Interventional Electrophysiology in Advanced Heart Disease
Atrial Fibrillation and Heart Failure

A thesis presented for the degree of
Doctor of Medicine (Research) - MD (Res)

Dr David Gareth Jones
BSc (Hons) MBBS MRCP

Imperial College London, National Heart & Lung Institute
and
Royal Brompton & Harefield Hospitals
London, United Kingdom

Supervisors
Dr Tom Wong
Dr Vias Markides
Professor Peter Collins
Acknowledgement

I am most grateful for the longstanding support, guidance and patience of my supervisors, Dr Tom Wong, Dr Vias Markides, and Professor Peter Collins.

I wish to thank all the staff at Royal Brompton & Harefield Hospitals, in particular the departments of cardiac physiology and imaging at both sites, whose generosity of time and effort made the clinical trial possible.

Special thanks go to Dr Shouvik Haldar for his time and effort helping to recruit and follow up patients during the latter part of the trial.

I am also grateful to St Jude Medical UK for their provision of an educational grant, and for the insightful knowledge of Dr Jack Wang and his colleagues.

I wish to thank Professor Nicholas Peters for introducing me to the field of electrophysiology; Dr Margaret Hood and Dr Warren Smith who guided me in my early electrophysiology training in Auckland; and Drs Andrew Marshall, Kevin Fox, Charles Ilsley, Mark Mason, and Wajid Hussain for providing me with their guidance and sharing their expertise throughout my cardiology training.

Finally, I dedicate this thesis to my beloved family and friends.
Declaration

I declare that I am the author of this thesis. The work contained herein is my own, and all content by others is appropriately referenced.

David Gareth Jones

London, September 2012
Abstract

The optimal therapy for atrial fibrillation (AF) associated with heart failure (HF) is unclear. Drug-based rhythm control has not proved clinically beneficial. Catheter ablation-based rhythm control improves cardiac function in HF patients, but impact on physiological performance has not been formally evaluated in a randomised trial.

A randomised trial was designed and conducted, comparing catheter ablation with rate control in adults with symptomatic heart failure, radionuclide left ventricular ejection fraction (EF) ≤35%, and persistent AF. The primary outcome was change in peak oxygen consumption (VO₂) at cardiopulmonary exercise test. Secondary endpoints included change in quality of life (Minnesota), 6-minute walk, BNP, and EF. Patients were followed-up for 12 months, and results analysed by intention-to-treat.

52 patients (63±9y, EF 24±8%, VO₂ 17.3±5.1ml/kg/min) were randomised, 26 to each arm. In the ablation arm, at 12 month follow up, 88% maintained SR, with a single procedure success of 69%. In the rate control arm, rate criteria were achieved in 96% at 12 months. At 12 months, peak VO₂ had increased by 2.13 (95%CI -0.1 to 4.36) ml/kg/min in the ablation arm, compared with a decrease (-0.94ml/kg/min, 95%CI -2.21 to 0.32) under rate control: mean benefit of ablation +3.07ml/kg/min, 95% CI 0.56-5.59, p=0.018. The change appeared progressive, with a difference of only 0.79ml/kg/min at 3 months (95% CI -1.01 to 2.60, p=0.38). Compared with rate control, ablation reduced 12-month Minnesota score (p=0.019) and BNP (p=0.045), and showed trends toward increased 6 min walk distance (p=0.095) and EF (p=0.055). LA size fell significantly after ablation (p=0.001).

Catheter ablation of persistent AF in patients with HF, with the ablation strategy achieving sinus rhythm in the majority, improves prognostically important objective cardiopulmonary exercise performance, symptoms and neurohormonal status. The effects are clear at 1 year but less distinct earlier, suggesting a period of cardiac remodelling and recovery.
Table of contents

Acknowledgement .................................................................................................................. 2

Declaration .............................................................................................................................. 3

Abstract .................................................................................................................................. 4

Table of contents ...................................................................................................................... 5

List of figures ........................................................................................................................ 12

List of tables .......................................................................................................................... 14

1 Introduction ......................................................................................................................... 15

1.1 Background ....................................................................................................................... 15

1.2 Atrial fibrillation in heart failure .................................................................................... 16

  1.2.1 Impact on morbidity and mortality ............................................................................. 17

  1.2.2 Atrial fibrillation promoting heart failure ................................................................. 19

  1.2.3 Heart failure promoting atrial fibrillation ................................................................. 20

1.3 Management of atrial fibrillation ................................................................................... 23

  1.3.1 Atrial fibrillation in context ...................................................................................... 23

  1.3.2 Medical therapy ......................................................................................................... 25

  1.3.3 Non-medical therapy ................................................................................................. 31

  1.3.4 Rate versus rhythm control ...................................................................................... 34

1.4 Interventional Electrophysiology ................................................................................... 42

  1.4.1 Historical Background .............................................................................................. 42

  1.4.2 Radiofrequency Ablation .......................................................................................... 42

  1.4.3 Development of AF ablation .................................................................................... 43

  1.4.4 Pulmonary Vein Isolation .......................................................................................... 47
1.4.5 Linear lesions.................................................................48
1.4.6 Complex fractionated electrograms........................................53
1.4.7 Mapping technologies.......................................................55
1.4.8 Complications of AF ablation .............................................56
1.5 Conclusion and hypothesis.....................................................57
1.5.1 Main hypothesis...............................................................58
1.5.2 Secondary aim and hypothesis.............................................58

2 Clinical trial design and methods ..............................................59
2.1 Introduction ........................................................................59
2.2 Clinical trial design ................................................................60
  2.2.1 Choosing a study population..............................................60
  2.2.2 Outcome measures..........................................................63
  2.2.3 Ethical approval and registration.......................................66
  2.2.4 Recruitment.....................................................................66
2.3 Baseline Investigations...........................................................67
  2.3.1 Radionuclide ventriculography (RNV).................................67
  2.3.2 Cardiopulmonary exercise test (MVO$_2$)............................68
  2.3.3 Quality of Life score (Minnesota LHFQ).............................69
  2.3.4 Blood tests and biomarkers...............................................69
  2.3.5 Holter monitoring..............................................................69
  2.3.6 Six minute walk test ..........................................................70
  2.3.7 Transthoracic echocardiogram............................................70
2.4 Randomisation Protocol.........................................................71
2.5 Post randomisation care .........................................................71
  2.5.1 Medical therapy (rate-control) group ....................................71
  2.5.2 Catheter ablation group.......................................................72
2.6 Catheter ablation protocol.......................................................73
2.7 Follow-up visits ........................................................................................................................................ 76
2.8 Power calculations and statistical analysis ................................................................................................. 77
  2.8.1 Power calculation .................................................................................................................................. 77
  2.8.2 Statistical analysis ............................................................................................................................... 78
3 High density mapping in human atria ............................................................................................................ 80
  3.1 Abstract .................................................................................................................................................... 80
    3.1.1 Introduction ......................................................................................................................................... 80
    3.1.2 Methods ............................................................................................................................................ 80
    3.1.3 Results ............................................................................................................................................... 80
    3.1.4 Conclusions ..................................................................................................................................... 81
  3.2 Background .............................................................................................................................................. 82
  3.3 Methods ................................................................................................................................................... 83
    3.3.1 Patient population ............................................................................................................................... 83
    3.3.2 Electrophysiology study and ablation procedure ............................................................................... 83
    3.3.3 High density mapping ...................................................................................................................... 84
    3.3.4 Activation mapping .......................................................................................................................... 85
    3.3.5 Complex fractionated electrogram (CFE) mapping ......................................................................... 86
    3.3.6 Radiofrequency ablation ................................................................................................................ 87
  3.4 Results .................................................................................................................................................... 87
    3.4.1 Group Results ..................................................................................................................................... 87
    3.4.2 Macro re-entrant tachycardias ......................................................................................................... 89
    3.4.3 Focal AT ............................................................................................................................................ 91
    3.4.4 Non-sustained AT ............................................................................................................................. 92
  3.5 Atrial fibrillation ....................................................................................................................................... 94
  3.6 Discussion ............................................................................................................................................... 98
    3.6.1 Benefits over existing technologies ................................................................................................ 99
    3.6.2 Emerging technologies .................................................................................................................... 101
3.6.3 Complications and safety .................................................................................................................................................. 101
3.6.4 Limitations ......................................................................................................................................................................... 102

3.7 Conclusion ........................................................................................................................................................................... 102

4 The impact of catheter ablation upon the AF substrate in heart failure .......... 104

4.1 Abstract ................................................................................................................................................................................ 104

4.1.1 Introduction ....................................................................................................................................................................... 104

4.1.2 Methods ........................................................................................................................................................................... 104

4.1.3 Results .............................................................................................................................................................................. 104

4.1.4 Conclusions ..................................................................................................................................................................... 105

4.2 Background ........................................................................................................................................................................ 106

4.3 Methods ............................................................................................................................................................................... 107

4.3.1 Patient population ............................................................................................................................................................ 107

4.3.2 Electrophysiology Procedure ........................................................................................................................................ 108

4.3.3 Complex fractionated electrogram (CFE) mapping ........................................................................................................ 109

4.3.4 Catheter ablation protocol ................................................................................................................................................ 111

4.3.5 Data analysis ..................................................................................................................................................................... 115

4.3.6 Statistical analysis ............................................................................................................................................................. 121

4.3.7 Follow-up ........................................................................................................................................................................... 122

4.4 Results .................................................................................................................................................................................. 123

4.4.1 Catheter ablation procedure ........................................................................................................................................... 123

4.4.2 Mapping procedure .......................................................................................................................................................... 123

4.4.3 Clinical outcome .............................................................................................................................................................. 127

4.5 Discussion ............................................................................................................................................................................. 131

4.5.1 Ablation of complex fractionated electrograms ........................................................................................................... 131

4.5.2 Linear lesions .................................................................................................................................................................... 133

4.5.3 Sequence of ablation in a stepwise approach .................................................................................................................. 134

4.5.4 Limitations ........................................................................................................................................................................ 135
5 The ARC-HF trial results .................................................................................. 137

5.1 Abstract ........................................................................................................... 137

5.1.1 Background .................................................................................................... 137

5.1.2 Methods ......................................................................................................... 137

5.1.3 Results .......................................................................................................... 137

5.1.4 Conclusions .................................................................................................. 138

5.2 Background ...................................................................................................... 139

5.3 Methods .......................................................................................................... 139

5.4 Results ............................................................................................................. 139

5.4.1 Primary end-point ......................................................................................... 142

5.4.2 Secondary endpoints ..................................................................................... 145

5.4.3 Other parameters .......................................................................................... 148

5.4.4 Rate-control ................................................................................................ 150

5.4.5 Catheter Ablation ........................................................................................ 151

5.4.6 Composite Endpoint for Major Adverse Clinical Events ............................ 154

5.5 Discussion ......................................................................................................... 156

6 Imaging in atrial fibrillation and heart failure .................................................... 158

6.1 Abstract .......................................................................................................... 158

6.2 Background ..................................................................................................... 158

6.3 Methods .......................................................................................................... 160

6.3.1 Radionuclide ventriculography (RNV) ......................................................... 160

6.3.2 Transthoracic echocardiography ................................................................ 161

6.3.3 Statistical analysis ....................................................................................... 162

6.4 Results ............................................................................................................. 162

6.4.1 Radionuclide ventriculography .................................................................... 162

6.4.2 Echocardiography ....................................................................................... 166
6.4.3 Reliability and co-relation of estimates of LV function ........................................ 170
6.4.4 Correlation with physiological outcomes/biomarkers ........................................ 174

6.5 Discussion ........................................................................................................... 176

6.6 Conclusion .......................................................................................................... 180

7 Biomarkers in atrial fibrillation and heart failure .............................................. 181

7.1 Abstract ............................................................................................................. 181

7.2 Background ......................................................................................................... 181

7.3 Methods .............................................................................................................. 184

7.3.1 Study population ............................................................................................. 184

7.3.2 Sample acquisition .......................................................................................... 184

7.3.3 Laboratory assays ............................................................................................ 185

7.3.4 Statistical analysis ........................................................................................... 185

7.4 Results ................................................................................................................. 187

7.4.1 Mid-regional atrial natriuretic peptide (MR-proANP) ....................................... 190

7.4.2 Apelin .............................................................................................................. 191

7.4.3 B-type natriuretic peptide (BNP) .................................................................... 192

7.4.4 Interleukin-6 (IL-6) ....................................................................................... 193

7.4.5 Correlation of biomarkers with ARC-HF endpoints ....................................... 194

7.5 Discussion .......................................................................................................... 196

7.5.1 Limitations .................................................................................................... 198

7.6 Conclusion .......................................................................................................... 200

8 Discussion ............................................................................................................. 201

8.1 The ARC-HF trial ............................................................................................... 201

8.1.1 Management of AF ......................................................................................... 202

8.1.2 Objective exercise performance ..................................................................... 202

8.1.3 Secondary endpoints ....................................................................................... 204

8.1.4 The left atrium ............................................................................................... 205
List of figures

Figure 1-1  Prevalence of AF in major heart failure trials. ................................................................. 16
Figure 1-2  Mortality in the COMET trial ....................................................................................... 18
Figure 1-3  Atrial fibrillation – the scale of the problem ................................................................. 25
Figure 1-4  AFFIRM trial: multivariate analysis of outcomes. .......................................................... 36
Figure 1-5  AF-CHF trial: main endpoints. ....................................................................................... 36
Figure 1-6  Impact of AF ablation on LV function ........................................................................... 40
Figure 1-7  The corridor procedure for atrial fibrillation ............................................................... 44
Figure 1-8  The Cox-Maze III procedure ....................................................................................... 45
Figure 1-9  Roof line ....................................................................................................................... 49
Figure 1-10 Mitral line ..................................................................................................................... 50
Figure 3-1  Spiral high-density mapping catheter ........................................................................... 85
Figure 3-2  Fontan atrial tachycardia ............................................................................................. 90
Figure 3-3  Left atrial tachycardia after previous AF ablation ....................................................... 91
Figure 3-4  Focal tachycardia in congenitally corrected transposition ........................................... 92
Figure 3-5  Non-sustained atrial tachycardia .................................................................................. 94
Figure 3-6  Complex fractionated electrogram maps in persistent AF ......................................... 97
Figure 4-1  Summary of ablation and CFE mapping protocol ..................................................... 110
Figure 4-2  Pulmonary vein isolation during atrial fibrillation ....................................................... 113
Figure 4-3  Confirmation of linear lesion block ............................................................................. 114
Figure 4-4  Surface marker annotation of CFE ............................................................................. 117
Figure 4-5  Sequential LA CFE maps ............................................................................................. 118
Figure 4-6  Sequential RA CFE maps ............................................................................................. 119
Figure 4-7  Left atrial segmentation ............................................................................................... 120
Figure 4-8  Right atrial segmentation ............................................................................................ 121
Figure 4-9  Impact of stepwise ablation on left atrial CFE-area ................................................... 124
Figure 4-10 Impact of stepwise ablation on right atrial CFE-area ................................................... 125
Figure 4-11  Atrial arrhythmia-free survival .................................................................128
Figure 4-12  Unblocked linear lesions: impact on success ........................................130
Figure 4-13  AF termination: impact on success ..........................................................130
Figure 5-1  CONSORT diagram for ARC-HF .................................................................140
Figure 5-2  Change in peak oxygen consumption (primary endpoint) .....................142
Figure 5-3  Individual patient responses in peak VO₂ – rate control group ................143
Figure 5-4  Individual patient responses in peak VO₂ – ablation group .......................144
Figure 5-5  Change in Minnesota LHFQ score (secondary endpoint) .........................145
Figure 5-6  Change in plasma BNP (secondary endpoint) ..........................................146
Figure 5-7  Change in 6-minute walk distance (6MWD, secondary endpoint) ..............147
Figure 5-8  Change in left atrial (LA) size .................................................................149
Figure 5-9  Single-procedure arrhythmia-free survival at 1 year ................................153
Figure 5-10  MACE-free survival by treatment group .................................................155
Figure 6-1  Radionuclide ventriculography - example 1 ..............................................163
Figure 6-2  Radionuclide ventriculography - example 2 ..............................................164
Figure 6-3  Left ventricular ejection fraction: impact of ablation vs. rate control ........166
Figure 6-4  Atrial size: impact of ablation vs. rate control ...........................................167
Figure 6-5  Reliability and correlation of LV parameters – baseline data ....................171
Figure 6-6  Reliability and correlation of LV parameters – 12-month follow-up data ......172
Figure 6-7  Scatter plots and correlation: atrial fibrillation and sinus rhythm ...............173
Figure 7-1  ARCHF biomarker sub-study flowchart ..................................................189
Figure 7-2  Mid-Regional proAtrial Natriuretic Peptide (MR-proANP) .........................190
Figure 7-3  Apelin ...........................................................................................................191
Figure 7-4  B-type Natriuretic Peptide (BNP) .............................................................192
Figure 7-5  Interleukin-6 (IL-6) ....................................................................................194
# List of tables

<table>
<thead>
<tr>
<th>Table 3-1</th>
<th>Patient characteristics and summary of ablation strategy</th>
<th>.........................................................88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 4-1</td>
<td>Baseline patient characteristics</td>
<td>........................................................................107</td>
</tr>
<tr>
<td>Table 4-2</td>
<td>Cox regression analysis model</td>
<td>........................................................................129</td>
</tr>
<tr>
<td>Table 5-1</td>
<td>Baseline characteristics</td>
<td>........................................................................141</td>
</tr>
<tr>
<td>Table 6-1</td>
<td>Radionuclide ventriculography data</td>
<td>........................................................................165</td>
</tr>
<tr>
<td>Table 6-2</td>
<td>Echocardiographic data</td>
<td>........................................................................168</td>
</tr>
<tr>
<td>Table 6-3</td>
<td>Correlation of LVEF measurements with other ARC-HF endpoints</td>
<td>.........................................................175</td>
</tr>
<tr>
<td>Table 7-1</td>
<td>Baseline characteristics</td>
<td>........................................................................188</td>
</tr>
<tr>
<td>Table 7-2</td>
<td>Correlation of biomarker measurements with other ARC-HF endpoints</td>
<td>..................195</td>
</tr>
</tbody>
</table>
1 Introduction

1.1 Background

In An anatomical disquisition on the motion of the heart and blood in animals (1628), William Harvey wrote:

“It is...evident that the auricles pulsate, contract...and throw the blood into the ventricles. The auricles are prime movers of the blood...whence they are subservient to sending the blood into the ventricles, which...more readily and forcibly expel the blood already in motion; just as the ball-player can strike the ball more forcibly and further if he takes it on the rebound than if he simply threw it”

Early physiological studies with mammalian heart preparations suggested that the systolic contraction of the atria contributed up to 50% of ventricular filling and subsequent ventricular stroke volume. Although this contribution was found to be nearer 10-15% in vivo with early pacing studies, it became apparent that the ‘primer pump’ function of the atrium is increasingly important in cardiac disease and during exercise, contributing upwards of 30% towards cardiac output in these states.

