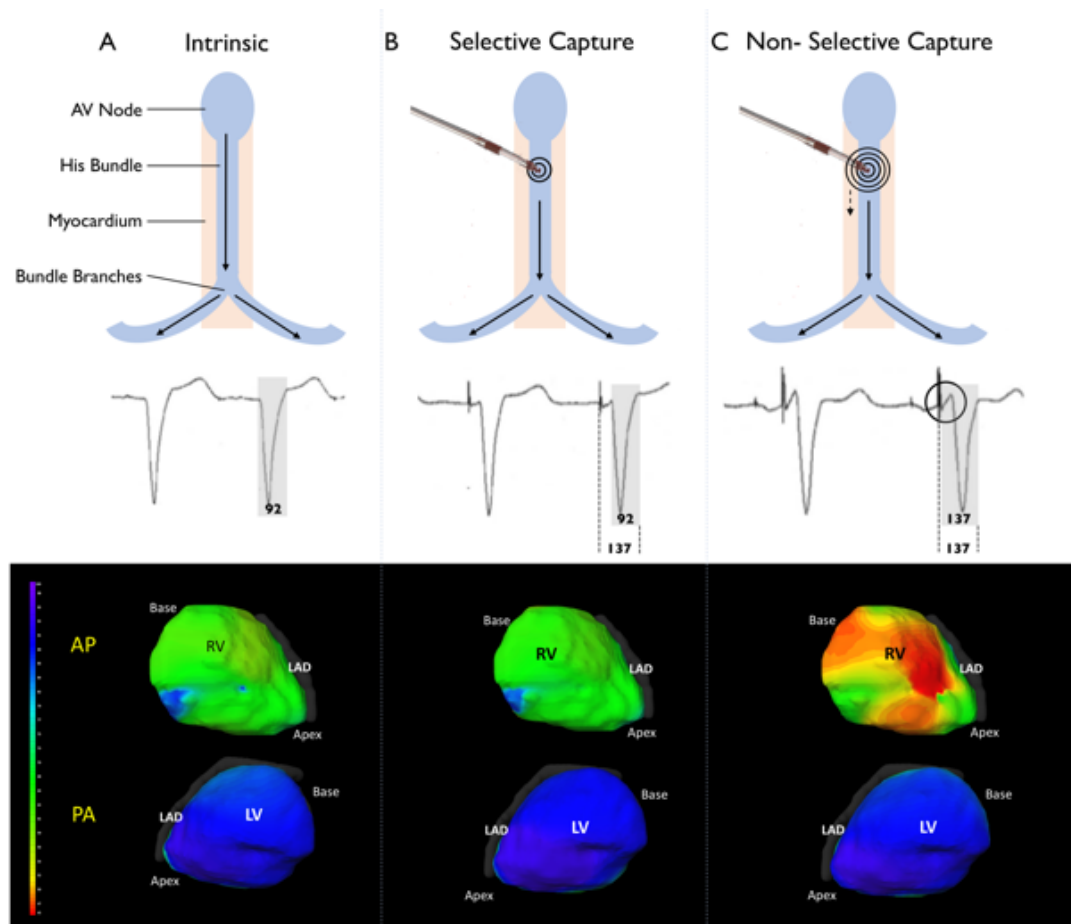


Figure 9-2 Differences between Selective and Non-Selective His bundle pacing.

A: Normal intrinsic conduction. The ECGi (Medtronic inc., Minneapolis, MN, USA) activation map shows rapid activation (each ventricle has homogenous colouring).

B: Selective His bundle pacing. Ventricular activation occurs solely via the His-Purkinje system, giving a normal QRS and normal activation map. The middle panel shows the short delay between the pacing spike and the onset of ventricular activation.

C: Non-Selective His bundle pacing, during which ventricular activation occurs via both local myocardial capture (seen as early activation in right ventricle (RV)[red colour]) and activation via the His Purkinje system. Left ventricular (LV)

activation time and pattern is the same as during intrinsic activation and with selective His pacing because activation of the left ventricle occurs via the His Purkinje system.

Table 9-2 Differences between Selective and Non-Selective His bundle pacing

Evidence for Selective His Bundle capture only (without localized RV capture)
The pacing stimulus is followed by an isoelectric interval before the onset of the QRS The isoelectric interval from pacing stimulus to QRS onset is equal to the interval from the native His electrogram to QRS onset (HV interval). [If the H-V interval is prolonged there may be shortening of the Stim-QRS interval but will still be greater than 30ms.] The stim to end QRS interval is equal to or shorter than the native His electrogram to end of QRS interval. [Shortening may occur due to resolution of bundle branch block or shortening of a prolonged HV interval.] The paced QRS morphology is identical or virtually identical to the native QRS morphology A discrete local ventriculogram is present on the pacing lead separate to the pacing stimulus
Evidence for Non-Selective His Bundle capture (local RV capture in addition to His Bundle capture)
The interval from pacing stimulus to QRS onset is very short and maybe zero as there is no isoelectric interval between the stimulus and the QRS The paced QRS duration will usually be longer than the native QRS duration (due to the presence of the pseudo-delta wave representing antero-septal RV myocardial capture occurring prior to His-Purkinje mediated ventricular activation) however the duration from native His electrogram to the end of the QRS is equal to the duration from pacing stimulus to the end of the QRS. [Shortening may occur due to resolution of bundle branch block or shortening of a prolonged HV time] The overall electrical axis of the paced QRS will be concordant with the electrical axis of the intrinsic QRS The local discrete ventriculogram on the His pacing lead will be largely absent due to instantaneous ventricular capture

9.4.4 Study Endpoints

9.4.4.1 Primary End-Point

The primary endpoint of the trial is peak oxygen uptake measured during cardiopulmonary exercise testing. This endpoint was selected because it is reproducible (Scott et al. 2001), a well-recognized measure of cardiac function reserve and a strong predictor of mortality in heart-failure (Cahalin et al. 2013). It has been used in many previous trials of heart-failure.

9.4.4.2 Secondary Endpoints

Secondary endpoints include echo measurements of LV volume, plasma concentration of BNP, quality of life scores, daily patient activity levels and hospitalization episodes.

9.4.5 Endpoint measurements

9.4.5.1 Cardiopulmonary exercise testing

Patients exercise on a treadmill using a smoothed modified Bruce protocol (Scott et al. 2001). Spirometry and gas exchange are monitored using the COSMED Quark CPX System (Cosmed, Italy). Exercise capacity is measured as peak oxygen consumption (peak VO₂) in ml/kg/min. Exercise time, VE/VCO₂ slope and oxygen uptake efficiency slope are also measured.

9.4.5.2 Echocardiogram

Echocardiographic measurements are made using a Phillips iE33 (Phillips, Netherlands). The following variables are measured: left ventricular dimensions, volumes and ejection fraction, Tissue-Doppler imaging, quantification of mitral regurgitation and maximum velocity through the aortic valve. Pulse wave Doppler through the mitral valve is also recorded for off-line analysis of E-A waves for assessment of AV filling patterns.

9.4.5.3 Quality of life

Quality of life (QOL) is scored using both the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the EQ-5D. The MLHFQ is a validated condition-specific measure with good sensitivity and discrimination. It is complemented by the EQ-5D which is a validated generic measure of QOL which enables comparison of findings with other outcome studies. These are completed by the patient. NYHA assessment is made by trial physicians.

9.4.5.4 Blood samples

Blood samples are taken for analysis of plasma B-type natriuretic protein (Abbott ARCHITECT immunoassay BNP).

9.4.5.5 Daily Patient Activity Levels

Daily patient activity levels are automatically recorded by the CRT device using an accelerometer. This gives a continuous assessment of daily activity levels for the entire duration of the study and has been shown to predict adverse cardiovascular events (Conraads et al. 2014).

9.4.5.6 Implant Data

Skin-to-skin time for device implantation is being recorded as is total fluoroscopy duration. The delivery sheath utilized to position the His lead is being noted and lead measurements including thresholds and sensing data for all leads are recorded.

9.4.6 Follow up location

All end-point assessments and hemodynamic optimizations (to determine the patient's optimal paced and sensed AV delays) are performed at the core centre (Imperial College London). This is to ensure that investigations are carried out within the required time frame of the study, measurement variability is minimized by using the same equipment and staff, and set-up and training costs are minimized.

9.4.7 Follow up duration

The study endpoint measurements are conducted at three set time points. Baseline measures are taken two months after the device has been implanted (during which time no His pacing is performed). The duration of each treatment arm is 6 months, to allow time for cardiac remodelling and to minimize any carryover effect. Further endpoint assessments take place six months after the baseline visit whilst patients have had either His pacing programmed on or off and then after a final six-month interval following cross-over to the alternate arm. Assessment of adverse events is continuous throughout the trial

9.4.8 Patient flow

A flow chart outlining the study design is provided in Figure 9-3.