Thomas Lewis was one of the first to recognise how this ‘primer pump’ function is lost in atrial fibrillation (AF) leading to a drop in cardiac output. In AF, the atria undergo rapid and chaotic excitation at rates of 300-600 per minute. In most circumstances the atrioventricular (AV) node prevent conduction of many of these impulses, thereby protecting the ventricles from life threatening rapidity. The ventricles are usually subject, however, to excitation at rates higher than normal, particularly during exercise, and to beat-to-beat variability leading to an irregular pulse and suboptimal haemodynamics. It is no surprise therefore that the co-
existence of this condition with reduced cardiac pump function can have significant consequences.

1.2 Atrial fibrillation in heart failure

Atrial fibrillation (AF) and chronic heart failure (HF) represent two major cardiovascular conditions associated with significant morbidity and mortality,\(^9\),\(^10\) and which impose a heavy burden on healthcare systems.\(^11\),\(^12\) They often coexist (Figure 1-1): AF is present in 10-15% of those with mild heart failure (NYHA II-III) and up to 50% of patients severe heart failure (NYHA IV).\(^13\)\^-\(^19\) In the Framingham cohort 22% of heart failure patients, without prior AF, developed the arrhythmia within just over 4 years.\(^20\)

![Prevalence of AF in major heart failure trials.](image)

**Figure 1-1 Prevalence of AF in major heart failure trials.**

Reproduced with permissions.\(^13\),\(^21\) CHF-STAT = Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy;\(^16\) CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study;\(^14\) DIAMOND CHF = Danish Investigations of Arrhythmia and Mortality on Dofetilide Congestive Heart Failure study;\(^22\) GESICA = Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina;\(^17\) SOLVD = Studies of Left Ventricular Dysfunction;\(^18\),\(^23\) V-HeFT = Vasodilator in Heart Failure Trial.\(^15\)
1.2.1 Impact on morbidity and mortality

The onset of AF in heart failure is associated with detrimental haemodynamic effects, increased hospitalisation, and increased mortality.\textsuperscript{18, 24, 25} Indeed, AF occurring in previously normal hearts can in some cases cause a (‘tachycardia-induced’) cardiomyopathy due to excessive ventricular rate.\textsuperscript{26, 27} The interplay between the two conditions can produce a vicious cycle of deterioration.\textsuperscript{28}

It remains unclear whether AF is an independent prognostic marker, or whether it is merely a marker of associated co-morbidity and disease severity. In the Vasodilator in Heart Failure trial, AF had no independent effect on mortality,\textsuperscript{15} and in a study of patients referred for transplant assessment, AF was not independently associated with reduced event-free survival.\textsuperscript{29} On the contrary, several studies have shown AF to be an independent prognostic marker in heart failure patients.

In the SOLVD study, baseline atrial fibrillation was an independent predictor of all-cause mortality (relative risk 1.34) – predominantly due to pump failure, and of hospitalization for heart failure.\textsuperscript{18} In the COMET study, AF at baseline was a univariate, but not multivariate, predictor of mortality (Figure 1-2a). New onset AF during the study was, however, a strong predictor of all-cause mortality in follow-up (Figure 1-2b).\textsuperscript{25}

Those with preserved systolic function may not fare better: in patients presenting to the emergency department with AF and heart failure, 5 year mortality was similar for those with depressed and preserved ejection fraction.\textsuperscript{30} Indeed, the CHARM data suggested AF was associated with a greater risk of major adverse events (cardiovascular death, hospitalization for worsening heart failure, and all-cause mortality), compared with sinus rhythm, and the effect was greater in those with preserved systolic function (EF>40%).\textsuperscript{31}
A further possible indicator of the negative effect of AF is the impact on mortality in the SCD-HeFT trial. In contrast to patients in sinus rhythm, the presence of AF was associated
with no mortality benefit from ICD implantation, in addition to being associated with increased frequency of both appropriate and inappropriate shocks. However, the number of patients in the AF sub-group was relatively small to draw definitive conclusions.

Reassuringly, the development of AF does not appear to negate the mortality reduction seen with cardiac resynchronisation therapy (CRT), although CRT does not appear to have a beneficial effect in reducing AF occurrence in the heart failure population. Restoration of sinus rhythm has been associated with improved survival. In the DIAMOND trial, which enrolled patients with EF <35% in NYHA class III and IV, maintenance of sinus rhythm was an independent marker of survival (risk ratio=0.44; 95% CI, 0.30-0.64; p<0.0001). Importantly, however, use of dofetilide (active treatment), like all other tried anti-arrhythmic agents examined to date, was not in itself associated with improved mortality.

1.2.2 Atrial fibrillation promoting heart failure

The onset of atrial fibrillation is associated with several factors that may impair cardiac function. These include loss of atrial contraction, irregularity of ventricular contraction, and rapid heart rate. The rapid heart rate can in itself lead to the development of a tachycardia-related cardiomyopathy. There is also evidence that AF leads to a significant decline in peak oxygen consumption compared with sinus rhythm.

Loss of atrial contraction leads to a reduction in end-diastolic filling and thus lowers stroke volume and cardiac output. The reduction in stroke volume may be greater than 20% due to this alone, and is of even greater significance in patients with low cardiac output at baseline and those with impaired diastolic filling.

Irregularity of ventricular contraction impairs haemodynamics independently of overall heart rate, and may also increase cardiac sympathetic activity. There are changes in coronary
blood flow, with increased resistance and reduced flow reserve. Together with increased cardiac work, all these factors may contribute to the development of angina in some AF patients – even in the presence of angiographically normal coronary arteries.\textsuperscript{10} Regularisation of the heart rate has been shown to improve left ventricular function.\textsuperscript{41}

\textit{Tachycardia} is associated with reduced diastolic time and thus left ventricular filling and stroke volume. AF patients may have high resting heart rates, and have suboptimal cardiac output with further increases in rate.\textsuperscript{42} Even in patients with controlled resting rates, there may be a disproportionate increase in heart rate on minimal activity, a finding exaggerated in those with heart failure – at least in part due to sympathetic drive.\textsuperscript{43} Prolonged periods of tachycardia in atrial fibrillation and other atrial arrhythmias, notably atrial flutter,\textsuperscript{44} have been recognised to lead to development of a cardiomyopathy. Restoration of sinus rhythm, control of ventricular rate by drugs or catheter ablation of the atrioventricular junction, have been shown to achieve clinical recovery in patients initially thought to have underlying idiopathic cardiomyopathy, ultimately leading to a revision of diagnosis to \textit{tachycardia-related cardiomyopathy}.\textsuperscript{26, 27} Equally, it is not uncommon for tachycardia to decompensate a pre-existing cardiomyopathy.

\textbf{1.2.3 Heart failure promoting atrial fibrillation}

It is well established that both systolic and diastolic heart failure are risk factors for the development of AF, and for the recurrence of AF after electrical cardioversion.\textsuperscript{9, 45}

The underlying mechanisms that lead to the development of AF are complex, under continued investigation, and an area of debate. Our current understanding of the mechanisms of AF includes contributions from the following mechanisms:
1.2.3.1 Focal initiation

Rapid atrial activity may arise focally by means of increased automaticity, triggered activity, or local re-entry, usually from the region of pulmonary veins.\textsuperscript{46, 47} Increased atrial pressure, so-called ‘stretch’, is known to increase the frequency of electrical discharge from the pulmonary veins, and may contribute to both initiation and maintenance of AF.\textsuperscript{48}

1.2.3.2 An atrial substrate capable of maintaining AF

Re-entry of \textit{multiple wavelets} was first suggested by Moe\textsuperscript{49} and then validated by Allessie in canine then human hearts.\textsuperscript{50} In this state, there must be multiple simultaneous re-entrant wavelets to maintain fibrillation. Prerequisites for re-entry are: presence of central unexcitable tissue, unidirectional conduction block, and maintenance of excitable tissue ahead of the wavefront (‘excitable gap’). Shortening of the local refractory period, and slowing of conduction are hence pro-arrhythmic. In addition, a critical mass of tissue is needed for simultaneous wavelet coexistence, so atrial dilatation and/or hypertrophy also lends itself to maintenance of AF.

Electrical \textit{rotors},\textsuperscript{51} which may maintain atrial fibrillation in the presence or absence of multiple wavelet re-entry, could contribute, although their existence and nature remains debated.

The autonomic nervous system may play a dominant role both in the process of focal initiation of atrial fibrillation, and in the process of maintenance of the arrhythmia. In particular, simultaneous sympathetic and parasympathetic discharge to the atrium can contribute towards increased automaticity, triggered activity, shortened refractoriness and re-entry.
1.2.3.3 Remodelling

A change in atrial substrate follows the onset of AF, can be both structural and electrical, and encourages its persistence. This is termed remodelling.

Reduction of L-type Ca\(^{2+}\) and transient outward K\(^{+}\) currents appear of particular importance in electrical remodelling, being associated with more easily inducible and longer-lasting AF in animal models, and probably playing a role in the progression from paroxysmal to persistent AF that is observed clinically ("AF begets AF"). Alterations in gap junctions expression and distribution are also observed in patients with AF, which may contribute to arrhythmogenesis via changes in intercellular conduction and hence intra-atrial conduction.

Atrial dilatation can accompany the increased diastolic pressures in the failing heart. Acute atrial dilatation in the isolated rabbit heart shortens the atrial refractory period and markedly increases AF inducibility. Conversely, an acute increase in atrial pressure in dogs is associated with lengthening of the atrial refractory period. This might not be expected to be pro-arrhythmic, but further investigation in the canine model has found increased dispersion of refractoriness, which was associated with greater AF inducibility. Similar changes appear to occur in humans, and atria in heart failure patients appear to have increased refractoriness, regional slowing of conduction, and areas of scar. Fibrosis leads to impaired cell-cell coupling, causing inhomogeneity of conduction, further contributing to a pro-fibrillatory state.

The nature of remodelling differs in heart failure and non-heart failure animal models of AF. In the non-heart failure goat and dog model, where repeated bursts of rapid atrial pacing (RAP) are used to induce and maintain the arrhythmia, the electrical changes that occur appear reversible within a few days, and fibrosis appears similar to controls. In the heart failure-model in dogs, prolonged rapid ventricular pacing is used to induce
cardiomyopathy: in one study the effect on AF inducibility in heart failure-dogs at 5 weeks was similar to that at 1 week in RAP-dogs (the delayed effect might be expected due to the ‘indirect’ nature of atrial perturbation in the former), and atrial fibrosis was markedly increased.\textsuperscript{61} In the same model, significant changes in ion current densities occur, but in those allowed to recover from ventricular pacing, these electrical changes reverse completely. However, the duration of induced AF and fibrosis did not recover, perhaps suggesting a primary contribution of \textit{structural remodelling} to AF maintenance in heart failure.\textsuperscript{62}

Angiotensin II, along with various protein kinase signalling pathways, has been implicated in the structural remodelling process. Myocardial stretch increases local protein kinase and angiotensin II levels,\textsuperscript{63, 64} which are associated with development of atrial fibrosis.\textsuperscript{65} As inhibition of endogenous angiotensin II can prevent the shortening of refractoriness after rapid atrial pacing, it may be that angiotensin II is also involved in the mechanism of \textit{electrical} remodelling.\textsuperscript{66} Either way, this underlies the interest in modulation of this angiotensin activity as a means of reducing AF recurrence.

\section*{1.3 Management of atrial fibrillation}

\subsection*{1.3.1 Atrial fibrillation in context}

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting 1% of the general population. Recent studies indicate that the lifetime risk may exceed 20\%.\textsuperscript{67} Prevalence increases with age, rising to 8\% over 80y,\textsuperscript{68} with median age 75y.\textsuperscript{69} It is estimated that there are 2.3 million people in the United States, and 4.5 million in the European Union with AF.\textsuperscript{10} The prevalence is increasing – in part due to population aging, but also due to an increase in age-adjusted AF incidence – which clearly has significant implications for health service planning during this century (Figure 1-3).
AF is associated with increased mortality. In the Framingham Study, AF conferred a relative all-cause mortality risk of 1.8. Much of this is attributable to stroke, the risk of which is increased 5-fold in those with AF – but varies according to age and co-morbidities.

AF is well known to be associated with several conditions, including hypertension, heart failure, coronary artery disease, valvular heart disease, and thyrotoxicosis. Many of these conditions can cause mechanical (including stretch and fibrosis) and electrical changes (remodelling) that, when coupled with a genetic predisposition and triggered by events that may be in part mediated by changes in cardiac autonomic activity, can precipitate AF. AF in itself enhances further remodelling, thus encouraging its own perpetuation. The pathogenesis of AF involves a complex interplay between mechanisms of initiation (extremely rapid electrical activity arising from pulmonary veins) and mechanisms of perpetuation (reentry or circus movement of electrical waves in the atria). These are in addition influenced by genetic makeup, atrial stretch, fibrosis, changes in the electrical properties of the heart, and autonomic nerves. It is no surprise that AF is highly heterogeneous and that attempting to combat it is highly challenging.
Figure 1-3  **Atrial fibrillation – the scale of the problem**

Projected number of persons with AF in the United States between 2000 and 2050, assuming no further increase in age-adjusted AF incidence (solid curve) and assuming a continued increase in incidence rate as evident in 1980 to 2000 (dotted curve).

Reproduced with permission from Miyasaka et al. 2006.  

### 1.3.2 Medical therapy

Optimal management requires

- Recognition of AF

- Assessment and optimization of thromboembolic risk

- Treatment of heart failure and its causes

- Treatment of AF (rate and/or rhythm control) and its causes

Although AF can be asymptomatic, in the setting of heart failure the onset of AF is often associated with significant symptomatic and prognostic decline. Increased recognition of AF
is facilitated by more frequent assessment of heart failure patients, and by utilizing the data stored in implanted devices.

Contemporary heart failure therapies already appear to have some impact in reducing AF incidence. *Renin-angiotensin system blockade* may reduce AF incidence in patients with hypertension,\(^\text{10, 72-74}\) and those with systolic dysfunction. The effect of renin-angiotensin modulation on established AF is not fully established. Although there appears to be a small increase in sinus rhythm maintenance after cardioversion,\(^{74}\) in non-randomized studies of patients undergoing catheter ablation, the use of ACE inhibitors or ARBs did not influence outcome at 1-year.

*Beta-blockers* are now recommended in most heart failure patients, and a recent meta-analysis of seven randomized placebo-controlled trials showed a significant reduction in AF incidence.\(^{75}\) Possible mechanisms include reduction of adverse ventricular remodelling, counteraction of sympathetic hyperactivity,\(^{76}\) ion channel effects,\(^{77}\) and reduction of atrial ischemia.\(^{78}\)

### 1.3.2.1 Anticoagulation

AF is a major cause of thromboembolic stroke, conferring a five-fold increase in annual risk. Stasis in the non-contracting atrium encourages thrombus formation, most commonly in the left atrial appendage. Hypercoagulability and endothelial dysfunction also play a role.\(^{10}\) The presence of heart failure further increases the stroke risk 3-fold.\(^{79}\)

Thromboembolic prophylaxis with warfarin reduces the risk of stroke. Although heart failure may increase the risk of major bleeding on anticoagulation,\(^{80}\) the balance of benefit/risk is in favour of anticoagulation in the heart failure population as a whole.\(^{81}\)
Stroke risk assessment may be performed using the CHADS\textsubscript{2} score (based on age, hypertension, diabetes, prior stroke or TIA and presence of chronic heart failure). The current recommendations for thromboprophylaxis in AF patients from the ACC/AHA/ESC Task force\textsuperscript{10} advocate warfarin for heart failure patients either aged over 65y, or with LVEF<35%. Those with paroxysmal AF should be stratified and treated in the same way as those with persistent AF.

**1.3.2.2 Rate control**

Drugs achieve control of the ventricular rate during AF by increasing refractoriness of the atrioventricular node. Ideally, rate-controlling agents should control the heart rate at rest and on exercise in a graded manner, but without negative inotropic effect.

Management of acute heart failure when AF is present is challenging as the two conditions may contribute to a vicious cycle of deterioration. Restoration and maintenance of sinus rhythm may be difficult or dangerous. In the absence of anticoagulation, in those without a clear history of AF onset within the last 48 hours, cardioversion requires prior transoesophageal echocardiography to rule out atrial thrombus – but this may not be feasible or appropriate. Moreover, AF often rapidly recurs in decompensated patients. In all these circumstances, early control of the ventricular rate plays a key role.

Suggested targets for rate-control are resting heart rate 60-80 beats/min, and 90-115 on moderate exercise.\textsuperscript{10} In the AFFIRM trial, goals were pre-defined as <80 bpm at rest, and <110bpm during 6-minute walk.\textsuperscript{82} In retrospective analysis of the RACE trial (target <100bpm at rest only) and AFFIRM data,\textsuperscript{83} the primary endpoint of mortality, cardiovascular hospitalization, and myocardial infarction did not differ between those who achieved or did not achieve rate target.
It is uncertain whether goals should be the same in heart failure. The on-going RACE II study, prospectively comparing ‘strict’ versus ‘lenient’ rate control (including in heart failure patients), may provide further guidance. Rate control during AF is also particularly important in patients with implanted devices to allow optimal benefit from cardiac resynchronization therapy (CRT) and to reduce inappropriate ICD shocks.

In heart failure patients, digoxin improves symptoms and reduces hospitalizations, albeit with a neutral effect on mortality. It can control the ventricular rate at rest but not during exercise. Digoxin is usually well tolerated, partly due to its lack of negative inotropic effect, may be the safest drug to initiate first, and is currently recommended as part of a rate-control strategy for those with LV dysfunction.

*Beta-blockers* control the ventricular rate at rest and on exertion, improve symptoms, and are particularly useful as *combination* therapy with digoxin, and are the agents of choice for rate control in patients with heart failure. They may also reduce ectopic triggers of AF.

Although the principal role of *amiodarone* in AF is as a rhythm controller, it can provide a modest degree of rate-control and may have a role especially where beta-blockers are not tolerated.

The use of *non-dihydropyridine calcium blockers* in patients with significant systolic heart failure is controversial, and caution should be exercised. The principal concern is the negative inotropic effect, which is more marked with *verapamil* than *diltiazem*. Acutely, like beta-blockers, the negatively inotropic effects of calcium blockers may be offset by the reduction in heart rate. Furthermore, diltiazem-related vasodilatation reduces afterload, leading to beneficial haemodynamics and may improve overall LV performance. Intravenous diltiazem has been studied in critically ill patients: in patients with significant systolic dysfunction, it achieved rate control with no worsening of heart failure, but caused
hypotension in 8%. In comparison with intravenous amiodarone it could control the heart rate faster and more effectively, but hypotension required discontinuation of therapy in 30% of patients. Long term use appears unsafe: although oral diltiazem has shown some benefit in early dilated cardiomyopathy, it is associated with poor outcomes in those with ischemic systolic heart failure.

In the non-heart failure population, oral diltiazem is safe and highly effective, and may be superior to beta blockers for exercise rate-control. Its use is reasonable in patients with relatively preserved systolic function, particularly if intolerant of other drugs, and should be considered after beta blockers/digoxin to assist rate control if a tachycardia-cardiomyopathy is suspected.