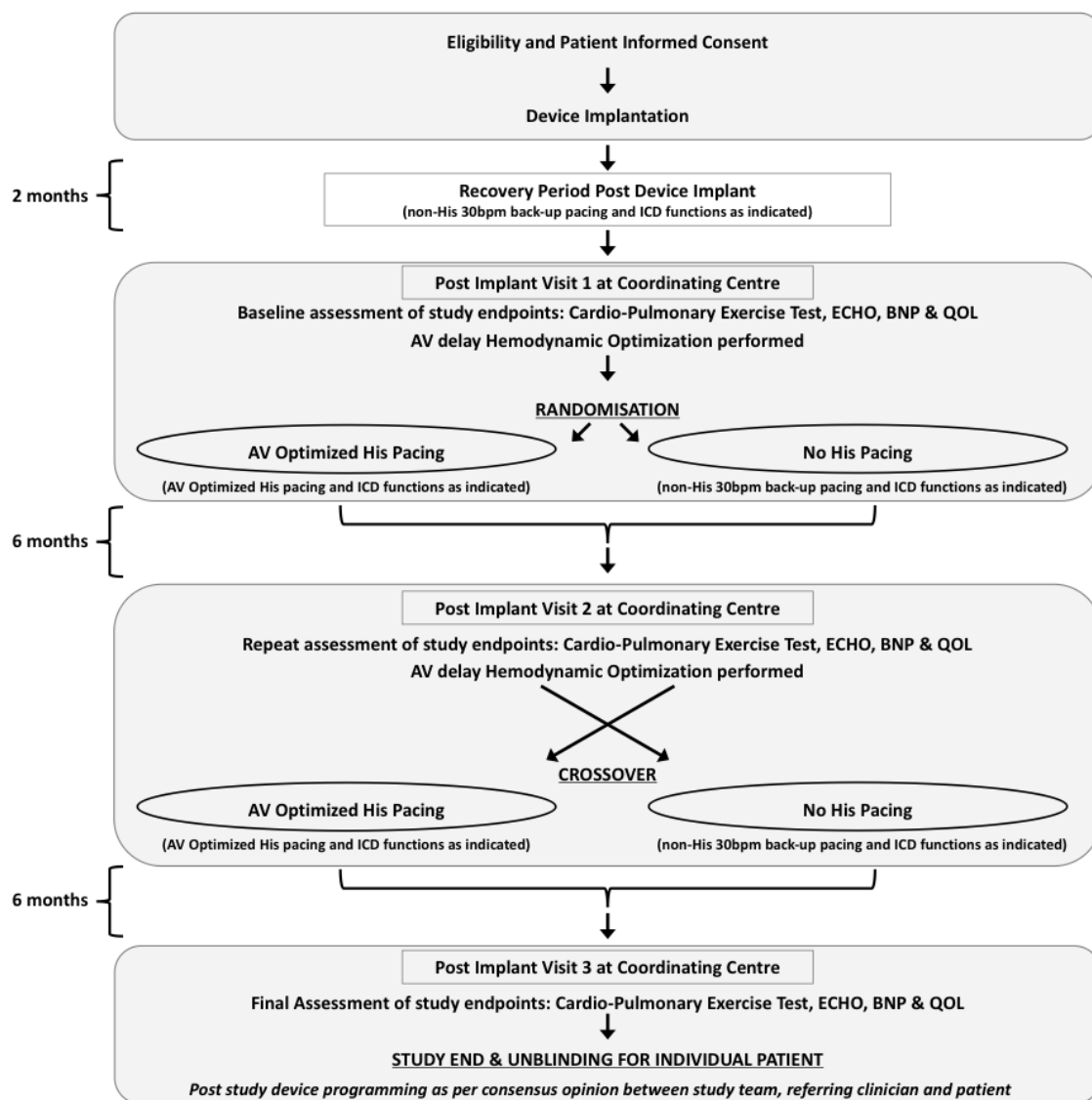


Figure 9-3 HOPE HF Study Flow Diagram

In brief, after device implantation, patients are programmed to receive non-His bundle backup pacing (VVI 30bpm (or DDI 30bpm if clinically indicated) utilizing either the right ventricular or Coronary Sinus lead if implanted), ICD therapies are enabled throughout the study in patients who have an ICD implanted. The two-month run in period allows patients to recover from the implant procedure and ensures that the His lead has integrated into the tissue prior to randomization.

Two months after implantation, study participants visit the core centre to have baseline measurements recorded which includes all endpoint measurements. AV delay optimisation is performed using continuous non-invasive blood pressure. Patients are then randomised to 6 months of AV optimized His pacing or 6 months of no His pacing. At the end of each 6-month period all the endpoints are measured. Patients then enter the other arm of the study.

9.4.9 Randomisation and Allocation Concealment

All patients have a commercially available CRT device implanted as part of the trial with a pacing lead permanently positioned on the His bundle. After the initial two-month period, patients are randomised 1:1 to AV optimized His bundle pacing or no His pacing.

The study is double-blinded with patients, and the staff conducting end-point assessments blinded to the pacing treatment allocation. To ensure blinding is maintained, special precautions are taken to prevent key staff from seeing the ECG even during exercise testing.

9.4.10 Maintaining blinding during the trial

AV optimization is performed at each study visit by a member of staff blinded to treatment allocation. Before the optimisation process, a separate non-blinded staff member programs the device to His pacing in readiness for the optimisation. After the

optimisation, this non-blinded study team member reprograms the device to either His pacing on or His pacing off according to the treatment arm, using the AV optimum determined by the blinded staff member during optimisation.

During Cardio Pulmonary Exercise Testing (CPET) it is essential to monitor the ECG for patient safety. To ensure blinding is maintained two members of the trial team are always present during a patient's test – one is blinded and the other not. The blinded member of the team leads the test but is not able to see the ECG. The role of the non-blinded trial team member is to observe the ECG for arrhythmias that would necessitate the test be stopped for safety reasons. The unblinded member does not communicate with the patient or the blinded member unnecessarily.

Echocardiography is performed and analysed by a blinded member of staff. No ECG is recorded during the procedure. Pacing checks are only conducted by a designated unblinded investigator.

9.4.11 Design of the AV delay haemodynamic optimisation protocol

In this study we use non-invasive acute hemodynamic measurements to identify the optimal paced and sensed AV delays for individual patients. This approach uses the approach detailed in the main Methods section of this thesis.

9.4.12 Analysis plan

All study data is being recorded in our institution's clinical trial database (Inform, version 4.6). The trial is conducted through the Imperial College Clinical Trials Unit, which provides monitoring and trial oversight to minimise the amount of missing data.

The primary end-point is peak oxygen uptake measured using cardiopulmonary exercise testing. The primary outcome will be analysed using a two-level hierarchical model. We will include treatment, period and sequence effect within the model. Random subject

effects will also be included in the regression model if appropriate. Differences in secondary outcomes will also be analysed using a two-level hierarchical model. Normality will be checked and appropriate transformation or non-parametric methods will be used if it is not met.

9.4.13 Planned subgroup analysis

9.4.13.1 Right Bundle Branch Block (RBBB) Cohort

We expect one-third of recruited patients to have RBBB. In these patients, His bundle pacing may shorten QRS duration by overcoming the RBBB. Potential mechanisms are shown in Figure 9-4.

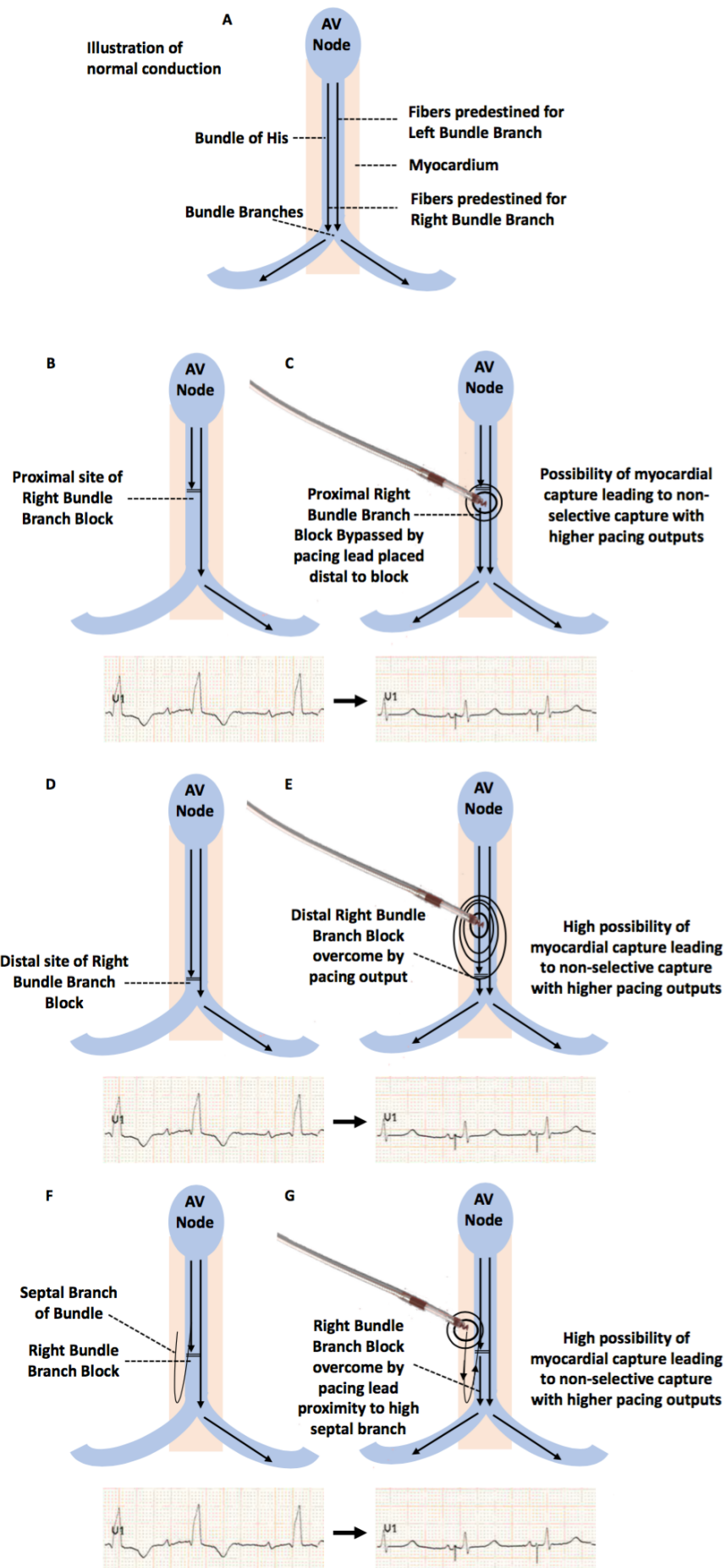


Figure 9-4 Potential Mechanisms for RBBB reversal

A, Normal ventricular activation, with activation travelling from the AV node down the Bundle of His and then into the Left and Right Bundle Branches. This illustration demonstrates that fibres within the bundle of His are already predestined for their respective Bundle Branches.