Combination therapy increases the possibility of significant bradycardia, due to effects on the sinus node (paroxysmal AF) or AV node (persistent AF). Nonetheless, combination treatment can be useful in selected cases. Conversely, some patients require pacemaker implantation for symptomatic bradycardia even without rate controlling drugs, or may have periods of tachycardia as well as bradycardia requiring hybrid treatment with rate slowing agents and a pacemaker.

**1.3.2.3 Rhythm control**

**1.3.2.3.1 Electrical cardioversion**

The presence of even mild-moderate heart failure reduces the likelihood of successful cardioversion and maintenance of sinus rhythm. Also, the risks of sedation and/or general anaesthetic are increased in those with severe heart failure, and attempts should be made to control heart failure prior to cardioversion.
1.3.2.3.2 Anti-arrhythmic drugs

Pharmacologic therapy may be preferable to electrical cardioversion in that it avoids general anaesthesia and may also help maintain sinus rhythm. Although restoration and maintenance of sinus rhythm is known to be a beneficial prognostic marker, no anti-arrhythmic drug has been proven to directly reduce mortality. The limited efficacy of pharmacologic therapy at restoring sinus rhythm means that from a practical perspective, electrical cardioversion with adjuvant pharmacologic therapy may be a reasonable approach.

The class I drugs flecainide, procainamide and propafenone, whilst suitable and often highly effective treatments for AF in patients with structurally normal hearts, have important negative inotropic effects, are potentially proarrhythmic, and should generally be avoided in heart failure patients, particularly those with previous myocardial infarction.\textsuperscript{101}

Class III agents appear safer in heart failure. Amiodarone, dofetilide, and sotalol can help restore and maintain sinus rhythm. Dofetilide is effective at restoration and maintenance of sinus rhythm and has neutral effect on mortality.\textsuperscript{35} However, the significant incidence of torsade de pointes around the time of initiation necessitates inpatient treatment. Amiodarone reduces incidence of AF in heart failure, and appears similarly neutral on mortality.\textsuperscript{16, 17, 102}

Significant impairment of LV function is unusual and, although sub-group analysis of SCD-HeFT trial data suggested a detrimental effect in NYHA III patients,\textsuperscript{103} amiodarone is currently the safest anti-arrhythmic agent available for use in heart failure.

New antiarrhythmic drugs have been developed – some with multiple ion-channel blocking effects that mimic the action of amiodarone, and some with specificity for atrial ion-channels ($I_{K_{Ach}}$ and $I_{K_{ur}}$). The most prominent of these is dronedarone, a multi-channel blocker similar in chemical structure to amiodarone, but without the iodinated component, was recently introduced and looked promising as a potential alternative antiarrhythmic in an early trial.\textsuperscript{104}
However the ANDROMEDA study,\textsuperscript{105} which evaluated the effect of dronedarone therapy in a cohort of patients with symptomatic severe LV dysfunction, showed excess early mortality due to worsening heart failure and was terminated early. In effect this has ruled out its use in patients with NYHA III/IV heart failure and/or significant LV impairment.

1.3.3 Non-medical therapy

1.3.3.1 Rate control

1.3.3.1.1 AV node ablation and implantation of permanent pacemaker

Patients who require rate control but who remain tachycardic despite optimal pharmacological treatment, have a further option: \textit{radiofrequency catheter ablation of the AV junction}. This necessitates implantation of a permanent pacemaker, but achieves rate control and regularization of the ventricular rate.\textsuperscript{106}

This “ablate and pace” strategy is generally effective and well tolerated, with many studies showing an improvement in quality of life and left ventricular function.\textsuperscript{26, 41, 106} However, a randomized trial (chronic AF, mean NYHA class 2.7) comparing ablation and VVIR pacing with pharmacological treatment showed no benefit on cardiac performance or quality of life,\textsuperscript{107} despite significant improvements in exercise tolerance and symptomatic palpitation. Failure of improvement in EF after this treatment may predict a poorer outcome.\textsuperscript{108}

More recently, the PAVE study looked at the optimal site of ventricular pacing in these patients.\textsuperscript{109} Prompting this were previous studies showing adverse perfusion and haemodynamics with long term right ventricular apical pacing (RVP),\textsuperscript{110} worse clinical outcomes from RVP in the DAVID defibrillator trial,\textsuperscript{111} and symptomatic benefit seen after upgrading from RVP to biventricular pacing (BVP) in a small cohort of ablate/pace patients.\textsuperscript{112} PAVE compared BVP with RVP in 184 patients, and suggested BVP preserves
EF while RVP is associated with falling EF. Six minute walk distance was 53% greater with BVP at 6 months. Subgroup analysis showed the main benefit was in NYHA class II and III, and with EF <45%. There was no significant impact on mortality.

Thus, when heart failure patients are selected for ‘ablate and pace’, implantation of a biventricular system should be seriously considered. Conversely, patients with permanent AF scheduled for implantation of a biventricular device may be considered for ablation of the AV node in order to benefit maximally from cardiac resynchronization unless ventricular rate control is so good that they are unlikely to conduct to the ventricles, even during exercise. However, given the availability of alternative therapies in contemporary era, as discussed below, this permanent and essentially irreversible commitment to pacing-dependency might more appropriately be deferred until proof exists that medical rate-control or alternative rhythm control strategies have failed.

Polymorphic ventricular tachycardia and sudden death can occur after AV junction ablation, but this may be prevented by pacing at a minimum of 80-90 bpm for the first 1-3 months.

1.3.3.2 Rhythm control

1.3.3.2.1 Surgical and catheter ablation

A theoretical solution to prevent maintenance of AF is to reduce electrically contiguous atrial mass. Based on the demonstration of multiple wavelet-AF in canine and subsequently human hearts, the Cox-Maze surgical technique was devised to electrically compartmentalize the atria by ‘cut and sew’. Results from experienced surgical centres are impressive: 5-year AF-freedom is 80-90%, and 68% in those who underwent concomitant mitral valve surgery. Pacemaker implantation rate was 10%, mostly due to underlying sinus node dysfunction, and mortality was low (0.9%) despite concomitant coronary or valve surgery in many. The effect on ventricular function is encouraging: in those with severe preoperative ventricular
impairment (EF <35%, n=11), there was an improvement in mean EF (31 to 53%) which was sustained at follow up. Another potential benefit is amputation of the left atrial appendage and theoretical reduction of stroke risk.

However, many centres have found it difficult to reproduce the results and low complication rates initially reported in expert hands with this complex surgical technique. Alternative methods have been developed, avoiding “cut and sew” and sometimes cardiopulmonary bypass. Bipolar radiofrequency, microwave and cryoablation are widely used in specialist centres, usually with concomitant cardiac surgery. Unipolar radiofrequency ablation is now used infrequently because of the potential for life-threatening oesophageal damage. Further long-term results are awaited.

1.3.3.2.2 Radiofrequency Catheter Ablation

The discovery in the late 1990s that AF could have a focal origin, often in the PV, led to the use of catheter ablation techniques to eliminate abnormal foci, and later to completely isolate the PV from the left atrium. Subsequently, advancing technology has enabled creation of linear atrial lesions similar to those used in surgical maze procedures. In patients with advanced AF, a combination of several ablation targets/techniques may be necessary to modify atrial electrophysiology enough to restore sinus rhythm and prevent AF. Possible ablation strategies include:

- Segmental or circumferential PV isolation
- Linear ablation to partly compartmentalize the atria
- Ablation in areas of slow, heterogeneous conduction (at sites of complex fractionated electrograms)
- Ablation at sites of ganglionic plexi
• Further linear ablation in refractory cases, but risking exclusion of atrial tissue from electrical activation and hence contraction.

These techniques have been greatly facilitated by the development of technologies for non-fluoroscopic catheter navigation and ablation. Systems such as CARTO™ (Biosense-Webster) and NavX™ (St Jude Medical) can localize catheters in a 3-dimensional environment and allow creation of a virtual atrial map. Imaging from CT or MRI can be integrated to improve accuracy.

Importantly, significant complications occur in 2-6% of patients and include transient ischaemic attack or stroke (0.5-1.5%), tamponade (0.5-4%), symptomatic PV stenosis (<1%), and right phrenic nerve palsy (0.3%, usually transient). Procedures are long (several hours), require specialist facilities and expertise, and are modestly more challenging in patients with heart failure, and less effective in those with dilated atria.

There is increasing evidence that restoration of sinus rhythm is desirable, even though studies based on pharmacologic therapy have failed to show a mortality advantage: this may be due to poor efficacy, or pro-arrhythmic and negatively inotropic effects of these drugs. It remains unclear at present whether catheter ablation offers a prognostic advantage, although some small studies have addressed this question in heart failure patients (see section 1.3.4.1).

1.3.4 Rate versus rhythm control

Although rate and rhythm control treatments have been available to treat AF for several decades, a significant evidence base for applying one or other strategy was not present until after the turn of this century.
The issue of rate versus rhythm control as initially investigated by large multicentre studies in the general AF population. Five studies compared rate-control with rhythm-control.\(^{82, 117-120}\)

Perhaps surprisingly, none found an advantage from rhythm-control. In AFFIRM, the largest of these trials, rate control appeared non-inferior to rhythm control, and was associated with fewer hospitalizations, strokes, and episodes of *torsade de pointes*. However, a much greater proportion of patients had anticoagulation withdrawn in the rhythm control arm once rhythm control was achieved, which may in part explain the increased risk of stroke. It was felt that the observed increase in stroke risk (a major adverse outcome) from rhythm control – attributable to cessation of anticoagulation after cardioversion and/or achievement of sinus rhythm – may have been avoided if appropriate anticoagulation had been maintained as in rate-control patients.\(^{121}\) More encouragingly, recent data have shown a *reduced* risk of stroke in a rhythm-control model.\(^{104}\)

Considering the heart failure population, the AFFIRM data was interesting in that rate control was significantly superior in the subgroup of patients without congestive heart failure, whilst those with congestive heart failure showed a trend towards superiority of rhythm control (Figure 1-4). Physicians are often faced with patients who present with exacerbations of heart failure at or soon after the onset of AF. In addition, although controlling the heart rate may counter some of the adverse effects of AF in this population, the loss of atrial contraction persists if AF is accepted. Perhaps on these bases, one might expect that restoring sinus rhythm would be superior to rate control. Naturally, conclusion could not been drawn from this subgroup analysis, and a clinical trial was needed in the heart failure population.
Figure 1-4  AFFIRM trial: multivariate analysis of outcomes.

Note that the presence of congestive heart failure showed a trend towards rhythm control, although this did not reach statistical significance. Reproduced with permission, Copyright Massachusetts Medical Society.

Figure 1-5  AF-CHF trial: main endpoints.

Reproduced with permission, Copyright Massachusetts Medical Society.
The AF-CHF trial was the first to prospectively compare rate and rhythm control specifically in a heart failure population. It randomised 1376 patients with NYHA II-IV functional class heart failure, a left ventricular ejection fraction ≤35%, and a history of AF, to rate control (mostly beta-blockers and digoxin) or rhythm control (mostly amiodarone; up to 2 DC cardioversions could be performed within 3 months of randomisation). There was no difference between the two strategies in terms of death from cardiovascular or all causes, stroke, or worsening heart failure (Figure 1-5). As in previous studies, rhythm control was associated with more hospitalisations, for cardioversion, bradycardia, or adjustment of antiarrhythmics. However, important information such as the effect on quality of life has yet to be published.

This may appear to answer the question of best prognostic treatment strategy for AF in heart failure. Rate control appears a sufficient therapy, and avoids the complications associated with rhythm control. However, another observation, that of the rhythm at outcome in these studies, prompts further evaluation. In AFFIRM, on-treatment analysis showed the presence of sinus rhythm was associated with a 47% reduction in mortality, while use of antiarrhythmic drugs was associated with increased mortality. In the RACE trial in a sub-study of patients in NYHA II/III heart failure, the successful maintenance of sinus rhythm in the rhythm control arm appeared beneficial at follow up, with a trend towards lower mortality, bleeding, heart failure hospitalization, and pacemaker implantation. Purely by intention-to-treat, more cardiovascular deaths, heart failure hospitalization, and bleeding occurred in patients randomized to rate control, whilst thromboembolic complications, drug side effects, and pacemaker implantation were more frequent under rhythm control. Restoration of sinus rhythm was associated with improved survival in the DIAMOND trial, which enrolled patients with EF <35% in NYHA class III/IV. Maintenance of sinus rhythm was an
independent marker of survival, although use of the rhythm-control drug – dofetilide – did not confer the same advantage.\textsuperscript{35}

A further consideration is that of the cohorts studied, in particular their rhythm status during and after therapy. In AFFIRM 54\% of patients were already in sinus rhythm at enrolment, as they included paroxysmal and persistent AF. Of those on rate control, 35\% were in sinus rhythm at 5 years. Similarly, in AF-CHF, only two thirds were in AF at trial onset; the outcomes are further weakened by a 21\% crossover from rhythm to rate control (due to ‘failure’ of rhythm control) and a 10\% crossover in the other direction (mostly for worsening heart failure); 58\% of rhythm-control patients had documented recurrent AF during the study. This highlights two problems: i) rate versus rhythm studies have not generally compared these treatment modalities for persistent AF, and ii) pharmacologically based rhythm control is not very effective. Ultimately, this means we cannot conclude that the strategy of rhythm control is not warranted, or that restoration of sinus rhythm would not be advantageous.

There is significant evidence that sinus rhythm is associated with improved symptoms, quality of life, hospitalisations and mortality. If AF is truly an independent risk factor for worsening heart failure, then the conclusion has to be there is another reason for apparent lack of benefit from rhythm-control strategies. The first may be their relative inefficacy in maintaining sinus rhythm, thus potentially weakening the statistical benefit in treatment groups. However a more compelling reason may be the adverse effects, including proarrhythmia, negative inotropy, and extra-cardiac complications, of antiarrhythmic drugs used in rhythm-control trials to date.\textsuperscript{123} Thus, the true benefit of maintaining sinus rhythm in heart failure patients may be difficult to establish using drug-based rhythm-control strategies.
1.3.4.1 Catheter ablation as an alternative rhythm-control strategy

Catheter ablation, a therapy which could restore sinus rhythm without the need for long-term antiarrhythmic drug therapy, might be the logical solution to determining and achieving the potential benefit of maintaining sinus rhythm in heart failure patients. Radiofrequency catheter ablation for AF has developed from two sources: first, the recognition that compartmentalisation of the atria by surgical cut-and-sew techniques (such as the Cox Maze), could restore and maintain sinus rhythm in patients with even persistent and permanent AF;\(^{115,116}\) secondly, the finding that the triggering, re-initiating, and maintaining foci of AF can be electrically isolated and/or destroyed in the region of the pulmonary veins,\(^ {47}\) with later work additionally showing the importance of ganglionated nervous plexi\(^ {125,126}\) and highly fractionated electrical activity.\(^ {127}\) The development of catheter and computerised mapping technology has allowed refinement of these techniques, so that now AF ablation can be offered to symptomatic AF patients who fail antiarrhythmic drug therapy,\(^ {128,129}\) and has been shown – largely in patients without significant ventricular dysfunction – to be superior to medical therapy in terms of quality of life and morbidity\(^ {130,131}\) and, in a retrospective, non-randomised trial, mortality.\(^ {132}\)

Whereas the greatest experience, and highest rate of success, has been in those with structurally normal hearts and paroxysmal AF,\(^ {128,129}\) small non-randomised studies have examined the feasibility and role of ablation in treating AF in patients with reduced systolic function and symptomatic heart failure. 58 patients with congestive cardiac failure and 58 matched controls without heart failure underwent ablation for (mostly persistent) AF.\(^ {133}\)
In the heart failure group, at mean follow up of 12 months, LVEF improved by average 21% (Figure 1-6), in line with exercise capacity and symptoms. Sinus rhythm was achieved in approximately 80% of patients at 1 year follow up. In 94 AF patients with impaired LV function, ablation resulted in maintenance of sinus rhythm in 73%, improvement in quality of life, and a non-significant improvement in LVEF for patients who maintained sinus rhythm. More recently, PVI in patients with paroxysmal AF was shown to improve left ventricular function in an observational study.
The PABA-CHF study was reported in mid-2008, and was a multicentre investigation of 81 patients with LVEF ≤40%, NYHA class II-III heart failure, and drug-resistant atrial fibrillation. Patients were randomised to undergo PVI or atrioventricular node ablation with biventricular pacing and followed up for 6 months, with a composite primary endpoint of quality of life score, 6-minute walk distance and echocardiographic left ventricular ejection fraction. The success rate of PVI in maintaining sinus rhythm was 71% off antiarrhythmic drugs: all three endpoints improved in the PVI group compared with AV nodal ablation. However, the population was a mixed bag of about half paroxysmal and half persistent AF, and AV node ablation (with pacing) was applied to patients with a mean QRS duration 90±10ms – which would not be routine practice unless patients had truly failed medical rate control (for which there was no pre-requisite). In fact, the baseline heart rate in the ‘rate-control’ arm was 82±11bpm, so these patients had reasonable rate control, a narrow QRS, and were often in sinus rhythm! Thus one could argue that the study was pre-designed to show an inevitable superiority of PVI over the alternative strategy of nodal ablation and biventricular pacing, which is non-physiological and almost certainly worse than intrinsic His-Purkinje activation. Rate regularisation would only be a benefit in those with persistent AF, and would of course be at least equalled by those treated with PVI assuming a reasonable rate of success in maintaining sinus rhythm. Overall, therefore, the PABA-CHF study does not provide much additional support for the application of PVI over optimal medical therapy, as it did not study or reflect contemporary optimal clinical practice.

Hence, at the time of commencement of this study in October 2008, catheter ablation for persistent AF in patients with heart failure had not been tested in a randomised trial, nor was it known whether ablation is superior to optimal medical rate-control management in this context.
1.4 Interventional Electrophysiology

1.4.1 Historical Background

The field of clinical cardiac electrophysiology has developed rapidly in the last few decades. The discipline of clinical electrocardiography gave rise to physicians and scientists focussed on elucidating the mechanism of clinical arrhythmias. At the same time there was an increasing understanding of cardiac anatomy and the conducting system. In the 1940s and 1950s it was discovered that cardiac electrical activity which could not be detected by surface ECG could be measured by placement of intracardiac electrode catheters. Thereafter Durrer et al,\textsuperscript{136} simultaneous with Coumel et al,\textsuperscript{137} showed that cardiac arrhythmias could be induced, studied and terminated by programmed stimulation. In turn this guided surgical, pharmacological, and later catheter-based approaches to treating cardiac arrhythmias.

1.4.2 Radiofrequency Ablation

In the late 1960s the first surgical interruption of an accessory pathway was performed at Duke University,\textsuperscript{138} and was later applied to interrupt atrioventricular conduction in patients with drug-refractory ventricular rates in AF. However surgical ablation carried with it a significant morbidity and mortality, and there was an impetus to find a less invasive and more readily applicable approach.

In 1982, Scheinman et al\textsuperscript{139} then Gallagher et al\textsuperscript{140} published their experience of direct current (DC) ablation of the AV node, and the era of interventional cardiac electrophysiology was born. Only 5 years later, Borggrefe et al were the first to use radiofrequency (high frequency alternating current) as the ablation energy source when treating an accessory pathway. Radiofrequency ablation provides a dose-related tissue response and well-defined controllable lesion size with both greater lesion longevity and lesser risk of collateral damage than DC
shock. As it uses frequencies in the range 300-1000Hz, skeletal and cardiac muscle are not stimulated and the applications is not usually painful, except in sites of epicardial cardiac nerve plexi.