B, Proximal site of RBBB, C, a pacing lead has been positioned in a site distal to this block allowing an electrical bypass of the RBBB and thus reversing the electrical abnormality.

D, Distal site of RBBB (unfeasible for pacing lead to be positioned distal to this) E, Remote electrical activation with a proximally placed lead could reverse this electrical abnormality. This could occur (1) because of high pacing outputs, (2) as a consequence of the source-sink-theory and a high likelihood of their being diseased fibres already in the proximal location or (3) the virtual electrode polarization theory.

F, Highlights that each bundle branch has multiple branches, G, A high septal branch may fortuitously be activated with a conventionally placed His lead. This could result in retrograde activation down the branch back to a place in the bundle branch which is distal to the site of block allowing antegrade activation from this site forward.

Therefore, patients may theoretically obtain benefit from ventricular resynchronization in addition to that obtained from optimisation of AV delay. Narrowing of QRS may occur by (i) positioning the pacing lead distal to the site of bundle branch block leading to an electrical bypass of the block, (ii) overcoming the block with sufficient stimulus to activate distal dormant tissue, relying on either source-sink relationships during pacing versus intrinsic impulse propagation or the virtual electrode polarization effects or (iii) retrograde activation via capture of an upper septal branch of the His Purkinje system or (iv) in the case of non-selective His bundle capture partial or full correction of the terminal RBBB pattern by fusion without recruiting the RBB fascicles.

We will perform a subgroup analysis to test for the possibility that RBBB patients show a larger benefit than the narrow QRS patients, which might signify the presence of dual benefit in bundle branch block patients.

9.4.13.2 PR interval

We will test whether there is a relationship between magnitude of improvement in the outcome measures with AV optimized His pacing and baseline PR interval. Such a relationship might be expected if there is a benefit from PR interval shortening. The PR interval of 200ms or above was chosen as the entry for the HOPE-HF because in the COMPANION trial patients with a PR interval longer than 200ms appeared to obtain greater benefit from CRT (Olshansky et al. 2012). However the MADIT-CRT study reported a larger difference in those whose PR interval was >230ms (Kutyifa et al. 2014), we wanted to recruit a broad range of patients which might permit later evaluation of the effect of PR interval.

9.4.13.3 E-A wave analysis

We will test whether the presence of E-A wave fusion predicts the size of any His pacing benefit.

Baseline E-A wave fusion on echocardiography suggests there is inefficient left ventricular filling and it is possible that it may be useful in selecting patients who are likely to benefit from AV optimisation with His pacing.

9.4.13.4 Selective vs Non-Selective His capture

If there are significant numbers of patients with non-selective His capture, we will perform an analysis to assess whether the type of His capture affects the outcome measures.

9.4.14 Sample size calculation

The smoothed modified Bruce protocol in patients with heart failure has a test-retest variability of 2.4ml/kg/min (Scott et al. 2001). Implantation of a cardiac resynchronization therapy pacemaker in patients with broad QRS duration and heart failure results in a 0.5-2.5(mean 1.5)ml/kg/min increase in peak oxygen uptake (Auricchio et al. 2003; Abraham et al. 2004). Acute hemodynamic data suggests that the benefit from His-bundle pacing in long PR narrow QRS patients is around 60% of the effect seen with CRT in left bundle branch block patients (Sohaib et al. 2015). We might therefore expect that the estimated increment in peak oxygen uptake of 60% would be 0.9 ml/kg/min. 126 patients would give 90% power at the 5% significance level to detect a 0.7ml/kg/min change. To account for combined mortality and dropout rates as high as 21% we will recruit at least 160 patients.

9.4.14.1 Compliance and loss to follow up

It is anticipated that some patients may request a change in their treatment arm, particularly if there is a change in their symptom status. If this occurs, we will try to encourage patients to continue with their designated treatment until they cross over or complete the study as scheduled. If however the clinical team judges that it is necessary

to turn on or off His pacing this will be done. Analysis will be on the standard intention to treat basis.

Follow up will be coordinated and carried out by a research team dedicated to this study. If patients decide they no longer wish to attend the core centre for follow-up then we will ask if they are willing at least to be contacted by the research team to ensure data on adverse events can be recorded.

9.4.15 Funding

HOPE-HF is an investigator-initiated trial, funded by the British Heart Foundation. Medtronic are supporting the study, by supplying the His pacing leads, sheaths, CRT-P devices (in those patients who do not have a clinical indication for ICD implantation) and the additional cost of a CRT device over dual-chamber ICD in those indicated for ICD implantation.

9.4.16 Timeline

Recruitment began in January 2016 and completed by February 2019. Follow-up is therefore expected to end by Spring 2020 and the trial to report in Summer 2020.

9.4.16.1 My Role

Although the initial idea for the trial was my supervisors. I was involved in the grant writing process. Furthermore, I completed the ethical application for the study and am a PI for as well as a member of 1) the Trial Management Group, 2) the Trial Steering Committee and 3) the Data Safety Monitoring Board. I have initiated each site involved within the study and have been responsible for the day-to-day running of the trial. This has included patient recruitment, patient device implantation, coordination and conduction of patient follow up visits and management of all serious adverse events.

9.5 Discussion and Conclusion

If AV optimized His pacing is found to deliver clinical benefits to patients with heart failure and a long PR interval without left bundle branch block, this procedure may become a new therapeutic option for this population of highly symptomatic patients. Pacing therapy for heart failure is not currently indicated for this population of patients and UK data suggest they form approximately 20% of all heart failure patients (Nikolaidou et al. 2017).

A positive result from this trial would provide the first adequately powered randomised controlled evidence of physiological benefit of His bundle pacing in these patients.

10 References

- Abdelrahman, M., Subzposh, F.A., Beer, D., Durr, B., Naperkowski, A., Sun, H., Oren, J.W., Dandamudi, G. and Vijayaraman, P. 2018. Clinical outcomes of his bundle pacing compared to right ventricular pacing. *Journal of the American College of Cardiology* 71(20), pp. 2319–2330.
- Abraham, W.T., Young, J.B., León, A.R., Adler, S., Bank, A.J., Hall, S.A., Lieberman, R., Liem, L.B., O’Connell, J.B., Schroeder, J.S., Wheelan, K.R. and Multicenter InSync ICD II Study Group 2004. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation* 110(18), pp. 2864–2868.
- Ajjijola, O.A., Upadhyay, G.A., Macias, C., Shivkumar, K. and Tung, R. 2017. Permanent His-bundle pacing for cardiac resynchronization therapy: Initial feasibility study in lieu of left ventricular lead. *Heart Rhythm* 14(9), pp. 1353–1361.
- Almendral, J.M., Rosenthal, M.E., Stamato, N.J., Marchlinski, F.E., Buxton, A.E., Frame, L.H., Miller, J.M. and Josephson, M.E. 1986. Analysis of the resetting phenomenon in sustained uniform ventricular tachycardia: incidence and relation to termination. *Journal of the American College of Cardiology* 8(2), pp. 294–300.
- Aquilina, O. 2006. A brief history of cardiac pacing. *Images in paediatric cardiology* 8(2), pp. 17–81.
- Arenal, A., Proclemer, A., Kloppe, A., Lunati, M., Martinez Ferrer, J.B., Hersi, A., Gulaj, M., Wijffels, M.C.E.F., Santi, E., Manotta, L., Mangoni, L. and Gasparini, M. 2016. Different impact of long-detection interval and anti-tachycardia pacing in reducing unnecessary shocks: data from the ADVANCE III trial. *Europace* 18(11), pp. 1719–1725.
- Arnold, A., Shun-Shin, M., Keene, D., Lim, P.-B., Peters, N., Lefroy, D., Kanagaratnam, P., Koa-Wing, M., Linton, N., Qureshi, N., Davis, D.W., Francis, D. and Whinnett, Z. 2017. Shortening AV delay appears to be the major mechanism through which cardiac resynchronization therapy improves acute cardiac function. *Heart Rhythm* 14(5), p. C-PO02-172.
- Arnold, A., Shun-Shin, M., Keene, D., Sohaib, A., Finegold, J., Lefroy, D., Davies, W., Lim, P.B., Kanagaratnam, P., Koa-Wing, M., Linton, N., Peters, N.S., Moore, P., Francis, D. and Whinnett, Z. 2016. 9-05: Both Selective And Non-Selective His Pacing Preserve Left Ventricle Activation. *EP Europace* 18(suppl_1), pp. i24–i24.
- Arnold, A.D., Shun-Shin, M.J., Keene, D., Howard, J.P., Sohaib, S.M.A., Wright, I.J., Cole, G.D., Qureshi, N.A., Lefroy, D.C., Koa-Wing, M., Linton, N.W.F., Lim, P.B., Peters, N.S., Davies, D.W., Muthumala, A., Tanner, M., Ellenbogen, K.A., Kanagaratnam, P., Francis, D.P. and Whinnett, Z.I. 2018. His resynchronization versus biventricular pacing in patients with heart failure and left bundle branch block. *Journal of the American College of Cardiology* 72(24), pp. 3112–3122.
- Auricchio, A., Stellbrink, C., Block, M., Sack, S., Vogt, J., Bakker, P., Klein, H., Kramer, A., Ding, J., Salo, R., Tockman, B., Pochet, T. and Spinelli, J. 1999. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. *Circulation* 99(23), pp. 2993–3001.
- Auricchio, A., Stellbrink, C., Butter, C., Sack, S., Vogt, J., Misier, A.R., Böcker, D., Block, M., Kirkels, J.H., Kramer, A., Huvelle, E., Pacing Therapies in Congestive Heart Failure II Study Group and Guidant Heart Failure Research Group 2003. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *Journal of the American College of Cardiology* 42(12), pp. 2109–2116.
- Badke, F.R., Boinay, P. and Covell, J.W. 1980. Effects of ventricular pacing on regional left

ventricular performance in the dog. *The American Journal of Physiology* 238(6), pp. H858-67.