Radiofrequency catheter ablation became the definitive treatment for a variety of clinical arrhythmias during the 1990s, including atrioventricular nodal reentry tachycardia (AVnRT), accessory pathways, atrial flutter, the atrioventricular node, and ventricular tachycardias.

1.4.3 Development of AF ablation

Development of strategies to treat these common arrhythmias relied upon a detailed understanding of the mechanisms involved in tachycardia initiation and maintenance. This was followed by surgical approaches to treatment in many cases, then direct current and latterly radiofrequency ablation. The challenge in treating atrial fibrillation was that mechanisms were not clearly understood, and to a certain extent this remains the greatest challenge in treating persistent AF.

Based upon the multiple wavelet hypothesis, compartmentalisation of the atria should lead to a substrate where wavefronts can no longer coexist and meander as they will encounter electrical barriers to propagation. An alternative option is to sequester areas of the atrium from activation during a beat originating from the sinus node. This latter approach was the basis for the ‘corridor’ procedure introduced by Giraudon and colleagues in 1985, and applied to patients with both chronic and paroxysmal AF. However, this inevitably leads to complete isolation of the left atrium, and the majority of the right, thus does not allow restoration or maintenance of normal haemodynamics as neither atrium contracts prior to ventricular systole (they remain in fibrillation). Its use was primarily for allowing the sinus
node to remain as pacemaker and to propagate through the normal conducting system to the ventricles, avoiding the need for AV node ablation (Figure 1-7).

**Figure 1-7  The corridor procedure for atrial fibrillation**

Schematic diagram showing the exclusion of the left and majority of the right atrium to allow propagation of the sinus impulse through to the atrioventricular node (AVN). The excluded atria remain in fibrillation: the only potential advantage of the procedure over AVN ablation was that ventricular pacing could be avoided compared with the AV nodal ablation technique. However, post-operative impairment of the sinus node could still necessitate pacemaker insertion.\textsuperscript{152, 153} Reproduced with permission.\textsuperscript{154}

James Cox separately developed the ‘maze’ procedure, which in contrast to the ‘corridor’ procedure sought to render the patient free of AF and maintain atrial activation, allowing restoration of the majority of atrial and atrio-ventricular haemodynamics, as well as preventing AF and permitting normal sino-atrial pacemaker function (Figure 1-8). Over many years of follow up this has been shown to be highly effective in treating AF, with
success rates around 70-90% at long term follow up, varying according to adherence to the full Maze-III lesion set, comorbidities, type of surveillance, and duration of follow up.\textsuperscript{155}

**Figure 1-8** The Cox-Maze III procedure

(a) Schematic showing propagation of the impulse from the sinoatrial node (SAN) through the post-Maze atrium to the atrioventricular node (AVN). Adapted and reproduced with permission\textsuperscript{156}

(b) Cox-Maze III lesion set as seen from a posterior view of the atria. The right shows the original operation, the left the more recent modification to avoid posterior wall isolation and potentially allow for greater contractile function of the left atrium. A cryo-lesion (black asterisk) is typically added at the epicardial coronary sinus as it has been shown to improve outcomes. Reproduced with permission\textsuperscript{157}
This procedure requires open-heart surgery including cardiopulmonary bypass and their associated morbidities; it is highly technically challenging and thus has been confined to relatively few centres with the sufficient surgical skill and experience; and approximately 10% of patients require pacemaker insertion for sinus node dysfunction subsequent to surgery.\textsuperscript{155} Alternative energy sources and techniques have been used, in an attempt to make the procedure technically easier, and quicker, but with the trade-off being potential lack of transmural lesion formation and reduced overall success; such techniques have included radiofrequency, microwave, and cryo-ablation. Most recently the Cox-Maze IV procedure was introduced, replacing the majority of Cox-Maze III surgical incisions with bipolar radiofrequency lesions, and in an experienced centre this has been shown to be highly effective.\textsuperscript{158}

A less invasive non-surgical approach was sought, in part inspired by the success of catheter ablation procedures for other arrhythmias. In 1994, Schwartz \textit{et al}\textsuperscript{159} and Haïssaguerre \textit{et al}\textsuperscript{160} attempted percutaneous treatment of AF by placement of linear radiofrequency lesions in the LA and RA respectively. Although the former showed great promise in terms of sinus rhythm restoration and maintenance, procedural times were in excess of 10 hours, and complications >20%. Catheter and sheath technology required further development, as did the lesion strategy.

Right-atrial lesions were shown to be effective in highly selected patients with paroxysmal and persistent AF, but it became apparent this strategy would not suffice in the majority.\textsuperscript{161,162}

During this period of development of catheter-based approaches aimed at reproducing linear lesions in the atria, Haïssaguerre, Jais and colleagues provided a new insight into the mechanism of AF initiation and in turn ushered in a new era in non-pharmacological management of AF. Up until 1996 the majority of computer modelling, animal experimental,
and surgical human mapping data supported the multiple wavelet hypothesis, and a focal mechanism was not considered likely. In a small series of 9 patients with paroxysmal AF, focal discharges leading to a surface ECG pattern of AF were demonstrated in both the right and left atrium, the latter from the pulmonary veins, and all were successfully treated with radiofrequency ablation. Following this, a larger series of 45 patients was studied, and 65/69 (94%) of atrial ectopic beats initiating AF originated from the pulmonary veins. Moreover, after radiofrequency ablation targeted at these sites, 62% of patients had no recurrence of AF.

### 1.4.4 Pulmonary Vein Isolation

This revelation led to the development of focal AF ablation, and later pulmonary vein isolation (PVI) as it was realised that multiple foci could exist within multiple veins. A complete barrier to electrical activation of the LA from the PV could be created by targeting all connecting muscle sleeves with radiofrequency ablation. The location of ablation gradually moved from the PV ostium further towards the LA to the so-called PV antrum, in order to reduce the risk of PV stenosis with ablation at deeper sites. Although some series suggested that complete isolation of the PV antrum was not necessary, merely a significant reduction in voltage or high-frequency signal within the area, it has gradually been accepted that complete PV isolation is associated with a superior outcome. In the majority of centres, PV isolation is assessed by the placement of a multipolar circular or spiral catheter within each the pulmonary veins; this may also be used to guide the site of ablation as it has long been recognised that complete circumferential ablation is not always necessary to achieve lasting isolation.
1.4.5 Linear lesions

Pulmonary vein isolation alone is highly effective in treating patients with paroxysmal AF, but found to be less so in those with persistent or longstanding persistent (previously called permanent) AF.\textsuperscript{164}

Hence interventional electrophysiologists have combined similar techniques to those first used by Schwartz, that is to reproduce similar lesions to the surgical maze procedure, in order to create not only PVI but also further compartmentalisation of the atrium. Many operators added such \textit{linear lesions} during the early period of AF ablation in 1998-2003. The ability to create complete transmural lesions was challenging with the available technology,\textsuperscript{167} the major advance in which was the use of constant saline irrigation through the catheter tip. This permitted the delivery of deeper lesions whilst minimising the risk of tissue overheating and char/thrombus formation.

1.4.5.1 Roof line

One of the bases for the original Cox-Maze III procedure and its later modifications, was that a barrier should exist at or near the posterior wall to prevent macroreentrant circuits from passing between the pulmonary veins. These may act as drivers of atrial fibrillation and/or be responsible for atrial tachycardia occurring after treatment of AF. The \textit{roof line} Figure 1-9 connects the contralateral encircling pulmonary vein lesions in the superior LA and, when complete, prevents conduction at this level between the anterior and posterior LA wall, whilst maintaining conduction inferiorly (around the septum and/or mitral annulus). Hocini \textit{et al} demonstrated that conduction block could be created in 96\% of cases, and resulted in improved success (arrhythmia free off antiarrhythmic drugs) from 69 to 87\% in a cohort of 90 patients with paroxysmal AF.\textsuperscript{170} Subsequently the technique has been shown to improve success rates for persistent AF ablation.\textsuperscript{171} The roof line is added after completion of PV
isolation, given the compelling evidence for PVI as the cornerstone of all types of AF ablation.

**Figure 1-9** Roof line

3D reconstruction of left atrium using NavX system (St Jude Medical, MN, USA). The left atrium is seen from above and behind, with left atrial appendage (LAA) top left. Ablation (red dots) has been performed in rings around each pair of pulmonary veins (LIPV = left inferior pulmonary vein; RSPV = right superior pulmonary vein). Following this, a line of ablation (arrow) has been created on the roof of the left atrium between the left and right isolation lines. After sinus rhythm restoration, pacing manoeuvres between the LAA and high posterior wall permit assessment of conduction block.
1.4.5.2 Mitral line

The Cox-Maze III lesion set included an incision from the lower portion of the PV and posterior wall exclusion zone connected to the mitral annulus, with a complementary lesion placed at the coronary sinus. The primary basis for this was again to prevent the existence of macroreentrant circuits that may drive AF and/or lead to post-AF atrial tachycardias, and failure to complete this lesion was associated with worse outcome.

Figure 1-10 Mitral line

The left atrial model from Figure 1-9 has been rotated to show a left lateral view. The mitral annulus is seen cut out from the geometry. A line of ablation (arrow) has been created between the annulus and the left inferior pulmonary vein (LIPV), joining the pulmonary vein encirclement. This lateral ‘mitral valve isthmus’ line can be checked for integrity by pacing from the coronary sinus (CS) and left atrial appendage (LAA), which approximate each side of the line. Ablation is sometimes required from within the CS, which apposes the epicardial surface of this region as shown.
Several different lesions may theoretically be able to prevent complete circumnavigation of the mitral valve annulus (MVA) and anterior/inferior LA. In the presence of a baseline PVI lesion set, with or without a roof line, the options are to place a linear lesion between the right PV and the septal MVA, an anterior line from the roof to the MVA, or a line from the left PV (under the LAA) to the MVA. Of these, the shortest is typically the latter – otherwise known as the lateral mitral isthmus (MVI), and the longest is the septal line. The lateral MVI may however be difficult to block due to non-transmural ablation, and some operators used the anterior approach. This, however, has the drawback – whether performed surgically or with catheter ablation – of causing a severe intraatrial conduction delay: the lateral LA and LAA are activated very late, thus producing ineffective atrial contraction as it would coincide with ventricular systole. Hence most operators performing this line use the lateral approach (Figure 1-10). Jais et al showed that addition of an MVI line to PVI and right flutter line increased arrhythmia-free survival from 69 to 87% in 100 patients treated for paroxysmal AF.

Creation of a transmural lesion and this block is more challenging, even with irrigated tip catheters. This may be due to thickness of the atrial muscle and/or the presence of an effective heat sink in the coronary sinus, which reduces conductive heating at the epicardial surface. In the above study, block could be achieved in 92% patients although two thirds required some ablation within the coronary sinus. Subsequent reports have highlighted the additional benefit of MVI ablation in treating persistent and longstanding persistent AF, with typically lower success rates for achieving block (70-90%) and but similar improvements in outcome compared with PVI alone. Epicardial ablation from within the CS is frequently needed; radiofrequency power is typically reduced here in order to minimise the risk of collateral damage to the CS and circumflex artery, although the clinical risk appears small.
1.4.5.3 Combined linear lesions

Several studies have prospectively compared PVI alone with PVI and combined linear lesions (roof and MVI) in treatment of persistent AF. The majority have shown a significant improvement in arrhythmia freedom at follow up with additional linear lesions at the baseline procedure.\textsuperscript{171, 176, 178} The downside of adding these lesions, other than the additional procedural time, is that incomplete lesions clearly predispose to atrial tachycardia during follow up.\textsuperscript{167, 171, 179, 180} Thus it is imperative that conduction block is obtained and confirmed during the index procedure whenever possible.

1.4.5.4 Other linear lesions

Other lines have been used during AF ablation, in both atria. Although a posterior line, in addition to the roof line, can create posterior wall isolation, there is concern regarding the risk of collateral damage to the oesophagus due to its proximity to the posterior wall. Some studies have suggested that the LA posterior wall is an important part of the AF substrate, and that isolation of this region may improve outcomes from AF surgery\textsuperscript{181} and catheter ablation.\textsuperscript{182, 183}

Long linear lesions in the right atrium were shown to be largely ineffective in early studies into catheter ablation. However, the addition of right atrial lesions has been shown to improve outcomes from AF surgery,\textsuperscript{184} and more recently in some catheter ablation studies.\textsuperscript{185, 186}

The addition of a right atrial flutter line, at the cavitricuspid isthmus (CTI) between the tricuspid valve and inferior caval vein, has been investigated in patients undergoing AF ablation. Initial data showed that elimination of atrial flutter can successfully treat paroxysmal AF.\textsuperscript{187} It remains unclear whether prophylactic CTI ablation should be routinely added in patients undergoing elective AF ablation. Some studies would support this,\textsuperscript{184}
particularly if atrial flutter has been seen clinically or within the electrophysiology laboratory,\textsuperscript{188} whilst others showed little or no benefit on arrhythmia freedom.\textsuperscript{189} Nevertheless, given the morbidity associated with recurrent atrial flutters and the relative simplicity of performing a CTI line during AF ablation, many centres perform this routinely during catheter ablation of persistent AF.\textsuperscript{190, 191}

### 1.4.6 Complex fractionated electrograms

The AF substrate is complex and the mechanisms remain incompletely understood. Given that the success rates of AF ablation were still significantly below that of SVT and flutter, there was impetus to find new or alternative techniques to achieve termination of AF and lasting sinus rhythm.

Allessie and colleagues noted that fragmented unipolar electrograms could be recorded at sites of wavefront pivot points or zones of slow conduction,\textsuperscript{192} during induced AF in humans. Such electrograms display high frequency, low amplitude, multicomponent signals of prolonged duration, and have also been recorded in the ventricle after healed myocardial infarction,\textsuperscript{193} and during atrial flutter.\textsuperscript{194} Given that sites showing complex fractionated electrograms (CFE) may represent sites of wavelet reentry, Nademanee \textit{et al} hypothesised that eliminating these area by catheter ablation such areas of slow conduction would stop multiple wavelet reentry and therefore AF. The initial study on 121 patients showed that 3D map-guided radiofrequency ablation of CFE site was associated with termination of AF in 115 (95\%), although 32 (28\%) required administration of the class III drug ibutilide. At 1 year, 87 (72\%) patients were free of arrhythmia and off antiarrhythmic drugs after a single ablation.\textsuperscript{127} A large proportion of CFEs were located in the pulmonary venous antrum, thus PVI may have also been an effective strategy in some of this cohort.
CFEs may be defined as fractionated and composed of ≥2 deflections ± perturbation of the baseline with continuous deflections from a prolonged activation complex, or atrial electrograms with a very short cycle length (≤120ms) typically with multiple potentials when compared with atrial cycle length from other parts of the atria.\textsuperscript{127}

There remains debate as to the aetiology and relevance of CFE, which may represent slow conduction,\textsuperscript{192, 193, 195, 196} localised reentry, collision of wavelets,\textsuperscript{50, 192} anisotropy-related behaviour,\textsuperscript{196, 197} or location of epicardial ganglionic plexi.\textsuperscript{198} Since the initial data from Nadamanee et al supporting CFE ablation to eradicate AF, many investigators have targeted CFE during AF ablation. Outcome data is varied. There is limited data on beneficial effect in paroxysmal AF.\textsuperscript{199} Regarding persistent AF, one study has shown a benefit with CFE ablation alone,\textsuperscript{200} while a number of studies have used CFE ablation in conjunction with antral PVI,\textsuperscript{201} or as part of a stepwise ablation strategy incorporating linear lesions.\textsuperscript{202, 203} Such discrepancies might relate to the heterogeneity of CFE mapping. Observational errors can occur with subjective operator-determined conventional CFE mapping, and use of an ablation catheter for CFE mapping has potential disadvantages, which include requirement of sequential single point map creation, low tip-ring resolution and catheter deformation of the atrial surface which may change local activation. Two published studies have used automated algorithms for mapping prior to ablation of CFE, with single point-by-point acquisition.\textsuperscript{201, 204} Although there are limitations with any automated process, the algorithm used here has been shown to have good sensitivity (0.75) and specificity (0.8) for correlation with physician-identified CFEs.\textsuperscript{205} The ability to rapidly acquire repeat CFE maps is desirable, given that 22% of CFE sites may show some degree of temporal change.\textsuperscript{206} To date the ideal ablation strategy for high burden, persistent and chronic AF has not been fully defined. Equally, the exact role of CFE guided ablation and its role particularly for persistent AF ablation is yet to be determined.
1.4.7 Mapping technologies

Catheter placement and tracking has traditionally been performed using fluoroscopy. With the development of more complex ablation techniques, including long linear lesions encircling the PV or joining atrial substructures, much investment has gone into developing technologies to allow non-fluoroscopic navigation and tracking systems in order to improve accuracy and efficacy of interventional electrophysiological procedures. Fluoroscopy provides 2-dimensional information, and does not provide visualisation of endocardial contours. In contrast, modern mapping systems have the ability to display catheters within a virtual 3-dimensional environment, reconstruct virtual endocardial contours, track catheter position, and record a variety of parameters at the endocardial surface including activation time, electrogram amplitude, ablation sites.

The principal technologies now used in AF ablation are CARTO (Biosense-Webster, Diamond Bar, CA) and EnSite NavX (St Jude Medical Inc, St Paul, MN). CARTO utilises a low intensity magnetic field, with a complementary sensor built into the mapping and ablation catheter, which in combination allow determination of the location and orientation of the tip electrode in addition to providing local electrical information. Hence the term electroanatomical mapping was coined. The latest version, CARTO3, also allows display of multiple catheters in order to improve orientation and navigation.

Ensite NavX is capable of locating and displaying any standard EP catheter within a 3-dimensional field. In contrast to CARTO it does not use a magnetic field and does not require specific catheters; the system consists of three pairs of patches placed on the body surface in orthogonal planes. A low power 5.7KHz electrical field is generated across each pair of patches; the voltage/impedance gradient is used to calculate the position of any electrode placed within the field. Importantly, unlike CARTO the system can record both anatomical
and electrical information simultaneously from up to 64 electrodes, and thus has the ability to be used to map rapidly with high resolution. In addition, the system is able to record long segments to allow retrospective assessment of the arrhythmia substrate.

Imaging from CT or MRI can also be integrated with either system to improve accuracy, although the latest iterations of mapping systems are now capable of providing accurate geometry of complex structures such as the posterior LA without this additional information.

1.4.8 Complications of AF ablation

Procedures for AF ablation are increasing, and with increased experience, improved technology, better targeting of effective lesions, and shorter procedure times, the high complication rates of the early procedures in the mid 1990s are thankfully historical.

However, significant complications occur in 2-6% of patients\textsuperscript{207} and include transient ischaemic attack or stroke (0.5-1.5%), tamponade (0.5-4%), symptomatic PV stenosis (<1%), and right phrenic nerve palsy (0.3%, usually transient). Procedures are long – often 3-6 hours for persistent AF, require specialist facilities and expertise, and are modestly more challenging in patients with heart failure in part due to concomitant atrial dilatation and an increased surface area to which lesions must be applied.
1.5 Conclusion and hypothesis

The coexistence of atrial fibrillation and heart failure carries significant morbidity and is associated with worsened mortality. The optimal management in the era of interventional treatments for AF remains unclear. Pharmacological therapy for AF rhythm-control offers no clear advantage over rate control, however compelling observational data exists that sinus rhythm is advantageous when it can be achieved without significant collateral morbidity.

The editorial associated with publication of the main AF-CHF trial outcomes, by Cain and Curtis, made the following comments:

“Driven by these circumstances, investigators should next focus on a rhythm-control strategy that eliminates the confounding contributions of low efficacy and high toxicity associated with antiarrhythmic drug therapy to better determine the desirability of maintaining sinus rhythm in patients with atrial fibrillation. Ablation therapy serves this purpose. ... Ultimately, studies must also test the superiority of ablation therapy, as compared with rate control, since ample data show that rate control is an acceptable strategy and one that is almost certainly more cost effective than any other approach.”

On this basis, the logical step would be to assess catheter ablation as a rhythm control strategy, in comparison with a rate control approach, in a prospective randomised controlled trial. Catheter ablation may allow not only better maintenance of sinus rhythm, but can in theory achieve it without the requirement for antiarrhythmic drugs.
1.5.1 Main hypothesis

A strategy of rhythm control by catheter ablation, compared with rate-control, for management of persistent atrial fibrillation in patients with heart failure, improves cardiovascular performance, symptoms, and neuroendocrine status.

This was investigated by a clinical trial, the design of which is presented in chapter 2. The results of the main trial outcomes are presented in chapter 5. Chapter 6 includes further analysis of the measured imaging parameters within the main trial. Chapter 7 presents the biomarker sub-study of the clinical trial.

1.5.2 Secondary aim and hypothesis

High-density contact mapping is a feasible method to investigate the human atrial substrate in advanced heart disease. It may have a role in assessing the impact, and facilitate optimisation, of catheter ablation procedures in persistent atrial fibrillation in heart failure.

These investigations are presented in chapters 3 and 4.
2 Clinical trial design and methods

2.1 Introduction

In order to investigate the hypothesis that catheter ablation-based rhythm control is superior to medical rate control, a prospective randomised controlled trial was designed to be conducted in a single tertiary cardiac centre (both sites of the Royal Brompton and Harefield NHS Foundation Trust), with recruitment from referral centres at district general hospitals, and the heart failure and arrhythmia services within the hosting Trust.

At the point of study commencement in 2008-9, having performed searches via Medline, PubMed, Clinicaltrials.gov, and the WHO ICTRP website, it was established that no trial had compared these strategies. Three studies intending to evaluate similar patient populations but with different outcome measures were in the recruitment phase. ‘Catheter Ablation Versus Standard Conventional Treatment in Heart Failure Patients With Atrial Fibrillation (CASTLE-AF)’, NCT00643188, scheduled to complete in 2013, had the primary outcomes of mortality and heart failure hospitalisation. Two smaller scale studies were also in recruitment: ‘Radiofrequency Ablation for Atrial Fibrillation in Advanced Chronic Heart Failure’, NCT00292162, using a primary outcome measure of LVEF, with no designated comparator group.* The third was ‘Atrial Fibrillation Management in Congestive Heart Failure With Ablation (AMICA)’, NCT00652522: all patients receive device (ICD/CRT) implantation, the comparator being ‘best medical treatment’, and a primary outcome of change in LVEF.

* This study was subsequently published as a comparison of radiofrequency ablation and continued medical treatment (rate control), despite this treatment arm allocation not being pre-defined on ClinicalTrials.gov (see MacDonald et al in Chapter 8)
2.2 Clinical trial design

A placebo-control/double-blind design would not feasible in view of the ethical issues with performing a 'sham' AF ablation procedure under anaesthesia, and indeed such types of study has been advised against under international guidelines. Thus an ‘open-label’ model was used, so that investigators administering therapies would be aware of patient allocation; however, assessment of the primary endpoint and imaging endpoints was performed by blinded physiologists and cardiologists respectively.

The study population was defined as patients with persistent atrial fibrillation (minimum 7 days), congestive heart failure with New York Heart Association (NYHA) functional class II – IV; and left ventricular ejection fraction (LVEF) ≤ 35%. The strategies of rate control and catheter ablation were compared in a 1:1 randomised fashion.

2.2.1 Choosing a study population

2.2.1.1 Type of atrial fibrillation

The majority of heart failure patients presenting with AF do so when it is persistent. Moreover, as discussed in the opening chapter, comparison of rate control with rhythm control are has some fundamental flaws when examining populations including those with paroxysmal AF. Rate-control is not a logical therapy to apply to a patient in sinus rhythm, although this argument can be balanced by the need for the same medication in heart failure (e.g. beta-blocker). In terms of how the investigatory science might alter clinical practice, a relatively homogeneous cohort would be required to allow conclusions to be drawn about the relative merits of rhythm control and rate control. Both the AFFIRM and AF-CHF studies had mixed populations of paroxysmal and persistent AF. Hence, unsurprisingly, a substantial proportion of patients in the rate-control group were in sinus rhythm: 54% of rate control
patients in sinus at baseline in AFFIRM, 35% at 5 years; whilst in AF-CHF the absolute difference in rhythm between groups was approximately 40% (where the target for an ideal comparison of rate versus rhythm control of AF would be approaching 100%). This, based upon the notion that it is a ‘sinus rhythm is better than AF’ hypothesis that is really being tested – would unfairly strengthen the relative outcome for rate control, versus rhythm control, in virtually all circumstances. Furthermore, paroxysmal AF is often poorly tolerated in patients with heart failure and catheter ablation would already be clinically justified in heart failure patients who cannot tolerate or receive amiodarone. In order to best examine the impact of AF and comparison of its maintenance versus its restoration to sinus rhythm in this cohort, only those with persistent (i.e. beyond 7 days continuous) AF were selected.

### 2.2.1.2 Degree of left ventricular dysfunction

Although it is increasingly recognised that there exists a spectrum of left ventricular (LV) dysfunction in patients with clinical heart failure, the vast majority of clinical trials in heart failure have been performed in those with significantly reduced LV systolic function, typically below 35-40% as assessed by radionuclide ventriculography, angiography, or echocardiography. Defining heart failure in those with preserved LV ejection fraction (LVEF) is challenging, and probably more in the presence of atrial fibrillation, particularly as its presence can be used in defining the condition. Hence the present study set out to enrol patients with at least moderate LV systolic dysfunction, with a cut off at LVEF 35% as assessed by radionuclide ventriculography.

### 2.2.1.3 Inclusion criteria

- Age ≥ 18 years ≤ 80 years

- Impairment of left ventricular systolic function (left ventricular ejection fraction ≤35% by radionuclide ventriculography)
• NYHA II-IV symptoms, on optimal heart failure therapy*

• Persistent AF (clinically present for > 7 days)

Optimal heart failure therapy included cardiac resynchronization therapy where appropriate (see exclusion criteria). Patients were all referred from cardiology and/or heart failure specialist services, and must have been established on stable heart failure therapy prior to enrolment. Pre-enrolment AF rate-control criteria were not specified.

### 2.2.1.4 Exclusion criteria

- CRT or ICD device implanted in the previous six months

- AV nodal ablation within previous three months

- Prior AV nodal ablation or complete heart block with a single chamber pacemaker

- Contraindication to anticoagulation

- Persistent thrombus in the left atrium despite anticoagulation

- Active malignancy

- Cerebrovascular accident within the previous 6 months

- Reversible causes of AF including thyroid disorders, acute alcohol intoxication, recent major surgical procedures, or trauma

- Reversible causes of heart failure including acute myocarditis, alcohol

- Cardiac events including myocardial infarction (MI), percutaneous coronary intervention (PCI), valve or coronary bypass surgery within the previous 3 months

---

* Patients with a recent diagnosis of heart failure were only recruited after a minimum of 3 months from initial diagnosis, and in the presence of unstable or NYHA class IV symptoms had been stabilised by in- or out-patient specialist heart failure nurse or physician-led therapy for a minimum of 1 month.
• Prior left atrial catheter ablation with the intention to treat AF
• Prior surgical interventions for AF such as the surgical MAZE procedure
• Previous heart transplant, or on urgent heart transplant waiting list
• Severe neuro-muscular disease
• Creatinine clearance <30 ml/min
• Serum bilirubin >50 micromol/L
• Body mass index >40 kg/m²
• Contraindication to general anaesthesia
• Active participation in another research study
• Unable to understand and comply with protocol or give written informed consent.

2.2.2 Outcome measures

Choosing a relevant and measurable endpoint is challenging in trials of heart failure. Despite contemporary optimal medical and/or device therapy, the prognosis of advanced heart failure is poor. For many patients mortality risk is less relevant than symptom burden, quality of life, and ability to perform routine tasks. A very large study cohort would be required to establish a mortality benefit of catheter ablation, which was outside the remit of this study, which instead sought to examine parameters that may be markers of prognosis, as well as symptomatic and functional status.

Impairment of exercise intolerance is both a hallmark symptom of heart failure and one of the most important indicators of long-term survival. Given that peak oxygen consumption is a strong prognostic indicator, may be a more reliable indicator of long-term survival than ejection fraction, and correlates with symptomatic status, change in peak oxygen
consumption (peak \(\text{VO}_2\)) at cardiopulmonary exercise treadmill testing was chosen as the primary endpoint in this study. Peak \(\text{VO}_2\) has been widely demonstrated to stratify mortality risk in chronic heart failure patients, both as a continuous variable,\(^{214}\) and as a threshold determinator in deciding on those who are candidates for cardiac transplantation.\(^{215}\) Cardiac resynchronisation therapy has been shown to improve peak \(\text{VO}_2\) in patients with underlying dyssynchrony.\(^{220}\) Beta-blockers have not been shown to affect peak \(\text{VO}_2\), but do favourably lower ventilation per unit increase in carbon dioxide production (VE/VCO\(_2\) slope).\(^{221}\) Peak \(\text{VO}_2\) is known to be lower in heart failure patients with AF than with sinus rhythm,\(^{222}\) and has previously been shown – albeit not specifically in heart failure patients - to increase after cardioversion if sinus rhythm is maintained.\(^{223-226}\)

Biomarkers, in particular \textit{B-type natriuretic peptide (BNP)} have become key elements in the diagnosis of heart failure.\(^{227,228}\) BNP also is one of the best predictor of prognosis available to date,\(^{229}\) improves outcomes when used as a guide to heart failure therapy,\(^{230,231}\) and it is now well established that improvements in the heart failure syndrome are associated with a reduction in BNP concentrations.\(^{231,232}\) BNP levels have been shown to fall after catheter ablation for paroxysmal and persistent AF, largely in patients without ventricular dysfunction.\(^{233,234}\) The study will prospectively examine the effect on BNP levels of ablation, versus rate-control, in this cohort of patients with significant LV dysfunction.

The left ventricular ejection fraction (LVEF) is frequently used as an endpoint or outcome in studies looking at heart failure therapies, including aforementioned studies of AF ablation. Multiple-gated acquisition radionuclide ventriculography is regarded as the gold standard for quantifying LVEF, and are highly reproducible (test variability <3% in our institution). As cardiac magnetic resonance imaging is contraindicated for patients who have implantable devices, and echocardiographic data are susceptible to inter-operator and intra/inter-scan variability, radionuclide imaging was the primary modality of choice in assessing left
ventricular function. However, LVEF does not take account of diastolic dysfunction, and is regarded insufficient as a global measure of heart failure severity. Clinical trials have shown a variable prognostic association of change in ejection fraction. Given the superiority of peak oxygen consumption as a prognosticating test, change in LVEF was a secondary outcome measure in this study.

2.2.2.1 Primary outcome

- Peak oxygen consumption (VO₂) at cardiopulmonary exercise test*

2.2.2.2 Secondary outcomes

- LV ejection fraction as detected by radionuclide ventriculography*

- Minnesota Living With Heart Failure Questionnaire (LHFQ) score*

- 6 minute walk distance*

- B-type natriuretic peptide (BNP)*

- Freedom from AF; freedom from atrial arrhythmias*

- LV dimensions and ejection fraction (Biplane Simpson’s method) as measured with transthoracic echocardiography; presence and amplitude of A wave on transmitral Doppler; left atrial size

- Combined endpoint of LVEF, 6 minute walk distance, and LHFQ score

- Composite endpoint of mortality and unplanned hospitalisation for major cardiovascular events (including worsening HF, myocardial infarction, unstable angina, ventricular arrhythmia, stroke, pulmonary embolism, cardiac transplantation)

* Indicates endpoints registered on ClinicalTrials.gov at trial commencement April 2009
2.2.3 Ethical approval and registration

The study was approved by the Hillingdon and Hounslow Research Ethics Committee in December 2008 on behalf of the UK National Research Ethics Service, and was approved by the institutional review board in April 2009. The trial, *ARC-HF,* was registered prior to commencement on ClinicalTrials.gov with identifier NCT00878384.

2.2.4 Recruitment

Patients were recruited from the cardiology and/or specialist heart failure services of Royal Brompton & Harefield NHS Foundation Trust (RBHT). Some were referred for assessment for eligibility from linked referring hospitals; however, all patients were then investigated and enrolled on the RBHT site. All relevant cardiologists and specialist nurses were informed about the trial by email or poster, and the procedure for referral. At onset of the study, the heart failure clinics at RBHT were screened for 1 year for all patients with AF and heart failure.

Patients apparently meeting the inclusion/exclusion criteria were then approached regarding possible participation. After verbal discussion, all patients were sent a detailed information sheet (see appendix). Consent forms were signed prior to patients undergoing any baseline investigations. All patients who were formally approached were logged on a candidate list form, and their final destiny recorded for purposes of the Consort diagram.

* * A Randomised Trial to Assess Catheter Ablation versus Rate-Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure
2.3 Baseline Investigations

All patients underwent clinical examination, 12 lead ECG, routine blood tests, and the following investigations prior to randomisation. Prior to commencing investigation, all patients were allocated a sequential study code to permit pseudo-anonymisation of data, which was used on the case report form (see appendix). After the baseline visit, data from the CRF were transferred to an electronic CRF in the form of an Excel spreadsheet, and stored on local NHS computer servers.

2.3.1 Radionuclide ventriculography (RNV)

2.3.1.1 Acquisition Technique

In vivo red blood cells were labelled with 800 MBq of $^{99m}$Tc. A dual-headed gamma camera with a high-resolution low-energy collimator was employed. For ECG gating an R-R window width was set at 20%, but widened up to 50% on each side in case of markedly irregular heart rate.$^{235}$ Wider window allows inclusion of beats with variable lengths, which may reduce image quality but is a true representation of the cardiac haemodynamics in arrhythmias. This avoids an otherwise long acquisition time, which may not be practicable for heart failure patients or can lead to patient motion and resultant low quality images. For planar imaging, using a single detector, a planar oblique acquisition with the best septal separation angle was selected. R-R interval was gated into 16 (Harefield) or 32 (Brompton) frames with matrix size of $64 \times 64$ pixel size of 0.39 cm. A total of nine million counts was acquired.

2.3.1.2 Image Analysis

On planar imaging, a semi-automated region of interest was selected around the left ventricular blood pool on both end-systolic and end-diastolic planar images. A further region of interest over a background area (usually the mediastinum) was also selected and used to
background-correct counts within the blood pool regions of interest. Left ventricular ejection fraction was calculated as the difference between corrected end-diastolic and end-systolic counts divided by the corrected end-diastolic counts. The planar EF was used for inclusion criterion purposes.

2.3.2 Cardiopulmonary exercise test (MVO₂)

Graded treadmill exercise testing was performed with continuous measurement of ventilation (VE), oxygen consumption (VO₂), and carbon dioxide production (VCO₂) were measured continuously with a respiratory mass spectrometer: Medgraphics Ultima CPX (Medical Graphics Corporation, St Paul, Minnesota, USA) system at Royal Brompton Hospital and Oxycon Pro (Jaeger, Hoechberg, Germany) at Harefield Hospital. Baseline and follow-up investigations were kept at the same hospital site to avoid the introduction of errors due to subtle differences between the equipment used.

All patients were encouraged to exercise to exhaustion on the modified Bruce protocol. This includes a stage 0 during which patients walk at 1 mph on a 5% gradient. The modified Bruce protocol was deemed suitable for patients with heart failure, including the elderly, and was the standard protocol used for this study: however if the patient was not able to keep up with the treadmill then the slower-onset Naughton protocol was used after a 5 minute rest period. Data were analyzed offline by cardiac physiologists blinded to the study protocol without reanalysis by study investigators.

Peak VO₂ was defined as the mean of the highest 2 consecutive values of 15-second averages of VO₂. The VE/VCO₂ slope was obtained by linear regression analysis of the data acquired throughout the entire period of exercise. All patients had baseline and follow tests performed with the same equipment and protocol. Continuous 12-lead ECG monitoring was
performed alongside respiratory gas analysis. Additional parameters recorded at each stage were respiratory exchange ratio (RER), heart rate, and blood pressure. The weight-adjusted peak VO₂ (ml/kg/min) was used as the primary outcome measure for the study.

**2.3.3 Quality of Life score (Minnesota LHFQ)**

The Minnesota LHFQ questionnaire (see appendix) is a 21 question validated quality of life assessment tool, with each question scoring 0-5, total 105. Higher scores reflect greater symptoms or impairment, and a lower quality of life. This was given to each patient for completion, without additional prompting by the investigator, at the beginning of each visit prior to clinical interview and/or examination. Patients were not allowed to see their score from previous attendance to reduce the chance of participant bias.

**2.3.4 Blood tests and biomarkers**

Blood tests were taken at rest, prior to radionuclide ventriculography and exercise testing: full blood count, urea and electrolytes, coagulation profile, liver function tests, thyroid function tests, C-reactive protein, and plasma for biomarkers (see below). BNP was measured using a Triage BNP immunoassay on a Beckman Access 2 analyser. Blood for other biomarkers was collected into 7ml ethylene-diamine-tetra-acetic acid-containing tubes and centrifuged at 1000G for 5 minutes, within 1 hour of sample acquisition. Plasma was extracted for freezer-storage of 1-2ml plasma aliquots at -70 degrees C, for later analysis (see Chapter 7).

**2.3.5 Holter monitoring**

Baseline 24h monitoring was performed (except in patients who had a recent equivalent recording and the data were available), with repeat recording at 6 and 12 months (48h for patient in the ablation arm). Data were analysed semi-automatically to produce mean,
minimum and maximum 1-minute-averaged heart rates, premature aberrant (ventricular ectopic) count, and the Holter was scanned for evidence of pauses (defined as >3 seconds) and any ventricular tachyarrhythmia (defined as ≥3 cycles). If Holter recordings were not complete in patients with implantable devices, with appropriate programming of atrial sensing and arrhythmia recording, lack of atrial arrhythmia and/or mode switch could be used as a surrogate for recording arrhythmia recurrence. In non-device patients, inadequate Holter recorders were repeated to ensure the minimal monitoring requirements were met.