Barba-Pichardo, R., Manovel Sánchez, A., Fernández-Gómez, J.M., Moriña-Vázquez, P., Venegas-Gamero, J. and Herrera-Carranza, M. 2013. Ventricular resynchronization therapy by direct His-bundle pacing using an internal cardioverter defibrillator. *Europace* 15(1), pp. 83–88.

Barba-Pichardo, R., Moriña-Vázquez, P., Fernández-Gómez, J.M., Venegas-Gamero, J. and Herrera-Carranza, M. 2010. Permanent His-bundle pacing: seeking physiological ventricular pacing. *Europace* 12(4), pp. 527–533.

Bardy, G.H., Lee, K.L., Mark, D.B., Poole, J.E., Packer, D.L., Boineau, R., Domanski, M., Troutman, C., Anderson, J., Johnson, G., McNulty, S.E., Clapp-Channing, N., Davidson-Ray, L.D., Fraulo, E.S., Fishbein, D.P., Luceri, R.M., Ip, J.H. and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators 2005. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *The New England Journal of Medicine* 352(3), pp. 225–237.

Beck, H. and Curtis, A.B. 2016. Right ventricular versus biventricular pacing for heart failure and atrioventricular block. *Current heart failure reports* 13(5), pp. 230–236.

Bhavnani, S.P., Giedrimiene, D., Coleman, C.I., Guertin, D., Azeem, M. and Kluger, J. 2014. The healthcare utilization and cost of treating patients experiencing inappropriate implantable cardioverter defibrillator shocks: a propensity score study. *Pacing and Clinical Electrophysiology* 37(10), pp. 1315–1323.

Blackburn, H., Taylor, H.L. and Keys, A. 1970. Coronary heart disease in seven countries. XVI. The electrocardiogram in prediction of five-year coronary heart disease incidence among men aged forty through fifty-nine. *Circulation* 41(4 Suppl), pp. I154-61.

Bonner, R.F., Clem, T.R., Bowen, P.D. and Bowman, R.L. 1981. Laser-Doppler Continuous Real-Time Monitor of Pulsatile and Mean Blood Flow in Tissue Microcirculation. In: Chen, S.-H., Chu, B., and Nossal, R. eds. *Scattering techniques applied to supramolecular and nonequilibrium systems*. Boston, MA: Springer US, pp. 685–701.

Borne, R.T., Varosy, P.D. and Masoudi, F.A. 2013. Implantable cardioverter-defibrillator shocks: epidemiology, outcomes, and therapeutic approaches. *JAMA internal medicine* 173(10), pp. 859–865.

Brecker, S.J., Xiao, H.B., Sparrow, J. and Gibson, D.G. 1992. Effects of dual-chamber pacing with short atrioventricular delay in dilated cardiomyopathy. *The Lancet* 340(8831), pp. 1308–1312.

Brignole, M., Auricchio, A., Baron-Esquivias, G., Bordachar, P., Wilson, C.M., et al. 2013. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *European Heart Journal* 34(29), pp. 2281–2329.

Cahalin, L.P., Chase, P., Arena, R., Myers, J., Bensimhon, D., Peberdy, M.A., Ashley, E., West, E., Forman, D.E., Pinkstaff, S., Lavie, C.J. and Guazzi, M. 2013. A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure. *Heart failure reviews* 18(1), pp. 79–94.

Cassano, P. and Fava, M. 2002. Depression and public health: an overview. *Journal of Psychosomatic Research* 53(4), pp. 849–857.

Catanzariti, D., Maines, M., Cemin, C., Broso, G., Marotta, T. and Vergara, G. 2006. Permanent direct his bundle pacing does not induce ventricular dyssynchrony unlike conventional right ventricular apical pacing. An inpatient acute comparison study. *Journal of Interventional Cardiac Electrophysiology* 16(2), pp. 81–92.

Cazeau, S., Ritter, P., Bakdach, S., Lazarus, A., Limousin, M., Henao, L., Mundler, O., Daubert, J.C. and Mugica, J. 1994. Four chamber pacing in dilated cardiomyopathy. *Pacing and Clinical Electrophysiology* 17(11 Pt 2), pp. 1974–1979.

Cazeau, S., Ritter, P., Lazarus, A., Gras, D., Backdach, H., Mundler, O. and Mugica, J. 1996. Multisite pacing for end-stage heart failure: early experience. *Pacing and Clinical Electrophysiology* 19(11 Pt 2), pp. 1748–1757.

Cevik, C., Perez-Verdia, A. and Nugent, K. 2009. Implantable cardioverter defibrillators and their role in heart failure progression. *Europace* 11(6), pp. 710–715.

Chen, S., Yin, Y., Lan, X., Liu, Z., Ling, Z., Su, L., Kiuchi, M.G., Li, X., Zhong, B., Krucoff, M.W. and PREDICT-Heart Failure study international group 2013. Paced QRS duration as a predictor for clinical heart failure events during right ventricular apical pacing in patients with idiopathic complete atrioventricular block: results from an observational cohort study (PREDICT-HF). *European Journal of Heart Failure* 15(3), pp. 352–359.

Cheng, S., Keyes, M.J., Larson, M.G., McCabe, E.L., Newton-Cheh, C., Levy, D., Benjamin, E.J., Vasan, R.S. and Wang, T.J. 2009. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *The Journal of the American Medical Association* 301(24), pp. 2571–2577.

Cleland, J.G., Abraham, W.T., Linde, C., Gold, M.R., Young, J.B., Claude Daubert, J., Sherfese, L., Wells, G.A. and Tang, A.S.L. 2013. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *European Heart Journal* 34(46), pp. 3547–3556.

Cleland, J.G.F., Daubert, J.-C., Erdmann, E., Freemantle, N., Gras, D., Kappenberger, L., Tavazzi, L. and Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators 2005. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *The New England Journal of Medicine* 352(15), pp. 1539–1549.

Coates, S. and Thwaites, B. 2000. The strength-duration curve and its importance in pacing efficiency: a study of 325 pacing leads in 229 patients. *Pacing and Clinical Electrophysiology* 23(8), pp. 1273–1277.

Compton, S.J., Swerdlow, C.D., Canby, R.C., Strobel, G.G., Zagrodzky, J.D., Cinbis, C., Carney, J.K. and Bhunia, S.K. 2012. Arrhythmia discrimination using hemoglobin spectroscopy in humans. *Heart Rhythm* 9(10), pp. 1585–1591.

Conraads, V.M., Spruit, M.A., Braunschweig, F., Cowie, M.R., Tavazzi, L., Borggrefe, M., Hill, M.R.S., Jacobs, S., Gerritse, B. and van Veldhuisen, D.J. 2014. Physical activity measured with implanted devices predicts patient outcome in chronic heart failure. *Circulation. Heart Failure* 7(2), pp. 279–287.

Correa de Sa, D.D., Hardin, N.J., Crespo, E.M., Nicholas, K.B. and Lustgarten, D.L. 2012. Autopsy analysis of the implantation site of a permanent selective direct his bundle pacing lead. *Circulation. Arrhythmia and Electrophysiology* 5(1), pp. 244–246.

Crisel, R.K., Farzaneh-Far, R., Na, B. and Whooley, M.A. 2011. First-degree atrioventricular block is associated with heart failure and death in persons with stable coronary artery disease: data from the Heart and Soul Study. *European Heart Journal* 32(15), pp. 1875–1880.

Curtis, A.B., Worley, S.J., Adamson, P.B., Chung, E.S., Niazi, I., Sherfese, L., Shinn, T., Sutton, M.S.J. and Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) Trial Investigators 2013. Biventricular pacing for atrioventricular block and systolic dysfunction. *The New England Journal of Medicine* 368(17), pp. 1585–1593.

Daubert, J.P., Zareba, W., Cannom, D.S., McNitt, S., Rosero, S.Z., Wang, P., Schuger, C., Steinberg, J.S., Higgins, S.L., Wilber, D.J., Klein, H., Andrews, M.L., Hall, W.J., Moss, A.J. and MADIT II Investigators 2008. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. *Journal of the American College of Cardiology* 51(14), pp. 1357–1365.

Deshmukh, P., Casavant, D.A., Romanynshyn, M. and Anderson, K. 2000. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation.

Circulation 101(8), pp. 869–877.

Doshi, R.N., Daoud, E.G., Fellows, C., Turk, K., Duran, A., Hamdan, M.H., Pires, L.A. and PAVE Study Group 2005. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *Journal of Cardiovascular Electrophysiology* 16(11), pp. 1160–1165.

Dougherty, C.M. 1995. Psychological reactions and family adjustment in shock versus no shock groups after implantation of internal cardioverter defibrillator. *Heart & lung : the journal of critical care* 24(4), pp. 281–291.

Epstein, A.E., Kay, G.N., Plumb, V.J., Dailey, S.M. and Anderson, P.G. 1998. Gross and microscopic pathological changes associated with nonthoracotomy implantable defibrillator leads. *Circulation* 98(15), pp. 1517–1524.

Fisher, J.D., Kim, S.G., Furman, S. and Matos, J.A. 1982. Role of implantable pacemakers in control of recurrent ventricular tachycardia. *The American Journal of Cardiology* 49(1), pp. 194–206.