2.3.6 Six minute walk test

A 15-metre corridor was used (30 metre lap). Baseline heart rate was recorded via apical auscultation over a period of 30 seconds. After the observing investigator demonstrated the course, the patient was given the following instruction:

Please walk as far as you can in 6 minutes. You should not run. I will inform you when you have reached about 3 minutes, and when you have about 1 minute left. If you need to rest please slow down or stop at one of the chairs, and resume walking when you are ready.

No encouragement was given from the observer. Laps were recorded on the CRF, and the total distance (including partial laps) calculated at completion. Apical heart rate was reassessed immediately at completion of exercise, over a period of 30 seconds, and recorded as the peak heart rate.

2.3.7 Transthoracic echocardiogram

A standardized protocol was used to acquire images on Vivid 7 or Vividi echocardiograph machines for subsequent analysis on EchoPAC software (GE Healthcare Milwaukee, WI, USA). Standard 2D, colour/pulsed/continuous Doppler was acquired. LA size and method-
of-discs LV ejection fraction (average 3 cycles) was calculated by 2 independent observers for final results analysis. At follow up post ablation, presence of atrial contraction was assessed by mitral A-wave Doppler, and where possible the A' tissue Doppler component (see chapter 6 for detailed discussion).

2.4 Randomisation Protocol

After baseline investigations, eligible patients were randomised by the Clinical Trials and Evaluation Unit, Royal Brompton Hospital, on a 1:1 basis to either catheter ablation, or a rate-control strategy. Randomisation was performed in permuted blocks, by age (≥50, <50) and presence/absence of pre-existing complete AV block, in order to minimize group imbalance. The study investigators were blinded to block-size.

2.5 Post randomisation care

2.5.1 Medical therapy (rate-control) group

Patients were managed with pharmacologic therapy as required to achieve a mean heart rate less than or equal to 80 bpm during rest and 110 bpm on activity (as measured during a 6 minute walk test). The drugs to be used were at the discretion of the treating physician: prospectively recommended drugs acceptable for this purpose included (but were not limited to) beta-blockers, digoxin, and amiodarone. The follow up period started from the day of commencement of the rate control protocol, i.e. the same day as randomisation – as any changes were immediately made and appropriate medication prescribed.

If rate-control criteria were not met at baseline, patients re-attended at 4 weeks for repeat resting and ambulatory rate control assessment, recommended to be assessed at 6 minute walk whenever possible. A further visit was scheduled at 8 weeks if rate control was not achieved.
Given that catheter ablation of AF, in patients who do not have an indication for pacing, could potentially avoid the need for either AV node ablation or pacemaker insertion, the protocol did not specifically recommend either pacing or pacing/ablation for those who failed rate control. These strategies were permitted if clinically indicated and the use of these techniques would be recorded for purposes of retrospective outcome analysis.

2.5.2 Catheter ablation group

Patients who were randomised into the catheter ablation group undergo percutaneous radiofrequency catheter ablation as set out in section 2.6. At randomisation, a provisional date was identified found for catheter ablation. Unless medically indicated, no adjustments to medication were made at this point. Once the date for ablation was confirmed, patients without pacemakers were given advice to half rate control medication on the day prior, and to omit this on the day of the procedure, to minimise the risk of profound sinus bradycardia on restoration of sinus rhythm.

The follow-up period did not start immediately at randomisation, but on the date of the first scheduled ablation procedure. Previous studies have been variable in reporting and execution of follow up after catheter ablation procedures: in some cases follow up has been commenced after the ‘last successful’ ablation procedure, which would theoretically allow ‘resetting’ of the follow up time indefinitely; alternatively a limited ‘treatment phase’ could be set, followed by follow up without treatment. The former would skew the true follow up times between groups in an intervention versus non-intervention study such as ARC-HF, so this type of approach was avoided. The latter could involve effectively withholding therapy for recurrent atrial arrhythmias, which may be readily amenable to ablation particularly if atrial tachycardia was the presenting rhythm, where it may reflect a positive transition on the ‘journey’ from AF towards lasting sinus rhythm. However it was deemed appropriate to
commence follow up once treatment in the ablation arm had begun, and not reset for repeat procedures.

### 2.6 Catheter ablation protocol

*For a more detailed procedural protocol please see chapter 4.*

Anticoagulation strategy for the procedure followed contemporary local protocol. Until December 2010, all patients undergoing AF ablation stopped oral anticoagulation (e.g. warfarin) five days before the procedure, and received subcutaneous injections of low molecular weight heparin (1.5mg/kg) until 24 hours prior to ablation. Bridging therapy was resumed after the procedure as below. From January 2011, all procedures were performed on uninterrupted warfarin with an INR in the range 2-3.5.

The procedure was performed under general anaesthesia in all cases. A trans-oesophageal echocardiogram (TOE) was performed to exclude thrombus in the left atrial appendage, assess patency of the interatrial septum, and assess pulmonary venous anatomy.

Thereafter radiofrequency catheter ablation was performed using a 3.5mm irrigated-tip ablation catheter guided by a three-dimensional mapping system. Catheter ablation involved the following strategies, in a stepwise fashion:\(^{243}\):

- Circumferential antral electrical isolation of all four pulmonary veins confirmed by a circular pulmonary vein mapping catheter.
- Linear ablation within the left atrium at the roof and mitral isthmus
- Further ablation guided by mapping of complex fractionated electrograms (CFE) within the left atrium
- DC cardioversion to sinus rhythm
• Linear ablation in the cavo-tricuspid isthmus (CTI) within the right atrium

In order to assess electrophysiological properties of the atria, prior to and after each stage of ablation during AF, the atrial fibrillation cycle length was recorded in both atria at the level of the appendages, and a contact map of local electrogram mean cycle length (see chapters 3 and 4) acquired using a multi-polar mapping catheter. The map acquired after roof and mitral isthmus line was guide ablation of CFE in the left atrium.

Once sinus rhythm was restored, all linear lesions were assessed for integrity by pacing and sensing manoeuvres from the left atrial appendage and posterior wall (for the roof and mitral lines) and the coronary sinus (for the CTI line). This technique is discussed in detail in chapter 4.

The minimal therapeutic goal was isolation of all pulmonary veins. If atrial tachycardia (AT) ensued at any point thereafter, the AF ablation protocol was terminated and the AT was mapped and ablated as appropriate. All those with persisting AF underwent further ablation in a stepwise fashion until completion of the left atrial ablation protocol or until sinus rhythm was restored. If sinus rhythm or AT was not achieved by the end of left atrial CFE ablation and final mapping, DC cardioversion was performed.

Peri-procedural fluid management was dealt with on a case-by-case basis: patients were generally not pre-hydrated, given the likelihood of a large amount of transcatheter irrigation during the procedures. Loop diuretics were given towards the end of procedure if appropriate, although were typically avoided earlier on to avoid hypotension under anaesthesia and the need for vasopressors.

For patients bridged off warfarin, anticoagulation with low-molecular weight heparin and warfarin was started 6 hours after the ablation in the absence of active bleeding. Patients were
routinely kept for a minimum 1-night stay, and routinely discharged if transthoracic echocardiography was satisfactory (without significant pericardial collection) the day after ablation.

A 2-month ‘blanking period’ was chosen when assessing arrhythmia recurrence. Although the contemporary international consensus statement recommended 3 months, the choice of 2 months would at worst underestimate success for catheter ablation, and is consistent with other clinical trials of 6-12 months duration, aiming to allow repeat intervention when necessary in this cohort of patients where rhythm fluctuation could be detrimental. During the blanking period, any recurrence of AF or new onset of atrial tachycardia could be treated by DC cardioversion. Further atrial tachyarrhythmias which developed after the ‘blanking’ period led to scheduling of a second ablative procedure. A maximum of 3 ablations could be performed during the study period.*

Antiarrhythmic therapy could be used at the discretion of the physician in the first 2 months. At a maximum of 2 months antiarrhythmic drugs, other than non-sotalol beta-blockers, were stopped unless there was a separate on-going indication (e.g. ventricular arrhythmias); after this time any continuation or initiation was recorded.

* Redo ablation procedures, when indicated, followed a similar protocol: i) pulmonary vein isolation was confirmed and re-established when necessary; ii) atrial tachycardia was diagnosed and treated in the conventional manner (see chapter 4); iii) linear lesions were re-ablated in sinus rhythm if there was reconnection until bidirectional block was confirmed with a minimum 15 minute waiting time; iv) CFE ablation was performed if AF persisted – within the left or right atrium; v) further lesions could be added in either atrium at operator discretion
2.7 Follow-up visits

The onset of the follow-up period was defined in the rate control group at commencement of therapy (i.e. upon randomisation), and at the first scheduled ablation procedure in the catheter ablation group. Thereafter, visits were scheduled for assessment and investigation at or near 3, 6, and 12 months. Patients underwent the following repeat assessments:

- Quality of Life Questionnaire (all visits)
- History and clinical examination (all)
- 12-lead ECG (all)
- Blood tests: full blood count, urea and electrolytes, liver function tests, thyroid function tests, lipid profile, CRP, BNP, plasma for biomarkers (all)
- Cardiopulmonary exercise test (baseline, 3, and 12 months)
- Six minute walk test (all)
- Radionuclide ventriculography (baseline and 12 months)
- 48 hour Holter monitoring (baseline, 6, and 12 months)
- Transthoracic echocardiogram (baseline, 6, and 12 months)

A flowchart showing the overall trial structure is shown in Chapter 7 (Figure 7-1)
2.8 Power calculations and statistical analysis

2.8.1 Power calculation

The primary endpoint, peak VO2, is known to be reduced in AF patients and has been shown to improve after cardioversion approximately 10-15%.\textsuperscript{223,225,226} It has been shown to be 13% lower in heart failure patients with AF compared to sinus rhythm.\textsuperscript{222}

The study was designed to detect an effect size in VO2, comparing ablation with rate-control, of 0.80 times the size of the standard deviation of difference, with two-sided alpha 0.05, power 80%. If the standard deviation per group was 12.5% (e.g. 2ml/kg/min for patients with VO2 of the order of 16 ml/kg/min) this would mean ability to detect a difference of 1.6 ml/kg/min (i.e. 10%) which would be deemed clinically relevant based on prior studies.\textsuperscript{217,246,247} The number of patients required was 25 in each group.

There was an expectation for some patients to drop out of the protocol during follow up, either through declining catheter ablation during the pre-procedural phase after randomisation, or for patients in the rate control arm wishing to undergo ablation. Although a recent randomised study of catheter ablation had shown no drop-out,\textsuperscript{240} that was a study with two interventional arms where patients may be motivated to continue. A contemporaneous study, from the same investigatory group, comparing catheter ablation with medical therapy (in a non-heart failure cohort) showed crossover rate of 9% and 63% interventional (ablation) and non-interventional (medical) arms respectively.\textsuperscript{241} The latter could be seen in the context of a multi-centre study where crossover was protocolised. In contrast, ARC-HF was designed as a single centre study to be coordinated by a single investigator, and where crossover was both strongly discouraged and not formally protocolised. Nevertheless, it was concluded that the proposed recruitment target should include an adjustment to account for
20% dropout, although this could be reviewed according to actual recruitment versus dropout rate during the study. This was reflected in the initial details registered on ClinicalTrials.gov in April 2009.

The *Minnesota Living With Heart Failure Questionnaire (LHFQ)* quality of life score has been shown to improve with heart failure intervention. In a study of CRT published 2002, there was an improvement in score from $78+/-24$ to $52+/-23$.\textsuperscript{112} More recently, an observational study found CRT in AF patients led to a 25.2 point improvement in score.\textsuperscript{248} In PABA-CHF the improvement was approximately 20 points.\textsuperscript{240} Based on the above sample size, the study would be powered to detect a change of 20 points assuming a group standard deviation of 25.

*Left ventricular ejection fraction (LVEF)*, as assessed by radionuclide ventriculography, might be expected to increase of the order 5-20% in those restored to sinus rhythm based on previous studies.\textsuperscript{133, 135} The study was powered (at 80%; alpha 0.05) to detect an absolute improvement of 10% in (SD 20) in LVEF between groups.

The study was designed to detect event endpoints. A composite endpoint for cardiovascular events and death was pre-specified as above in order to collect relevant data, but power calculation was deemed inappropriate.

### 2.8.2 Statistical analysis

Continuous baseline variables are presented as mean ± standard deviation (SD). Categorical variables are presented as frequency/percentage(%), and compared with Fisher’s-exact or Chi-squared test. Outcomes were assessed, on an intention-to-treat basis, by independent comparison of absolute changes from baseline. Parametric data were analysed by t-test and
represented as mean and 95% confidence interval (CI); non-parametric/ordinal data were analysed by Mann-Whitney U-test and represented as median and interquartile range (IQR).

A composite endpoint (using the Hochberg modification of the Bonferroni procedure\textsuperscript{249} for multiple tests of significance, with 3 parameters similar to recent published studies\textsuperscript{240, 250, 251}) was defined, consisting of ejection fraction, 6-minute walk distance (6MWD), and LHFQ score. The endpoint would be achieved if all 3 component endpoints have P value <0.05, if two have P < 0.025, or if one had an endpoint <0.017.

The composite (secondary) endpoint for major cardiovascular events was analysed by the Kaplan-Meier method and represented as an event-free survival curve. Arrhythmia-free survival was also analysed by Kaplan-Meier method.

A two-sided level of p < 0.05 was considered statistically significant. All the above calculations and further exploratory or post-hoc analyses were performed with SPSS version 20 (IBM).
3 High density mapping in human atria

3.1 Abstract

3.1.1 Introduction

There is an increasing need for catheter ablation procedures to treat complex atrial tachycardias (AT) and atrial fibrillation (AF), often requiring detailed endocardial mapping. Sequential point-to-point contact mapping of complex arrhythmias is time consuming and may not always be feasible. This study assessed the utility of a novel spiral duo-decapolar high-density (HD) mapping catheter to delineate complex arrhythmia substrates for ablation.

3.1.2 Methods

Patients underwent HD mapping using a spiral catheter (AFocusII) and the EnSite NavX system, during catheter ablation procedures to treat atrial arrhythmias.

3.1.3 Results

In 26 patients, a total of 32 atrial arrhythmias were mapped and ablated, comprising 5 focal AT, 8 macroreentrant AT, 11 persistent AF and 8 paroxysmal AF. The HD catheter was used to acquire endocardial surface geometries in all cases, and to map the pulmonary veins in patients undergoing AF ablation. In persistent AF, HD catheter mapping permitted creation of highly detailed complex fractionated electrogram (CFE) maps (left atrium 449±128 points in 7.2±2.6min, right atrium 411±113 points in 6.7±1.6min). In AT, activation mapping was performed with acquisition of 305±158 timing points in 7.3±2.6 minutes, guiding successful
ablation in all cases. During follow up of 7.0±2.6 months, all AT patients remained free of significant arrhythmia.

### 3.1.4 Conclusions

High-density contact mapping with a novel spiral multipolar catheter allows rapid assessment of focal and macroreentrant AT, and complex fractionated electrical activity in the atria. It has further multi-functional capabilities as a pulmonary vein mapping catheter, and for accurate geometry creation when used with a 3 dimensional mapping system.
3.2 Background

Over the past decade there have been major advances in the mapping and ablation of both atrial and ventricular tachycardias. The exponential rise in catheter ablation cases has resulted from both an increased incidence of atrial arrhythmias and the expectations of electrophysiologists to successfully treat them by catheter ablation. The recent focus in technology has been to generate electro-anatomical maps superimposed upon patient-specific geometries derived from CT/MRI/real-time echocardiograms of the cardiac chamber in question. This has been very successful in both delineating arrhythmia mechanisms and the identification of suitable targets for ablation.\footnote{252} However, the creation of electrical-anatomical maps still requires detailed point-by-point contact data acquisition that is time consuming, lacks resolution and may be difficult for irregular or non-sustained atrial tachycardias (AT). Non-contact mapping has the advantage in mapping non-sustained arrhythmias but there may be loss of resolution in the unipolar electrogram reconstruction process compared with contact bipolar systems\footnote{253} particularly in scarred atria. Accuracy is dependent on distance of the endocardial surface from the mapping array which further limits its use in dilated and complex chambers such as the left atrium.\footnote{254}

There is an increasing recognition that patients with persistent atrial fibrillation (AF) may benefit from ablation of complex fractionated electrograms (CFE).\footnote{127} These electrograms are often of low amplitude, beyond the resolution of a non-contact mapping array, and their identification by sequential point-to-point mapping is a time consuming process that significantly prolongs procedure times.\footnote{255}, \footnote{256} The process of sequential data collection could be improved by the use of multipolar contact mapping.\footnote{257}, \footnote{258} The pre-existing multispline catheter may be utilised for this,\footnote{205}, \footnote{242} although its distal configuration may not be optimal for all endocardial surfaces, for example the pulmonary venous antra where a conventional
circular mapping catheter might additionally be required. However, the latter catheter is not specifically designed for en face mapping of the atrial wall, requiring multiple overlapping sites to create a detailed map.

The followed study assessed the utility of a novel spiral high-density (HD) contact mapping catheter used in conjunction with a 3D mapping system to delineate complex arrhythmia substrates for ablation.

3.3 Methods

3.3.1 Patient population

Patients referred for electrophysiology study and catheter ablation of atrial arrhythmias between February and July 2009 at Royal Brompton Hospital, Harefield Hospital, and The Heart Hospital, London, were included in the study. The study population comprised unselected patients with complex arrhythmias in whom the HD mapping catheter was used in this time period. All patients gave written informed consent prior to the procedures.

3.3.2 Electrophysiology study and ablation procedure

Procedures were performed under conscious sedation (n=10) or general anaesthesia (n=16) in a post-absorptive state. Transoesophageal echocardiography was performed to exclude intracardiac thrombus prior to mapping and ablation. Femoral venous access was used in all cases and either standard single or double transseptal puncture performed to allow a sheath and catheter to access the left atrium when necessary, depending on operator preference, followed by anticoagulation with Heparin to maintain an activated clotting time of 250-350 seconds.
In all cases, the Ensite NavX 3-dimensional mapping system (St Jude Medical, St Paul, MN) was employed to display real-time catheter positions, create 3D chamber geometries, display bipolar electrogram information, and to guide catheter navigation for mapping and ablation.\textsuperscript{252, 259} For all procedures, an intracardiac electrode was chosen as a stable geometric reference, either within the coronary sinus or using a fixed reference in the right atrium. No image CT/MRI image integration was performed as per local practice.

### 3.3.3 High density mapping

The HD (AFocusII, St Jude Medical) catheter is a 20-pole catheter with a distal spiral configuration (7F shaft, 4F spiral ring). This can be used for both geometry creation and high-density contact electrogram mapping, deployed in the appropriate chamber through a long sheath (Preface, Biosense Webster or Mullins/SL1, St Jude Medical). The HD catheter has a primary unidirectional deflectable curve controlled at the handle. During the study period 2 versions were available – one having close-paired bipoles with 7-1-7mm spacing, and the other with even 4-4-4mm spacing (Figure 3-1). The latter may therefore be configured to record 19 simultaneous bipolar signals (1-2, 2-3 and so forth), although for purposes of this study and consistency of point density, 10 bipoles were recorded from each catheter. No comparison was made between the two types of spiral catheter, as the majority of cases used the 4-4-4 spaced catheter which has been the only prototype made available commercially. The catheter was used to create 3D reconstructions of the atria and pulmonary veins as required, and then for endocardial activation and voltage mapping during spontaneous and/or induced atrial arrhythmia.
3.3.4 Activation mapping

ATs were mapped by a combination of entrainment and activation mapping, the latter using the Diagnostic Landmark Mapping feature of the system. A time window for activation was set just below the tachycardia interval usually encompassing at least 90% of tachycardia cycle length. Where a P wave was inscribed, at least 100ms of the window was allocated prior to P-wave onset.
To study local activation time (LAT), data from all available bipoles were acquired. Using the diagnostic landmark function, electrogram deflections were automatically annotated by a QS morphology or max –dV/dt and displayed in a standard colour to time coded isochronal sequence map on the reconstructed 3D chamber geometry. At each collection point, the data for up to 10 cycles were stored and analysed for consistency. Data points were deemed inaccurate if poor contact or noise artefact occurred. These points were manually checked and deleted or re-sampled to an appropriate cycle retrospectively for inclusion. After multipoint acquisitions, annotation markers were checked for consistency - defining local activation as the first steep deflection from baseline. Interpolation and surface projection settings were set at 10mm. Thus, points not in contact (<10mm) with the atrial surface were rejected automatically and not analysed. AT mechanism was defined, after analysis of isochronal and propagation maps, as macroreentrant (MR) if continuous activation could be mapped accounting for >95% of cycle length (CL), and confirmed whenever possible by concealed entrainment from within the circuit. AT was defined as focal (FAT) if mapping defined a focally-emanating source with centrifugal activation.

### 3.3.5 Complex fractionated electrogram (CFE) mapping

CFEs were defined as fractionated high frequency potentials exhibiting multiple deflections from the isoelectric line and were characterised using the CFE-mean tool within the NavX system. CFE-mean is defined as the mean time between consecutive deflections during a predefined recording period, and has been recently described in detail.\(^{257}\) CFEs were defined when the CFE-mean was between 30 and 120ms, with colour spectrum set across the range 80-120ms (30-79ms white, >120ms purple), although this could be altered retrospectively. On the basis of published data 5 seconds was chosen as the recording duration at each site.\(^ {257}\) The catheter was maintained in a stable position for at least 5 seconds prior to each
acquisition. Signals were sampled at 1,200Hz, band-pass filtered between 32 and 300Hz and annotated using the ‘Diagnostic Landmark’ (St Jude Medical) tool on 1-second update. Settings were standardised to: dV/dt detecting width 10ms, refractory period 30ms, sensitivity 0.04-0.1mV, interpolation and surface projections 10mm based on previous studies.\textsuperscript{201, 205, 257} Points >10mm from the geometric surface were considered as non-contact (‘unused’) points and not displayed on the CFE map. In patients undergoing CFE mapping, the following parameters were recorded: time for complete mapping of each chamber and net points acquired (total minus ‘unused’).

3.3.6 Radiofrequency ablation

Radiofrequency ablation (RFA) was then performed in all cases using an open-irrigated 3.5mm or 4mm tip catheter (Celsius Thermocool, Biosense Webster, Diamond Bar, CA; Cool Path Duo, St Jude Medical), flow rate 17-30ml/min, with temperature limited to 48\textdegree{}C, power limits of 30-35W in the LA, 30W on posterior wall, 25W near venous ostia or within coronary sinus, and 45W in the cavotricuspid isthmus.

3.4 Results

3.4.1 Group Results

Patient characteristics, underlying diagnoses, and intra-procedural findings are presented in Table 3-1. A total of 26 patients (22 male), 59±11 years old (24-77years), were studied. 3 patients had complex congenital heart disease, 8 had paroxysmal AF and 11 had persistent AF. 4 patients had AT (2 persistent) following prior AF ablation, refractory to anti-arrhythmic drugs ± attempts at cardioversion.
Table 3-1 Patient characteristics and summary of ablation strategy

Atrial tachycardia cases are shown in bold

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Aetiology</th>
<th>Diagnosis</th>
<th>Ablation</th>
<th>PT (min)</th>
<th>ST (min)</th>
<th>RF (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>58</td>
<td>hypertension</td>
<td>PAF</td>
<td>PVI</td>
<td>303</td>
<td>35</td>
<td>125</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>76</td>
<td>transplant</td>
<td>AT (macro)</td>
<td>CTI flutter</td>
<td>224</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>72</td>
<td>post-surgical</td>
<td>AT (macro/focal)</td>
<td>peri-right atriotomy</td>
<td>244</td>
<td>53</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>63</td>
<td>congenital (l-TGA)</td>
<td>AT (focal)</td>
<td>lateral RA (crista)</td>
<td>180</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>63</td>
<td>hypertension, prior PVI</td>
<td>AT (focal)</td>
<td>septum, posterior LA, PVI</td>
<td>360</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>57</td>
<td>hypertension, prior PVI</td>
<td>AT (macro)</td>
<td>peri-mitril</td>
<td>230</td>
<td>51</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>24</td>
<td>congenital (Fontan)</td>
<td>AT (macro)</td>
<td>right atriotomy, peri-IVC</td>
<td>300</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>62</td>
<td>ischaemic</td>
<td>persAF</td>
<td>PVI, CFE</td>
<td>360</td>
<td>39</td>
<td>55</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>62</td>
<td>ischaemic</td>
<td>persAF</td>
<td>PVI, linear</td>
<td>170</td>
<td>66</td>
<td>47</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>62</td>
<td>dilated cardiomyopathy</td>
<td>PAF</td>
<td>PVI, CFE</td>
<td>180</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>54</td>
<td>hypertension</td>
<td>persAF</td>
<td>PVI, linear, CFE</td>
<td>270</td>
<td>51</td>
<td>45</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>58</td>
<td>lone</td>
<td>PAF</td>
<td>PVI, CTI</td>
<td>275</td>
<td>79</td>
<td>41</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>52</td>
<td>chronic RV pacing</td>
<td>AT (macro)</td>
<td>perimiral, perim-right PV</td>
<td>295</td>
<td>70</td>
<td>21</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>77</td>
<td>ischaemic</td>
<td>persAF</td>
<td>PVI, linear, CFE</td>
<td>290</td>
<td>70</td>
<td>41</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>59</td>
<td>dilated cardiomyopathy</td>
<td>persAF</td>
<td>PVI, CFE</td>
<td>270</td>
<td>36</td>
<td>49</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>59</td>
<td>congenital (anomalous PV)</td>
<td>persAF</td>
<td>PVI, CFE</td>
<td>191</td>
<td>58</td>
<td>52</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>38</td>
<td>lone</td>
<td>persAF</td>
<td>PVI</td>
<td>142</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>43</td>
<td>dilated cardiomyopathy</td>
<td>PAF</td>
<td>PVI</td>
<td>300</td>
<td>68</td>
<td>87</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>60</td>
<td>dilated cardiomyopathy</td>
<td>persAF</td>
<td>PVI, linear, CFE</td>
<td>204</td>
<td>73</td>
<td>42</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>68</td>
<td>ischaemic</td>
<td>persAF</td>
<td>PVI, linear, CFE</td>
<td>215</td>
<td>69</td>
<td>52</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>60</td>
<td>hypertension</td>
<td>persAF</td>
<td>PVI, linear, CFE</td>
<td>224</td>
<td>69</td>
<td>60</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>60</td>
<td>lone</td>
<td>PAF</td>
<td>PVI</td>
<td>184</td>
<td>24</td>
<td>44</td>
</tr>
<tr>
<td>23</td>
<td>M</td>
<td>56</td>
<td>lone</td>
<td>PAF</td>
<td>PVI, CTI</td>
<td>186</td>
<td>29</td>
<td>61</td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>66</td>
<td>diabetes, prior PVI</td>
<td>PAF</td>
<td>PVI, linear, CTI</td>
<td>375</td>
<td>72</td>
<td>61</td>
</tr>
<tr>
<td>25</td>
<td>M</td>
<td>63</td>
<td>ischaemic</td>
<td>persAF</td>
<td>PVI, linear, CFE</td>
<td>270</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>65</td>
<td>lone, prior PVI</td>
<td>AT (macro)</td>
<td>perimiral, PVI</td>
<td>180</td>
<td>45</td>
<td>35</td>
</tr>
</tbody>
</table>

PAF=paroxysmal AF, persAF=persistent AF; macro=macroreentrant AT; PVI = antral pulmonary vein isolation. PT=procedure time (total cath lab time including anaesthesia), ST = fluoroscopy screening time, RF = total radiofrequency ablation time

A total of 32 atrial arrhythmias were mapped and ablated: 5 were defined as focal AT (3 RA, 2 LA), 8 as macroreentrant (MR) AT (4RA, 4LA), 11 persistent AF and 8 paroxysmal AF. A close-paired spacing spiral catheter was used in 9 early cases (cases 1-8 and 12), and evenly-spaced in the remaining 17. For the patients with AT, a total of 305±158 HD derived LAT points were collected over 7.3±2.6 minutes. The range of point-acquisition rates was wide at 24-112 points per minute, explained by the differing anatomies and presence of non-sustained tachycardias. Macroreentrant circuits were found involving the following structures: cavotricuspid isthmus (n=1), RA atriotomy (3), mitral isthmus (3), and peri-right PV utilising
the septal mitral isthmus (1) all with demonstrable concealed entrainment. Focal ATs were found to emanate from: Crista terminalis (1), Peri-RA atriotomy (2), LA septum (1), and posterior LA (1). In addition, a left upper pulmonary vein tachycardia was seen in patient 22 during initial PV mapping and terminated during antral PV isolation (PVI). The study did not prospectively define a follow up period or minimal ECG monitoring, as the intention was to investigate the acute handling and mapping capabilities of the spiral catheter. However, during 7.0±2.6 months follow up, patient 3 had one documented episode AT on his device which was terminated by anti-tachycardia pacing (previously ineffective for AT prior to ablation), whilst all other patients remained free of AT, as judged by clinical,12 lead ECG and minimum 48 hour Holter at follow up.

Examples of the different atrial arrhythmias mapped by the HD catheter are discussed below.

3.4.2 Macro re-entrant tachycardias

3.4.2.1 Patient 7 – Fontan atrial tachycardia

This 24 year old woman with a past history of Fontan surgery for univentricular physiology had repeated hospitalisations for AT episodes often with 1:1 AV conduction. Burst pacing induced her clinical AT CL 300ms with 1:1 AV conduction. HD mapping was used from the outset to create a map of the RA with 288 surface points in 5 minutes.

This showed a macroreentrant circuit around the inferior border of the atriotomy scar. Linear ablation connecting the scarred zone to the IVC terminated tachycardia (Figure 3-2). A further macroreentrant tachycardia was induced, utilising a small mid-atriotomy channel, which was mapped (345 points, 7 minutes) and ablated in a similar fashion, rendering all AT non-inducible.
Figure 3-2  Fontan atrial tachycardia.
Right anterior oblique (left) and left posterior oblique (right) projections of Fontan atrium in patient 7. Yellow dots show mapping points superimposed on acquired geometry surface. Isochronal map during initial tachycardia (CL 300ms), with peri-IVC circuit through scar-IVC isthmus (solid arrow); broken arrows show colliding wavefronts at the superior border of the anterolateral atriotomy scar. Lower EGM panel shows highly fractionated (asterisks) electrogram in slow conduction zone (arrowed) between atriotomy and IVC, where ablation (brown dots) terminated AT (upper panel). SVC = superior vena cava; IVC = inferior vena cava

3.4.2.2 Patient 26 – Left atrial tachycardia post AF ablation
This 65 year old man with previous lone AF had undergone PVI but had recurrent paroxysmal AF, with other ECGs suggestive of atrial tachycardia. A cavotricuspid isthmus line was initially created to prevent typical isthmus dependent flutter identified. Burst atrial pacing then induced a stable tachycardia identical to the clinical AT on surface ECG. The ATCL was 220ms, with PPI TCL+8ms from septal mitral valve isthmus. A rapid activation map was acquired (143 points in 5 minutes; Figure 3-3) demonstrating peri-mitral flutter, which
slowed and terminated during linear ablation at the lateral mitral isthmus (involving both CS-epicardial and endocardial approach). Bidirectional block was confirmed conventionally, and no tachycardia was inducible thereafter.

Figure 3-3  **Left atrial tachycardia after previous AF ablation.**

Posterior (left) and anterior (right) projections of the left atrium (patient 26), showing isochronal mapping data during peri-mitral (solid arrow) left atrial tachycardia. The timing window is set to demonstrate ‘head-meets-tail’ (purple-white-red) in the region of the posterolateral mitral valve isthmus, and caudocranial block at the posterior roof (broken arrows show colliding wavefronts). Ablation points are shown as red dots on the endocardium between left inferior pulmonary vein and mitral valve annulus, and the free floating orange balls show the position of ablation lesions within coronary sinus to achieve mitral isthmus block. EGM panel shows mitral isthmus block after ablation: while pacing HD catheter from LAA (left atrial appendage) there is proximal to distal activation in the coronary sinus recording indication no activation from the isthmus end

### 3.4.3 Focal AT

#### 3.4.3.1 Patient 4 – Focal AT in congenital heart disease

A 63 year old man with congenitally corrected transposition (ventricular inversion), an atrial septal defect and moderately impaired systemic RV function presented with recurrent drug-refractory attacks of AT. He had not undergone any prior cardiac surgery. His clinical AT
with CL 250ms was induced. Conventional mapping excluded isthmus dependent flutter. The RA activation sequence suggested a high RA or high superior PV origin. The focally-emanating AT was rapidly localised by HD mapping (563 points in 5 minutes) to the superior part of the crista terminalis (Figure 3-4), and successfully ablated.

**Figure 3-4** Focal tachycardia in congenitally corrected transposition.
Modified lateral (left) and postero-inferior (right) views of biatrial geometry and superimposed isochronal map in Patient 4. 563 points were acquired in 5 minutes allowing rapid identification of a focally emanating source (white) near the Crista terminalis, which was successfully ablated (brown dots). Inset panel shows a highly fractionated local bipolar electrogram (arrowed) at the successful ablation site

### 3.4.4 Non-sustained AT

#### 3.4.4.1 Patient 3 – non-sustained AT after prior cardiac surgery

A 72 year old man with a prior Starr-Edwards aortic valve replacement for rheumatic aortic valve disease, left ventricular impairment and a CRT-D device presented to pacing clinic with
increasing dyspnoea and ankle oedema. Sustained AT was noted, and pace-terminated via the device. Device interrogation revealed earlier non-sustained ATs. At the procedure, after geometry creation in sinus rhythm, burst pacing induced AT with CL 460ms. The tachycardia terminated early during right atrial mapping. Right atrial geometry and bipolar voltage was acquired in sinus rhythm, showing an area of very low voltage on the lateral wall consistent with a prior atriotomy. Empiric ablation was performed at the cavitricuspid isthmus, achieving bidirectional block. Attempts at re-induction always produced non-sustained (5-20 second) runs of AT. Using live and recorded electrogram data, HD mapping was used to assess activation and voltage in the region of interest (peri-atriotomy). All tachycardias (AT2 CL 430-450ms, inferior to mid-scar; AT3 490-510ms, lateral scar border) appeared to be focally emanating from the peri-scar region in the lateral RA wall, however on further inspection it was apparent the first of these was probably macroreentrant involving a discrete channel in the atriotomy scar (Figure 3-5); entrainment manoeuvres were not feasible as the tachycardia would not sustain. Radiofrequency energy was applied to the channel during both tachycardia and CS pacing and 2 regions of early activation as identified by prior mapping. No tachycardia was inducible thereafter.
Figure 3-5  Non-sustained atrial tachycardia.

Right and left anterior oblique projection of right atrial activation map in AT1, patient 3. The area of low-voltage (bipolar amplitude <0.05mV) from mapping in sinus rhythm is outlined in black. Note incomplete RA map due to non-sustained tachycardia (89 points taken in real-time), although rapid mapping of the scar border zone revealed likely macroreentry, utilising a channel in the scar. Ablation at this site (arrowed, with local electrogram) rendered AT1 non-inducible. Two further non-sustained AT were focally emanating and ablated inferior and lateral to scar border (brown ablation points). TVA=tricuspid valve annulus; CS=coronary sinus

3.5 Atrial fibrillation

The AF cases were considered as a group. 8 patients with paroxysmal AF, and 11 with persistent AF were studied. In all cases the HD catheter was used to create LA geometries,
and as a pulmonary vein mapping catheter. The HD catheter was also used to confirm conduction block of antral isolating lines by pacing. A total of 73 PVs were mapped with the HD catheter (3 cases of common left pulmonary vein), and subsequent isolation established in all cases by confirmation of PV entrance block or dissociated PV potentials.

In persistent AF cases, CFE maps (Figure 3-6) were acquired in 9 patients (total 9 RA maps, 23 LA maps). Acquisition times (mean±SD) for complete endocardial colour coverage (at 10mm interpolation), number of points acquired (net, after exclusion of unused off-surface points), and calculated points /minute (p/min) for each atrium were as follows: RA 6.7±1.6 min, 411±113 points, 63±15 p/min; LA 7.6±2.4min, 449±128 points, 64±24 p/min. PVI is performed as the first step in persistent AF ablation, with linear and/or CFE ablation performed at operator discretion. CFE ablation here was performed using algorithmic map data and/or conventional RF-catheter information.

Persistent AF was converted to atrial flutter with ablation in 2/11 cases. One was successfully ablated, and the other had multiple ATs of changing morphology and cycle length, and sinus rhythm was restored by DC cardioversion. At 5.1±1.6 months follow up, 5/11 (45%) persistent AF patients had recurrence of AF, 4 of whom underwent repeat ablation; 3/8 (37.5%) of paroxysmal patients had recurrence of arrhythmia requiring repeat ablation (all of these had PV reconnection; 1 patient had AT from the right PV terminated by re-isolation).

Geometry acquisition, handling and mapping characteristics were comparable to a standard multipolar circular mapping catheter, although this was not quantitatively assessed. Reconstruction around venous ostia, at the venous carina, and at the left atrial appendage ridge appeared accurate based on fluoroscopic assessment and 3D mapping, as long as the usual reassignment to multiple geometries is made to avoid false interpolation. No geometries required ‘touch-up’ from the mapping/ablation catheter. There was no significant learning
curve observed with the catheter, although we noted some unique handling characteristics which differ from standard circular catheters: i) the shaft is central relative to the spiral head, rather than eccentric as is necessitated by the design of circular catheters, which allows ‘telescoping’ of the central portion (poles 15-20) relative to the outer ring, which in turn permits mapping around irregular structures, smaller diameter pulmonary vein ostia, and permits minimal ‘tenting’ of the LA walls to create a surface which may be closely tracked by the subsequent mapping/ablation catheter; ii) the spiral head may become deformed and flattened relative to the shaft (default is perpendicular axis), however withdrawal into the sheath usually solves the problem – rarely the catheter had to be removed and restored to its perpendicular confirmation; iii) in 2 cases the pull-wire flexion mechanism failed, although in both it was during a long AF case with multiple catheter manipulations, and appeared to be where the whole of the flexible portion was not outside the transseptal sheath. Flexing only with the catheter fully advanced may avoid this complication.
Figure 3-6  **Complex fractionated electrogram maps in persistent AF.**

Posterior (left) and antero-superior (right) projection of left atrial complex fractionated electrogram (CFE) maps acquired by the HD catheter at baseline (*upper panel*), and after ablation (red dots - antral pulmonary venous isolation and roof line; *lower panel*). LAA= left atrial appendage. Colour settings: white <80ms, red-blue 80-120ms, >120ms purple. Sample contact bipolar electrograms (1 second snapshot) are shown, this example demonstrating a significant organisational effect of PVI and linear ablation with marked prolongation of local mean cycle lengths (CFE mean)
3.6 Discussion

This study describes the initial experience with a novel spiral multipolar catheter with high-density mapping capabilities used for a variety of atrial arrhythmias.