Foley, P.W.X., Patel, K., Irwin, N., Sanderson, J.E., Frenneaux, M.P., Smith, R.E.A., Stegemann, B. and Leyva, F. 2011. Cardiac resynchronisation therapy in patients with heart failure and a normal QRS duration: the RESPOND study. *Heart* 97(13), pp. 1041–1047.

Francis, D.P. 2013. How to reliably deliver narrow individual-patient error bars for optimization of pacemaker AV or VV delay using a “pick-the-highest” strategy with haemodynamic measurements. *International Journal of Cardiology* 163(3), pp. 221–225.

Funck, R.C., Mueller, H.-H., Lunati, M., Piorkowski, C., De Roy, L., Paul, V., Wittenberg, M., Wuensch, D., Blanc, J.-J. and BioPace study group 2014. Characteristics of a large sample of candidates for permanent ventricular pacing included in the Biventricular Pacing for Atrio-ventricular Block to Prevent Cardiac Desynchronization Study (BioPace). *Europace* 16(3), pp. 354–362.

Gamble, J.H.P., Herring, N., Ginks, M., Rajappan, K., Bashir, Y. and Betts, T.R. 2016. Procedural success of left ventricular lead placement for cardiac resynchronization therapy. *JACC: Clinical Electrophysiology* 2(1), pp. 69–77.

Gasparini, M., Proclemer, A., Klersy, C., Kloppe, A., Lunati, M., Ferrer, J.B.M., Hersi, A., Gulaj, M., Wijfels, M.C.E.F., Santi, E., Manotta, L. and Arenal, A. 2013. Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the ADVANCE III randomized clinical trial. *The Journal of the American Medical Association* 309(18), pp. 1903–1911.

Gervais, R., Leclercq, C., Shankar, A., Jacobs, S., Eiskjaer, H., Johannessen, A., Freemantle, N., Cleland, J.G.F., Tavazzi, L., Daubert, C. and CARE-HF investigators 2009. Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial. *European Journal of Heart Failure* 11(7), pp. 699–705.

Gibson, D.G., Chamberlain, D.A., Coltart, D.J. and Mercer, J. 1971. Effect of changes in ventricular activation on cardiac haemodynamics in man. Comparison of right ventricular, left ventricular, and simultaneous pacing of both ventricles. *British heart journal* 33(3), pp. 397–400.

Gilmore, J.P., Sarnoff, S.J., Mitchell, J.H. and Linden, R.J. 1963. Synchronicity of ventricular contraction: observations comparing haemodynamic effects of atrial and ventricular pacing. *British heart journal* 25, pp. 299–307.

Gold, M.R., Feliciano, Z., Gottlieb, S.S. and Fisher, M.L. 1995. Dual-chamber pacing with a short atrioventricular delay in congestive heart failure: a randomized study. *Journal of the American College of Cardiology* 26(4), pp. 967–973.

Grimm, W., Flores, B.F. and Marchlinski, F.E. 1993. Symptoms and electrocardiographically documented rhythm preceding spontaneous shocks in patients with implantable cardioverter-defibrillator. *The American Journal of Cardiology* 71(16), pp. 1415–1418.

Hamer, A.W., Rubin, S.A., Peter, T. and Mandel, W.J. 1984. Factors that predict syncope during

ventricular tachycardia in patients. *American Heart Journal* 107(5 Pt 1), pp. 997–1005.

Hamer, A.W., Zaher, C.A., Rubin, S.A., Peter, T. and Mandel, W.J. 1985. Hemodynamic benefits of synchronized 1:1 atrial pacing during sustained ventricular tachycardia with severely depressed ventricular function in coronary heart disease. *The American Journal of Cardiology* 55(8), pp. 990–994.

Higgins, S.L., Hummel, J.D., Niazi, I.K., Giudici, M.C., Worley, S.J., Saxon, L.A., Boehmer, J.P., Higginbotham, M.B., De Marco, T., Foster, E. and Yong, P.G. 2003. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *Journal of the American College of Cardiology* 42(8), pp. 1454–1459.

Holmqvist, F., Hellkamp, A.S., Lee, K.L., Lamas, G.A., Daubert, J.P. and MOST investigators 2014. Adverse effects of first-degree AV-block in patients with sinus node dysfunction: data from the mode selection trial. *Pacing and Clinical Electrophysiology* 37(9), pp. 1111–1119.

Hou, X., Qian, Z., Wang, Y., Qiu, Y., Chen, X., Jiang, H., Jiang, Z., Wu, H., Zhao, Z., Zhou, W. and Zou, J. 2019. Feasibility and cardiac synchrony of permanent left bundle branch pacing through the interventricular septum. *Europace* 21(11), pp. 1694–1702.

Hu, Y., Gurev, V., Constantino, J. and Trayanova, N. 2013. Efficient preloading of the ventricles by a properly timed atrial contraction underlies stroke work improvement in the acute response to cardiac resynchronization therapy. *Heart Rhythm* 10(12), pp. 1800–1806.

Huang, W., Su, L., Wu, S., Xu, L., Xiao, F., Zhou, X. and Ellenbogen, K.A. 2017. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. *The Canadian Journal of Cardiology* 33(12), p. 1736.e1-1736.e3.

Imholz, B.P., Wieling, W., van Montfrans, G.A. and Wesseling, K.H. 1998. Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. *Cardiovascular Research* 38(3), pp. 605–616.

Jones, S., Lumens, J., Sohaib, S.M.A., Finegold, J.A., Kanagaratnam, P., Tanner, M., Duncan, E., Moore, P., Leyva, F., Frenneaux, M., Mason, M., Hughes, A.D., Francis, D.P., Whinnett, Z.I. and BRAVO Investigators 2017. Cardiac resynchronization therapy: mechanisms of action and scope for further improvement in cardiac function. *Europace* 19(7), pp. 1178–1186.

Josephson, M.E., Almendral, J. and Callans, D.J. 2014. Resetting and entrainment of reentrant ventricular tachycardia associated with myocardial infarction. *Heart Rhythm* 11(7), pp. 1239–1249.

Kawashima, T. and Sasaki, H. 2005. A macroscopic anatomical investigation of atrioventricular bundle locational variation relative to the membranous part of the ventricular septum in elderly human hearts. *Surgical and radiologic anatomy : SRA* 27(3), pp. 206–213.

Kaye, G.C., Linker, N.J., Marwick, T.H., Pollock, L., Graham, L., Pouliot, E., Poloniecki, J., Gammage, M. and Protect-Pace trial investigators 2015. Effect of right ventricular pacing lead site on left ventricular function in patients with high-grade atrioventricular block: results of the Protect-Pace study. *European Heart Journal* 36(14), pp. 856–862.

Keene, D. GB2017050848 A METHOD AND AN APPARATUS FOR DETERMINING HAEMODYNAMIC STATUS [Online]. Available at: <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2017163088> [Accessed: 27 March 2018].

Keene, D., Arnold, A., Shun-Shin, M.J., Howard, J.P., Sohaib, S.A., Moore, P., Tanner, M., Quereshi, N., Muthumala, A., Chandresekaran, B., Foley, P., Leyva, F., Adhya, S., Falaschetti, E., Tsang, H., Vijayaraman, P., Cleland, J.G.F., Stegmann, B., Francis, D.P. and Whinnett, Z.I. 2018. Rationale and design of the randomized multicentre His Optimized Pacing Evaluated for Heart Failure (HOPE-HF) trial. *ESC heart failure* 5(5), pp. 965–976.

Keene, D., Shun-Shin, M., Arnold, A. and Whinnett, Z. 2018. His-bundle pacing - UK experience and HOPE for the future. *British Journal of Cardiology*.

Kirkfeldt, R.E., Johansen, J.B., Nohr, E.A., Jørgensen, O.D. and Nielsen, J.C. 2014. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *European Heart Journal* 35(18), pp. 1186–1194.

Koneru, J.N., Swerdlow, C.D., Wood, M.A. and Ellenbogen, K.A. 2011. Minimizing inappropriate or “unnecessary” implantable cardioverter-defibrillator shocks: appropriate programming. *Circulation. Arrhythmia and Electrophysiology* 4(5), pp. 778–790.

Kop, W.J., Gottdiener, J.S., Tangen, C.M., Fried, L.P., McBurnie, M.A., Walston, J., Newman, A., Hirsch, C. and Tracy, R.P. 2002. Inflammation and coagulation factors in persons > 65 years of age with symptoms of depression but without evidence of myocardial ischemia. *The American Journal of Cardiology* 89(4), pp. 419–424.

Kosowsky, B.D., Scherlag, B.J. and Damato, A.N. 1968. Re-evaluation of the atrial contribution to ventricular function: study using His bundle pacing. *The American Journal of Cardiology* 21(4), pp. 518–524.

Kronborg, M.B., Mortensen, P.T., Poulsen, S.H., Gerdes, J.C., Jensen, H.K. and Nielsen, J.C. 2014. His or para-His pacing preserves left ventricular function in atrioventricular block: a double-blind, randomized, crossover study. *Europace* 16(8), pp. 1189–1196.

Kutyifa, V., Stockburger, M., Daubert, J.P., Holmqvist, F., Olshansky, B., Schuger, C., Klein, H., Goldenberg, I., Brenyo, A., McNitt, S., Merkely, B., Zareba, W. and Moss, A.J. 2014. PR interval identifies clinical response in patients with non-left bundle branch block: a Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy substudy. *Circulation. Arrhythmia and Electrophysiology* 7(4), pp. 645–651.

Kypta, A., Steinwender, C., Kammler, J., Leisch, F. and Hofmann, R. 2008. Long-term outcomes in patients with atrioventricular block undergoing septal ventricular lead implantation compared with standard apical pacing. *Europace* 10(5), pp. 574–579.

Kyriacou, A., Whinnett, Z.I., Sen, S., Pabari, P.A., Wright, I., Cornelussen, R., Lefroy, D., Davies, D.W., Peters, N.S., Kanagaratnam, P., Mayet, J., Hughes, A.D., Francis, D.P. and Davies, J.E. 2012. Improvement in coronary blood flow velocity with acute biventricular pacing is predominantly due to an increase in a diastolic backward-travelling decompression (suction) wave. *Circulation* 126(11), pp. 1334–1344.

Ladwig, K.-H., Baumert, J., Marten-Mittag, B., Kolb, C., Zrenner, B. and Schmitt, C. 2008. Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: results from the prospective living with an implanted cardioverter-defibrillator study. *Archives of General Psychiatry* 65(11), pp. 1324–1330.

Lamas, G.A., Lee, K.L., Sweeney, M.O., Silverman, R., Leon, A., Yee, R., Marinchak, R.A., Flaker, G., Schron, E., Orav, E.J., Hellkamp, A.S., Greer, S., McAnulty, J., Ellenbogen, K., Ehler, F., Freedman, R.A., Estes, N.A.M., Greenspon, A., Goldman, L. and Mode Selection Trial in Sinus-Node Dysfunction 2002. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *The New England Journal of Medicine* 346(24), pp. 1854–1862.

Leahy, M.J., de Mul, F.F.M., Nilsson, G.E. and Maniewski, R. 1999. Principles and practice of the laser-Doppler perfusion technique. *Technology and Health Care*.

Leclercq, C., Cazeau, S., Lellouche, D., Fossati, F., Anselme, F., Davy, J.-M., Sadoul, N., Klug, D., Mollo, L. and Daubert, J.-C. 2007. Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: The RD-CHF Study. *Pacing and Clinical Electrophysiology* 30 Suppl 1, pp. S23–30.

Li, A., Kaura, A., Sunderland, N., Dhillon, P.S. and Scott, P.A. 2016. The significance of shocks in implantable cardioverter defibrillator recipients. *Arrhythmia & electrophysiology review* 5(2), pp. 110–116.

Lima, J.A., Weiss, J.L., Guzman, P.A., Weisfeldt, M.L., Reid, P.R. and Traill, T.A. 1983. Incomplete filling and incoordinate contraction as mechanisms of hypotension during ventricular tachycardia in man. *Circulation* 68(5), pp. 928–938.

Linde, C., Leclercq, C., Rex, S., Garrigue, S., Lavergne, T., Cazeau, S., McKenna, W., Fitzgerald, M., Deharo, J.-C., Alonso, C., Walker, S., Braunschweig, F., Bailleul, C. and Daubert, J.-C. 2002. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. *Journal of the American College of Cardiology* 40(1), pp. 111–118.

Lustgarten, D.L., Crespo, E.M., Arkhipova-Jenkins, I., Lobel, R., Winget, J., Koehler, J., Liberman, E. and Sheldon, T. 2015. His-bundle pacing versus biventricular pacing in cardiac resynchronization therapy patients: A crossover design comparison. *Heart Rhythm* 12(7), pp. 1548–1557.

Magnani, J.W., Wang, N., Nelson, K.P., Connelly, S., Deo, R., Rodondi, N., Schelbert, E.B., Garcia, M.E., Phillips, C.L., Shlipak, M.G., Harris, T.B., Ellinor, P.T., Benjamin, E.J. and Health, Aging, and Body Composition Study 2013. Electrocardiographic PR interval and adverse outcomes in older adults: the Health, Aging, and Body Composition study. *Circulation. Arrhythmia and Electrophysiology* 6(1), pp. 84–90.

Maloney, J., Khoury, D., Simmons, T., Wilkoff, B., Morant, V., Trohman, R. and Castle, L. 1992. Effect of atrioventricular synchrony on stroke volume during ventricular tachycardia in man. *American Heart Journal* 123(6), pp. 1561–1568.

Manisty, C.H., Al-Hussaini, A., Unsworth, B., Baruah, R., Pabari, P.A., Mayet, J., Hughes, A.D., Whinnett, Z.I. and Francis, D.P. 2012. The acute effects of changes to AV delay on BP and stroke volume: potential implications for design of pacemaker optimization protocols. *Circulation. Arrhythmia and Electrophysiology* 5(1), pp. 122–130.

Manolis, A.S. 2006. The deleterious consequences of right ventricular apical pacing: time to seek alternate site pacing. *Pacing and Clinical Electrophysiology* 29(3), pp. 298–315.

Mark, D.B., Anstrom, K.J., Sun, J.L., Clapp-Channing, N.E., Tsiatis, A.A., Davidson-Ray, L., Lee, K.L., Bardy, G.H. and Sudden Cardiac Death in Heart Failure Trial Investigators 2008. Quality of life with defibrillator therapy or amiodarone in heart failure. *The New England Journal of Medicine* 359(10), pp. 999–1008.

Maurer, D. 2003. Quality of life and exercise capacity in patients with prolonged PQ interval and dual chamber pacemakers: a randomized comparison of permanent ventricular stimulation vs intrinsic AV conduction. *Europace* 5(4), pp. 411–417.

McCready, M.J. and Exner, D.V. Quality of Life and Psychological Impact of Implantable Cardioverter Defibrillators: Focus on Randomized Controlled Trial Data. *Cardiac Electrophysiology Review*.

Mirowski, M., Reid, P.R., Mower, M.M., Watkins, L., Gott, V.L., Schauble, J.F., Langer, A., Heilman, M.S., Kolenik, S.A., Fischell, R.E. and Weisfeldt, M.L. 1980. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *The New England Journal of Medicine* 303(6), pp. 322–324.

Molhoek, G.P., Wesseling, K.H., Settels, J.J., van Vollenhoven, E., Weeda, H.W., de Wit, B. and Arntzenius, A.C. 1984. Evaluation of the Penàz servo-plethysmo-manometer for the continuous, non-invasive measurement of finger blood pressure. *Basic Research in Cardiology* 79(5), pp. 598–609.

Moss, A.J., Hall, W.J., Cannom, D.S., Klein, H., Brown, M.W., Daubert, J.P., Estes, N.A.M., Foster, E., Greenberg, H., Higgins, S.L., Pfeffer, M.A., Solomon, S.D., Wilber, D., Zareba, W. and MADIT-CRT Trial Investigators 2009. Cardiac-resynchronization therapy for the prevention of heart-failure events. *The New England Journal of Medicine* 361(14), pp. 1329–1338.

Moss, A.J., Schuger, C., Beck, C.A., Brown, M.W., Cannom, D.S., Daubert, J.P., Estes, N.A.M., Greenberg, H., Hall, W.J., Huang, D.T., Kautzner, J., Klein, H., McNitt, S., Olshansky, B., Shoda, M., Wilber, D., Zareba, W. and MADIT-RIT Trial Investigators 2012. Reduction in inappropriate therapy and mortality through ICD programming. *The New England Journal of Medicine* 367(24), pp. 2275–2283.

- Moss, A.J., Zareba, W., Hall, W.J., Klein, H., Wilber, D.J., Cannom, D.S., Daubert, J.P., Higgins, S.L., Brown, M.W., Andrews, M.L. and Multicenter Automatic Defibrillator Implantation Trial II Investigators 2002. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *The New England Journal of Medicine* 346(12), pp. 877–883.
- Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V. and Ustun, B. 2007. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *The Lancet* 370(9590), pp. 851–858.
- Nabutovsky, Y., Pavek, T. and Turcott, R. 2012. Chronic performance of a subcutaneous hemodynamic sensor. *Pacing and Clinical Electrophysiology* 35(8), pp. 919–926.
- Namerow, P.B., Firth, B.R., Heywood, G.M., Windle, J.R. and Parides, M.K. 1999. Quality-of-life six months after CABG surgery in patients randomized to ICD versus no ICD therapy: findings from the CABG Patch Trial. *Pacing and Clinical Electrophysiology* 22(9), pp. 1305–1313.
- Narula, O.S. 1977. Longitudinal dissociation in the His bundle. Bundle branch block due to asynchronous conduction within the His bundle in man. *Circulation* 56(6), pp. 996–1006.
- Nielsen, J.B., Pietersen, A., Graff, C., Lind, B., Struijk, J.J., Olesen, M.S., Haunsø, S., Gerds, T.A., Ellinor, P.T., Køber, L., Svendsen, J.H. and Holst, A.G. 2013. Risk of atrial fibrillation as a function of the electrocardiographic PR interval: results from the Copenhagen ECG Study. *Heart Rhythm* 10(9), pp. 1249–1256.
- Nielsen, J.C., Thomsen, P.E.B., Højberg, S., Møller, M., Riahi, S., Dalsgaard, D., Mortensen, L.S., Nielsen, T., Asklund, M., Friis, E.V., Christensen, P.D., Simonsen, E.H., Eriksen, U.H., Jensen, G.V.H., Svendsen, J.H., Toff, W.D., Healey, J.S., Andersen, H.R. and DANPACE investigators 2012. Atrial fibrillation in patients with sick sinus syndrome: the association with PQ-interval and percentage of ventricular pacing. *Europace* 14(5), pp. 682–689.
- Nikolaidou, T., Pellicori, P., Zhang, J., Kazmi, S., Goode, K.M., Cleland, J.G. and Clark, A.L. 2017. Prevalence, predictors, and prognostic implications of PR interval prolongation in patients with heart failure. *Clinical Research in Cardiology* 107(2), pp. 108–119.
- Nishimura, R.A., Hayes, D.L., Holmes, D.R. and Tajik, A.J. 1995. Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: an acute Doppler and catheterization hemodynamic study. *Journal of the American College of Cardiology* 25(2), pp. 281–288.
- Noble, M.I.M. 1988. An introduction to modern work on the Bowditch phenomenon. *Cardiovascular Research* 22(8), pp. 586–586.
- Occhetta, E., Bortnik, M., Magnani, A., Francalacci, G., Piccinino, C., Plebani, L. and Marino, P. 2006. Prevention of ventricular desynchronization by permanent para-Hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right ventricular pacing. *Journal of the American College of Cardiology* 47(10), pp. 1938–1945.
- Olshansky, B., Day, J.D., Sullivan, R.M., Yong, P., Galle, E. and Steinberg, J.S. 2012. Does cardiac resynchronization therapy provide unrecognized benefit in patients with prolonged PR intervals? The impact of restoring atrioventricular synchrony: an analysis from the COMPANION Trial. *Heart Rhythm* 9(1), pp. 34–39.
- Padeletti, L., Lieberman, R., Schreuder, J., Michelucci, A., Collella, A., Pieragnoli, P., Ricciardi, G., Eastman, W., Valsecchi, S. and Hettrick, D.A. 2007. Acute effects of His bundle pacing versus left ventricular and right ventricular pacing on left ventricular function. *The American Journal of Cardiology* 100(10), pp. 1556–1560.
- Piccini, J.P., Koontz, J.I. and Jackson, K.P. 2011. Use of ventricular synchronized triggered atrial pacing to facilitate hemodynamic support during mapping and catheter ablation of ventricular tachycardia. *Journal of Cardiovascular Electrophysiology* 22(10), pp. 1174–1178.
- Ploux, S., Eschalier, R., Whinnett, Z.I., Lumens, J., Derval, N., Sacher, F., Hocini, M., Jaïs, P.,

Dubois, R., Ritter, P., Haïssaguerre, M., Wilkoff, B.L., Francis, D.P. and Bordachar, P. 2015. Electrical dyssynchrony induced by biventricular pacing: implications for patient selection and therapy improvement. *Heart Rhythm* 12(4), pp. 782–791.

Poole, J.E., Gleva, M.J., Mela, T., Chung, M.K., Uslan, D.Z., Borge, R., Gottipaty, V., Shinn, T., Dan, D., Feldman, L.A., Seide, H., Winston, S.A., Gallagher, J.J., Langberg, J.J., Mitchell, K., Holcomb, R. and REPLACE Registry Investigators 2010. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. *Circulation* 122(16), pp. 1553–1561.

Poole, J.E., Johnson, G.W., Hellkamp, A.S., Anderson, J., Callans, D.J., Raitt, M.H., Reddy, R.K., Marchlinski, F.E., Yee, R., Guarnieri, T., Talajic, M., Wilber, D.J., Fishbein, D.P., Packer, D.L., Mark, D.B., Lee, K.L. and Bardy, G.H. 2008. Prognostic importance of defibrillator shocks in patients with heart failure. *The New England Journal of Medicine* 359(10), pp. 1009–1017.

Proietti, R., Labos, C., Davis, M., Thanassoulis, G., Santangeli, P., Russo, V., Di Biase, L., Roux, J.-F., Verma, A., Natale, A. and Essebag, V. 2015. A systematic review and meta-analysis of the association between implantable cardioverter-defibrillator shocks and long-term mortality. *The Canadian Journal of Cardiology* 31(3), pp. 270–277.

Rajan, V., Varghese, B., van Leeuwen, T.G. and Steenbergen, W. 2009. Review of methodological developments in laser Doppler flowmetry. *Lasers in medical science* 24(2), pp. 269–283.

van Rees, J.B., Borleffs, C.J.W., de Bie, M.K., Stijnen, T., van Erven, L., Bax, J.J. and Schalij, M.J. 2011. Inappropriate implantable cardioverter-defibrillator shocks: incidence, predictors, and impact on mortality. *Journal of the American College of Cardiology* 57(5), pp. 556–562.

Ruschitzka, F., Abraham, W.T., Singh, J.P., Bax, J.J., Borer, J.S., Brugada, J., Dickstein, K., Ford, I., Gorcsan, J., Gras, D., Krum, H., Sogaard, P., Holzmeister, J. and EchoCRT Study Group 2013. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *The New England Journal of Medicine* 369(15), pp. 1395–1405.

Salden, F.C.W.M., Kutyifa, V., Stockburger, M., Prinzen, F.W. and Vernooy, K. 2017. Atrioventricular dromotopathy: evidence for a distinctive entity in heart failure with prolonged PR interval? *Europace* 20(7), pp. 1067–1077.

Salgado, M.A.M., Salgado-Filho, M.F., Reis-Brito, J.O., Lessa, M.A. and Tibirica, E. 2014. Effectiveness of laser Doppler perfusion monitoring in the assessment of microvascular function in patients undergoing on-pump coronary artery bypass grafting. *Journal of Cardiothoracic and Vascular Anesthesia* 28(5), pp. 1211–1216.

Samet, P. 1973. Hemodynamic sequelae of cardiac arrhythmias. *Circulation* 47(2), pp. 399–407.

Schron, E.B., Exner, D.V., Yao, Q., Jenkins, L.S., Steinberg, J.S., Cook, J.R., Kutalek, S.P., Friedman, P.L., Bubien, R.S., Page, R.L. and Powell, J. 2002. Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. *Circulation* 105(5), pp. 589–594.

Schuchert, A., Muto, C., Maounis, T., Frank, R., Boulogne, E., Polauck, A., Padeletti, L. and MASCOT study group 2013. Lead complications, device infections, and clinical outcomes in the first year after implantation of cardiac resynchronization therapy-defibrillator and cardiac resynchronization therapy-pacemaker. *Europace* 15(1), pp. 71–76.

Schukro, C., Leitner, L., Siebermair, J., Pezawas, T., Stix, G., Kastner, J. and Schmidinger, H. 2013. Impact of accelerated ventricular tachyarrhythmias on mortality in patients with implantable cardioverter-defibrillator therapy. *International Journal of Cardiology* 167(6), pp. 3006–3010.

Scott, A.C., Francis, D.P., Davies, L.C., Coats, A.J. and Piepoli, M.F. 2001. Validation of a treadmill exercise test protocol with improved metabolic plateau formation in patients with chronic congestive heart failure. *The American Journal of Cardiology* 87(11), pp. 1328–1331.

Scott, P.A., Silberbauer, J., McDonagh, T.A. and Murgatroyd, F.D. 2014. Impact of prolonged implantable cardioverter-defibrillator arrhythmia detection times on outcomes: a meta-analysis.

Heart Rhythm 11(5), pp. 828–835.

Sham'a, R.A., Nery, P., Sadek, M., Yung, D., Redpath, C., Perrin, M., Sarak, B. and Birnie, D. 2014. Myocardial injury secondary to ICD shocks: insights from patients with lead fracture.

Pacing and Clinical Electrophysiology 37(2), pp. 237–241.

Sharma, P.S., Dandamudi, G., Herweg, B., Wilson, D., Singh, R., Naperkowski, A., Koneru, J.N., Ellenbogen, K.A. and Vijayaraman, P. 2017. Permanent His-bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: A multicenter experience. *Heart Rhythm*.

Sharma, P.S., Dandamudi, G., Naperkowski, A., Oren, J.W., Storm, R.H., Ellenbogen, K.A. and Vijayaraman, P. 2015. Permanent His-bundle pacing is feasible, safe, and superior to right ventricular pacing in routine clinical practice. *Heart Rhythm* 12(2), pp. 305–312.

Sharma, P.S., Naperkowski, A., Bauch, T.D., Chan, J.Y.S., Arnold, A.D., Whinnett, Z.I., Ellenbogen, K.A. and Vijayaraman, P. 2018. Permanent his bundle pacing for cardiac resynchronization therapy in patients with heart failure and right bundle branch block. *Circulation. Arrhythmia and Electrophysiology* 11(9), p. e006613.

Shurrab, M., Healey, J.S., Haj-Yahia, S., Kaoutskaia, A., Boriani, G., Carrizo, A., Botto, G., Newman, D., Padeletti, L., Connolly, S.J. and Crystal, E. 2017. Reduction in unnecessary ventricular pacing fails to affect hard clinical outcomes in patients with preserved left ventricular function: a meta-analysis. *Europace* 19(2), pp. 282–288.

Singer, I., Hutchins, G.M., Mirowski, M., Mower, M.M., Veltri, E.P., Guarnieri, T., Griffith, L.S., Watkins, L., Juanteguy, J. and Fisher, S. 1987. Pathologic findings related to the lead system and repeated defibrillations in patients with the automatic implantable cardioverter-defibrillator.

Journal of the American College of Cardiology 10(2), pp. 382–388.

Sohaib, S.M.A., Wright, I., Lim, E., Moore, P., Lim, P.B., Koawing, M., Lefroy, D.C., Lusgarten, D., Linton, N.W.F., Davies, D.W., Peters, N.S., Kanagaratnam, P., Francis, D.P. and Whinnett, Z.I. 2015. Atrioventricular optimized direct his bundle pacing improves acute hemodynamic function in patients with heart failure and PR interval prolongation without left bundle branch block. *JACC: Clinical Electrophysiology* 1(6), pp. 582–591.

Steinbach, K.K., Merl, O., Frohner, K., Hief, C., Nürnberg, M., Kaltenbrunner, W., Podczeck, A. and Wessely, E. 1994. Hemodynamics during ventricular tachyarrhythmias. *American Heart Journal* 127(4 Pt 2), pp. 1102–1106.

Steinbeck, G., Dorwarth, U., Mattke, S., Hoffmann, E., Markewitz, A., Kaulbach, H. and Tassani, P. 1994. Hemodynamic deterioration during ICD implant: predictors of high-risk patients. *American Heart Journal* 127(4 Pt 2), pp. 1064–1067.

Stockburger, M., Moss, A.J., Klein, H.U., Zareba, W., Goldenberg, I., Biton, Y., McNitt, S. and Kutyla, V. 2016. Sustained clinical benefit of cardiac resynchronization therapy in non-LBBB patients with prolonged PR-interval: MADIT-CRT long-term follow-up. *Clinical Research in Cardiology* 105(11), pp. 944–952.

Sutton, R. 2018. Pacing supplement: Early days of pacing in the UK - the British contribution to the field of pacing. *British Journal of Cardiology*.

Sweeney, M.O., Bank, A.J., Nsah, E., Koullick, M., Zeng, Q.C., Hettrick, D., Sheldon, T., Lamas, G.A. and Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACE) Trial 2007. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. *The New England Journal of Medicine* 357(10), pp. 1000–1008.

Sweeney, M.O., Hellkamp, A.S., Ellenbogen, K.A., Greenspon, A.J., Freedman, R.A., Lee, K.L., Lamas, G.A. and MODe Selection Trial Investigators 2003. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 107(23), pp. 2932–2937.

Teng, A.E., Lustgarten, D.L., Vijayaraman, P., Tung, R., Shivkumar, K., Wagner, G.S. and

Ajjola, O.A. 2016. Usefulness of his bundle pacing to achieve electrical resynchronization in patients with complete left bundle branch block and the relation between native QRS axis, duration, and normalization. *The American Journal of Cardiology* 118(4), pp. 527–534.

Teng, A.E., Massoud, L. and Ajijola, O.A. 2016. Physiological mechanisms of QRS narrowing in bundle branch block patients undergoing permanent His bundle pacing. *Journal of Electrocardiology* 49(5), pp. 644–648.

The DAVID Trial Investigators* 2002. Dual-Chamber Pacing or Ventricular Backup Pacing in Patients With an Implantable Defibrillator. *JAMA* 288(24), p. 3115.

Theuns, D.A.M.J., Brouwer, T.F., Jones, P.W., Allavatam, V., Donnelley, S., Auricchio, A., Knops, R.E. and Burke, M.C. 2018. Prospective blinded evaluation of a novel sensing methodology designed to reduce inappropriate shocks by the subcutaneous implantable cardioverter-defibrillator. *Heart Rhythm* 15(10), pp. 1515–1522.

Tops, L.F., Schalij, M.J. and Bax, J.J. 2009. The effects of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. *Journal of the American College of Cardiology* 54(9), pp. 764–776.

Tse, H.F. and Lau, C.P. 1997. Long-term effect of right ventricular pacing on myocardial perfusion and function. *Journal of the American College of Cardiology* 29(4), pp. 744–749.

Tung, L., Tovar, O., Neunlist, M., Jain, S.K. and O'Neill, R.J. 1994. Effects of strong electrical shock on cardiac muscle tissue. *Annals of the New York Academy of Sciences* 720, pp. 160–175.

Turakhia, M.P., Zweibel, S., Swain, A.L., Mollenkopf, S.A. and Reynolds, M.R. 2017. Healthcare utilization and expenditures associated with appropriate and inappropriate implantable defibrillator shocks. *Circulation. Cardiovascular Quality and Outcomes* 10(2).

Turcott, R.G. and Pavek, T.J. 2008. Hemodynamic sensing using subcutaneous photoplethysmography. *American Journal of Physiology. Heart and Circulatory Physiology* 295(6), pp. H2560–72.

Turcott, R.G. and Pavek, T.J. 2010. Identification of hemodynamically unstable arrhythmias using subcutaneous photoplethysmography. *Journal of Cardiovascular Electrophysiology* 21(4), pp. 448–454.

Vijayaraman, P., Dandamudi, G., Lustgarten, D. and Ellenbogen, K.A. 2017. Permanent His bundle pacing: Electrophysiological and echocardiographic observations from long-term follow-up. *Pacing and Clinical Electrophysiology* 40(7), pp. 883–891.

Vijayaraman, P., Dandamudi, G., Zanon, F., Sharma, P.S., Tung, R., Huang, W., Koneru, J., Tada, H., Ellenbogen, K.A. and Lustgarten, D.L. 2017. Permanent His bundle pacing: Recommendations from a Multicenter His Bundle Pacing Collaborative Working Group for standardization of definitions, implant measurements, and follow-up. *Heart Rhythm*.

Vijayaraman, P., Herweg, B., Ellenbogen, K.A. and Gajek, J. 2019. His-Optimized Cardiac Resynchronization Therapy to Maximize Electrical Resynchronization. *Circulation. Arrhythmia and Electrophysiology* 12(2), p. e006934.

Vijayaraman, P., Naperkowski, A., Subzposh, F.A., Abdelrahman, M., Sharma, P.S., Oren, J.W., Dandamudi, G. and Ellenbogen, K.A. 2017. Permanent His-bundle pacing: Long-term lead performance and clinical outcomes. *Heart Rhythm*.

Watanabe, E., Okajima, K., Shimane, A., Ozawa, T., Manaka, T., Morishima, I., Asai, T., Takagi, M., Honda, T., Kasai, A., Fujii, E., Yamashiro, K., Kohno, R., Abe, H., Noda, T., Kurita, T., Watanabe, S., Ohmori, H., Nitta, T., Aizawa, Y., Kiyono, K. and Okumura, K. 2017. Inappropriate implantable cardioverter defibrillator shocks-incidence, effect, and implications for driver licensing. *Journal of Interventional Cardiac Electrophysiology* 49(3), pp. 271–280.

Whang, W., Albert, C.M., Sears, S.F., Lampert, R., Conti, J.B., Wang, P.J., Singh, J.P., Ruskin, J.N., Muller, J.E., Mittleman, M.A. and TOVA Study Investigators 2005. Depression as a predictor for appropriate shocks among patients with implantable cardioverter-defibrillators: results from the Triggers of Ventricular Arrhythmias (TOVA) study. *Journal of the American*

College of Cardiology 45(7), pp. 1090–1095.

Whinnett, Z.I., Davies, J.E.R., Nott, G., Willson, K., Manisty, C.H., Peters, N.S., Kanagaratnam, P., Davies, D.W., Hughes, A.D., Mayet, J. and Francis, D.P. 2008. Efficiency, reproducibility and agreement of five different hemodynamic measures for optimization of cardiac resynchronization therapy. *International Journal of Cardiology* 129(2), pp. 216–226.

Whinnett, Zachary I, Davies, J.E.R., Willson, K., Chow, A.W., Foale, R.A., Davies, D.W., Hughes, A.D., Francis, D.P. and Mayet, J. 2006. Determination of optimal atrioventricular delay for cardiac resynchronization therapy using acute non-invasive blood pressure. *Europace* 8(5), pp. 358–366.

Whinnett, Z I, Davies, J.E.R., Willson, K., Manisty, C.H., Chow, A.W., Foale, R.A., Davies, D.W., Hughes, A.D., Mayet, J. and Francis, D.P. 2006. Haemodynamic effects of changes in atrioventricular and interventricular delay in cardiac resynchronisation therapy show a consistent pattern: analysis of shape, magnitude and relative importance of atrioventricular and interventricular delay. *Heart* 92(11), pp. 1628–1634.

Whinnett, Z.I., Francis, D.P., Denis, A., Willson, K., Pascale, P., van Geldorp, I., De Guillebon, M., Ploux, S., Ellenbogen, K., Haïssaguerre, M., Ritter, P. and Bordachar, P. 2013. Comparison of different invasive hemodynamic methods for AV delay optimization in patients with cardiac resynchronization therapy: implications for clinical trial design and clinical practice. *International Journal of Cardiology* 168(3), pp. 2228–2237.

Wilkoff, B.L., Cook, J.R., Epstein, A.E., Greene, H.L., Hallstrom, A.P., Hsia, H., Kutalek, S.P., Sharma, A. and Dual Chamber and VVI Implantable Defibrillator Trial Investigators 2002. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *The Journal of the American Medical Association* 288(24), pp. 3115–3123.

Wilson, C.M., Allen, J.D., Bridges, J.B. and Adgey, A.A. 1988. Death and damage caused by multiple direct current shocks: studies in an animal model. *European Heart Journal* 9(11), pp. 1257–1265.

Yu, Z., Chen, R., Su, Y., Chen, X., Qin, S., Li, M., Han, F. and Ge, J. 2017. Integrative and quantitative evaluation of the efficacy of his bundle related pacing in comparison with conventional right ventricular pacing: a meta-analysis. *BMC Cardiovascular Disorders* 17(1), p. 221.

Zanon, F., Bacchiega, E., Rampin, L., Aggio, S., Baracca, E., Pastore, G., Marotta, T., Corbucci, G., Roncon, L., Rubello, D. and Prinzen, F.W. 2008. Direct His bundle pacing preserves coronary perfusion compared with right ventricular apical pacing: a prospective, cross-over mid-term study. *Europace* 10(5), pp. 580–587.

Zanon, F., Baracca, E., Aggio, S., Pastore, G., Boaretto, G., Cardano, P., Marotta, T., Rigatelli, G., Galasso, M., Carraro, M. and Zonzin, P. 2006. A feasible approach for direct his-bundle pacing using a new steerable catheter to facilitate precise lead placement. *Journal of Cardiovascular Electrophysiology* 17(1), pp. 29–33.

Zanon, F., Ellenbogen, K.A., Dandamudi, G., Sharma, P.S., Huang, W., Lustgarten, D.L., Tung, R., Tada, H., Koneru, J.N., Bergemann, T., Fagan, D.H., Hudnall, J.H. and Vijayaraman, P. 2018. Permanent His-bundle pacing: a systematic literature review and meta-analysis. *Europace* 20(11), pp. 1819–1826.

Zareba, W., Klein, H., Cygankiewicz, I., Hall, W.J., McNitt, S., Brown, M., Cannom, D., Daubert, J.P., Eldar, M., Gold, M.R., Goldberger, J.J., Goldenberg, I., Lichstein, E., Pitschner, H., Rashtian, M., Solomon, S., Viskin, S., Wang, P., Moss, A.J. and MADIT-CRT Investigators 2011.

Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 123(10), pp. 1061–1072.