The principal advantage of this catheter is its ability to simultaneously acquire contact electrograms from multiple bipoles over a $3\text{cm}^2$ area allowing rapid, high-resolution data collection with minimal chamber distortion. Spiral conformation of the distal catheter obviates the need for multiple overlapping acquisitions as required with a standard circular catheter, and qualitatively appears to improve contact in complex areas such as around the PV anatomy compared with a multispline catheter. When combined with the 3D mapping system, extensive numbers of activation points can be collected in a relatively short time (mean 305 points in 7.3 minutes), allowing focal and macroreentrant ATs to be characterized quickly. It can be particularly useful for non-sustained tachycardias where rapidity of mapping is paramount: mapping with conventional techniques may either require repeated tachycardia inductions (if possible) or use of non-contact mapping.

As with existing multipolar catheter mapping,\(^{242}\) there are some caveats in the use of the HD catheter. When mapping circuits causing AT, not all electrodes may be in contact with the chamber wall at any one time and caution must be exercised in accepting all points during data collection. Those points out of timing with the general activation map should be checked for annotation accuracy to avoid misinterpretation. However, the mapping system can be programmed to display points in order of timing or acquisition, so one can readily identify incorrect annotations and/or unusual patterns of activation. Once these simple rules were followed, in conjunction with the NavX isochronal and propagation map functions, the differentiation of the 5 focal and 8 macro re-entrant AT was straightforward, including
patients with complex atrial substrates and multiple tachycardias (range 1-3). All of the 13 mapped AT were successfully identified and ablated.

3.6.1 Benefits over existing technologies

3.6.1.1 Atrial tachycardia

Increased rapidity and/or coverage of mapping should confer benefit in cases of relative haemodynamic instability, and in cases of non-sustained arrhythmia. As demonstrated in cases 2 and 26, complete maps with high-density point acquisition throughout are not necessary in most cases. However, higher density mapping can be rapidly performed in regions of interest, including at scar boundaries or near critical isthmuses. Furthermore, the case of patient 3 highlights potential capabilities of this system for mapping non-sustained arrhythmia, something that may otherwise require non-contact mapping. Our results compare favourably with mapping using a multi-spline catheter: Patel and colleagues mapped post-AF AT circuits, acquiring mean 365±108 points in 8±3 minutes; as commented in their study, this is faster than can be typically achieved with conventional point-to-point mapping.\textsuperscript{242} Although not specifically examined in this study, this form of mapping would be expected to reduce the time for scar-isthmus mapping in complex atrial substrates, and therefore may be superior to conventional point-to-point mapping.\textsuperscript{261}

3.6.1.2 Atrial Fibrillation

The flexible spiral design, in particular the telescoping property of the central portion of the spiral, allows the HD catheter to also be used for pulmonary vein ostial mapping, and subjectively facilitates accurate geometric reconstruction of complex structures such as the venous carina and appendage ridge. The pulmonary veins were mapped with the HD catheter alone in this series, to guide ablation and isolation. No PVs required additional mapping with
another catheter. In patients with persistent or chronic AF, high density mapping of CFEs was also performed to create local cycle length or ‘fibrillation interval’ maps, using the NavX system to guide ablation.

Similar high density mapping has been previously described by using a multi-spline catheter, but the shape of the spline catheter is less well adapted for PV mapping. Since the initial data supporting CFE ablation to eradicate AF, many investigators have targeted CFE during AF ablation, although outcome data is varied. A recent clinical trial reported that CFE-map guided CFE ablation combined with PVI improves success in patients with high AF burden (STAR-AF), however a recent randomised study showed that up to 2 hours of conventional CFE mapping and ablation after PVI provided no additional clinical benefit. Such discrepancies might relate to the heterogeneity of CFE as a substrate for ablation or the mapping techniques used. Observational errors can occur with subjective operator-determined conventional CFE mapping, and use of an ablation catheter for CFE mapping has potential disadvantages, which include requirement of sequential single point map creation, low tip-ring resolution and catheter deformation of the atrial surface which may change local activation. Two published studies have used automated algorithms for CFE-mapping, with single point-by-point acquisition resulting in mapping density only around 25% of the HD-acquired maps. The algorithm used here has been shown to have good sensitivity (0.75) and specificity (0.8) for correlation with physician-identified CFEs. The ability to rapidly acquire repeat CFE maps is desirable, given that 22% of CFE sites may show some degree of temporal change. This study has shown that the HD catheter could be an ideal tool for rapid high density mapping of CFE in the atria, if they are to be targeted during catheter ablation of AF.
3.6.2 Emerging technologies

High-density mapping is also possible with the recently available Mesh catheters (Bard, MA), giving a high spatial resolution of bipolar electrograms, shown to be a feasible and effective technique for mapping PV ostia.265, 266 The more recent innovation of the high-density mesh ablator (HDMA, Bard, MA) facilitates a single catheter approach to mapping and ablation of AF in situations where PVI is all that is required. However, the success rates for acute PV isolation and medium-late freedom from AF are significantly lower than for conventional irrigated-tip catheter ablation.267, 268 The success of PV isolation alone for treatment of persistent AF has been shown to be disappointing. Furthermore, these non-steerable expandable catheter technologies are not appropriately designed for mapping of the atrial walls, unlike the steerable multi-spline, circular or spiral catheters. If PV isolation alone is the goal, perhaps newer versions of these catheters will be appropriate for single-catheter solutions to AF. In the setting of persistent AF and/or post-AF atrial tachycardia, there is likely to be advantages of multi-polar mapping with suitably adapted catheters. Currently, this is only possible with the RF-impedance-based system used in this report, however novel catheter technology is being developed for magnetic-based mapping systems which will allow similar rapid geometry creation and activation mapping.269

3.6.3 Complications and safety

There were no unexpected difficulties encountered in manipulating the catheter around the atria and no complications encountered in any of the cases, including mitral valve entanglement or perforations. However, there should be vigilance for potential valve apparatus entanglement and appropriate knowledge of correct untangling manoeuvres (clockwise rotation of the shaft with withdrawal back into a long sheath to free the catheter).
3.6.4 Limitations

This was a dual-centre pilot assessment of the handling characteristics, safety, and utility of the spiral HD mapping catheter. The study did not set out to assess follow-up outcomes, thus the follow up period is relatively short and it is not possible to draw conclusions about long term arrhythmia freedom using this technique. No comparison was made with a conventional point-point 4mm-tip ablation catheter for tachycardia mapping, or with a circular catheter for PV mapping or geometry collection. Although the improved resolution of HD mapping may allow more accurate representation of scar boundaries and reduce wavefront misinterpretation due to low-density interpolation, investigation of this would require a comparative study with conventional point-point mapping. A higher density of points may be recorded with the even-spaced catheter if 19 sequential bipoles are acquired, and may allow less map interpolation and improved accuracy – particularly for CFE mapping, although only 10 were acquired during this study for consistency with the earlier close-spaced device. Larger randomised studies are required to assess the full clinical utility of the catheter on procedure/fluoroscopy time, and clinical outcomes from ablation.

3.7 Conclusion

A novel, multielectrode, mapping catheter with spiral distal conformation has been shown capable of multiple roles during catheter procedures for atrial arrhythmias. It permits pulmonary vein mapping, rapid coverage of the atria for activation (and voltage) mapping of focal and macro-reentrant AT, and rapid high-density mapping of complex fractionation during persistent AF. When used with a 3D mapping system capable of simultaneous multi-electrode sampling it may have a role in reducing the duration of complex ablation procedures, particularly those where CFE are targeted. The catheter also facilitates three-
dimensional geometry creation and may be used for conventional assessment of conduction block at the pulmonary veins or across linear lesions.

**Acknowledgement**

This work was performed in collaboration with the Heart Hospital, London, with Dr Anthony WC Chow and colleagues, who contributed some of the patient data and studies for analysis. The chapter has been published in modified form as a manuscript in *Journal of Interventional Cardiac Electrophysiology*.270
4 The impact of catheter ablation upon the AF substrate in heart failure

4.1 Abstract

4.1.1 Introduction

Ablation of persistent atrial fibrillation (AF) can be challenging, often involving not only pulmonary vein isolation (PVI) but also additional linear lesions and ablation of complex fractionated electrograms (CFE). This study examined the impact of stepwise ablation on a human model of advanced atrial substrate: persistent AF in heart failure.

4.1.2 Methods

Patients with persistent AF and left ventricular ejection fraction ≤35% were enrolled, including all patients randomised to the ablation arm of the ARC-HF study, and those who underwent ablation using the same protocol at the end of the study follow up period having been in the rate-control arm. High-density CFE maps were recorded bi-atrially at baseline, in the left atrium (LA) after PVI and linear lesions (roof and mitral isthmus), and bi-atrially after LA CFE ablation. The surface area of CFE (≤120ms) remote to PVI and linear lesions was defined as CFE-area.

4.1.3 Results

In 30 patients, a total of 168 CFE maps were recorded. CFE-area was reduced after PVI (18.3±12.03cm$^2$ to 10.2±7.1cm$^2$, p<0.001), and again after linear lesions (7.7±6.5cm$^2$, p=0.001). Complete mitral isthmus block predicted greater CFE reduction (p=0.02). Right
atrial CFE-area was reduced by LA ablation, from 25.9±14.1 to 12.9±11.8 cm$^2$ (p<0.001). AF terminated in 6 pts. Estimated 1-year arrhythmia-free survival was 72% after a single procedure. Incomplete linear lesion block was an independent predictor of any arrhythmia recurrence (HR 4.69, 95% CI 1.05-21.06, p=0.04).

4.1.4 Conclusions

Remote LA CFE-area was reduced following PVI and linear lesions. Furthermore, LA ablation reduced remote right atrial CFE-area. CFE reduction was greater in the presence of complete mitral block. Block of all lines was associated with a successful clinical outcome. The reduction of CFE-area by ablation at remote sites would suggest many of these phenomena do not represent sites of source activity driving fibrillation elsewhere. Robust linear ablation, following PVI, in an advanced persistent AF substrate, diminishes the target area for CFE ablation and also resulted in a favourable clinical outcome in this cohort.
4.2 Background

Catheter ablation of paroxysmal atrial fibrillation (AF) via *pulmonary vein isolation* (PVI) is highly effective.\textsuperscript{164, 271} In contrast, in the majority of those with persistent AF, particularly if long-lasting or associated with structural heart disease, PVI is crucial but alone is often insufficient for long-term maintenance of sinus rhythm.\textsuperscript{272} Ablation of *complex fractionated electrograms* (CFE), which may contribute towards – or reflect severity of – the atrial substrate,\textsuperscript{127} has shown variable benefit in randomized studies.\textsuperscript{244, 256} *Linear lesions* at the left atrial roof and lateral mitral isthmus can also improve outcomes.\textsuperscript{171, 176, 178} Combining these approaches appears beneficial,\textsuperscript{273} although the optimal ablation strategies and order of their application remain uncertain.

In patients with structurally normal hearts, PVI reduces remote left atrial CFE.\textsuperscript{274, 275} Experimental and clinical models suggest that, unlike the reversible *electrical* remodelling associated with atrial tachymyopathy or ‘lone’ AF, where remote CFE reduction might be explained by acute electrical remodelling, a more advanced atrial substrate is seen in heart failure with evidence of *structural* remodelling including dilatation and fibrosis, which are not acutely reversible.\textsuperscript{28, 58, 59, 65} In the latter population, the effect of PVI and linear lesions on CFE remote from ablation sites is not known.

This study sought to investigate the biatrial impact of stepwise ablation on CFE in patients with the advanced atrial substrate of persistent AF and HF, using the high-density mapping protocol developed in chapter 3, and to assess factors influencing procedural outcome.
4.3 Methods

4.3.1 Patient population

A total of 30 patients were recruited from the Ablation versus Rate Control for persistent atrial fibrillation in Heart Failure (ARC-HF) trial (ClinicalTrials.gov, NCT00878384). The population included all patients randomised to the ablation arm (n=24), and those in the rate control who underwent ablation using the same protocol at the end of their follow-up period (n=6). All had symptomatic persistent AF, without prior ablation, and left ventricular ejection fraction ≤35%.

Table 4-1  Baseline patient characteristics

n=30. AF = atrial fibrillation, BNP = B-type natriuretic peptide, BMI = Body Mass Index, LA = left atrial, LV = left ventricular

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD or N (%)</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63±10</td>
<td>62</td>
<td>56-71</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>25/5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of AF (months)</td>
<td>50±38</td>
<td>44</td>
<td>20.5-72</td>
</tr>
<tr>
<td>Current AF episode (months)</td>
<td>24±21</td>
<td>16.5</td>
<td>6.25-36</td>
</tr>
<tr>
<td>History of heart failure (months)</td>
<td>63±58</td>
<td>54</td>
<td>21-75</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>50±7</td>
<td>49</td>
<td>46-51.75</td>
</tr>
<tr>
<td>LV ejection fraction (radionuclide,% )</td>
<td>24±9</td>
<td>26.5</td>
<td>16.5-30</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>406±334</td>
<td>286</td>
<td>183-566</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29±5</td>
<td>29</td>
<td>25-32</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>12 (40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (23%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medications

- Beta-blockers 28 (93%)
- Angiotensin/aldosterone blockade 30 (100%)
- Amiodarone 3 (10%)
4.3.2 Electrophysiology Procedure

Procedures were performed on continuous oral anticoagulation (except prior to January 2011 patients received bridging low molecular weight heparin). After induction of general anaesthesia, transoesophageal echocardiography was performed to rule out intracardiac thrombus, assess atrial/PV anatomy, and subsequently to guide transseptal puncture for access to the left atrium. After transseptal puncture and placement of two long sheaths (Preface Biosense Webster, Diamond Bar, CA, USA) within the left atrium, all patients were additionally heparinised to achieve target activated clotting time (ACT) >300 seconds: the initial bolus dose was 7000-10000 I.U. in those not on warfarin, and 5000-8000 I.U. in those with a therapeutic INR, judged according to prevailing INR and patient body mass. ACT was measured after 5 minutes, and 10 minutes after any repeat bolus doses of heparin (1000-4000 I.U.) if given for ACT<300 seconds, and thereafter at 30-minute intervals throughout the procedure. Additionally, whenever possible, the transseptal sheaths were left on continuous side-arm flush with heparinised saline at 25-50ml per hour.

Catheters were inserted via the femoral veins: (i) a steerable decapole (CR Bard, Lowell, MA, USA) was positioned distally in the coronary sinus (CS), in order to act as a stable geometric reference for the duration of the long ablation procedure; (ii) a second roving decapole was placed initially in the right atrial appendage (RAA) to allow assessment of RAA cycle length (CL), and later in the CS proximal to the reference catheter, in order to permit pacing and sensing manoeuvres to assess linear block within the mitral and cavitricuspid isthmus towards the end of the procedure; (iii) a 20-pole high-density mapping catheter (AFocusII, St Jude Medical, St Paul, MN, USA) was inserted via a long sheath (Preface, Biosense Webster, Diamond Bar, CA, USA) to the right atrium (RA) and left atrium (LA) sequentially; (iv) a 3.5mm irrigated-tip F-curve catheter (Thermocool, Biosense Webster) was used for ablation,
with power limit of 35W in the anterior LA, 30W on posterior wall, 25W within CS, and 40W in the cavitricuspid isthmus (CTI). When necessary for navigation within a markedly dilated left atrium, a steerable transseptal sheath was utilised (Agilis, St Jude Medical).

The NavX system (version 8, St Jude Medical) was used with the AFocusII catheter to create separate left and right atrial geometries, within each using segmental geometries for venous structures to improve accuracy. Sequential atrial CFE maps were performed using the methods detailed below and in Figure 4-1: i) at baseline (RA and LA), ii) after PVI (LA only), iii) after both roof and mitral lines (LA only), and iv) after LA CFE ablation (RA and LA). RAA and left atrial appendage (LAA) cycle length (CL) was recorded at each stage by averaging the recording from a bipolar signal over 10 cycles.

### 4.3.3 Complex fractionated electrogram (CFE) mapping

To systematically identify CFE, high-frequency potentials exhibiting multiple deflections from the isoelectric line were characterised using the \textit{CFE-mean} tool within the Diagnostic Landmark mapping feature of NavX. \textit{CFE-mean} is defined as the mean time between consecutive deflections during a predefined recording period. The system monitors electrical deflections from the isoelectric line and annotates all deflections meeting the pre-specified criteria as set-out below. Annotations are shown by yellow tick-marks as shown in Figure 4-5.
Figure 4-1 Summary of ablation and CFE mapping protocol

Mapping shown in dark grey boxes, ablation/therapy shown in white boxes, AF termination in light grey boxes.

RA = right atrium, LA = left atrium, PVI = pulmonary vein isolation,
CFE = complex fractionated electrograms, LL = linear lesions, CTI= cavotricuspid isthmus
CFE were defined as sites with CFE mean ≤120ms, using a 5-second recording duration on the basis of published data.\textsuperscript{257, 260} Signals were recorded from all bipoles, producing 19 simultaneous electrograms at each time point. Signals were sampled at 1,200Hz and band-pass filtered between 32 and 300Hz. Settings were: dV/dt detection on 1-sec update; electrogram width 10ms (to remove far-field signals), refractory period 30ms (values below this being regarded as non-physiologic for local re-activation), interpolation and surface projection 10mm based on previous studies,\textsuperscript{201, 257, 260} points >10mm from the surface were deleted. Voltage detection threshold was adjusted to exclude background noise, and fixed for subsequent maps. Scar was defined as <0.05mV. Acquisitions were made until the whole endocardial surface was covered. Points displaying electrical interference or inappropriate detection were deleted. The mitral and tricuspid annuli were defined by typical atrial and ventricular electrograms and the contained area excluded.

For purposes of graphical display during procedures, the CFE-mean colour maps were set to show CFE between 30 and 120ms, with a colour spectrum between 80 and 120ms. Thus, all areas with CFE-mean >120ms were coloured purple, those below 80ms (and above 30ms) as white, and the range 80-120ms within the colour spectrum (Figure 4-4).

\section*{4.3.4 Catheter ablation protocol}

See also Figure 4-1

Radiofrequency ablation was commenced in the left atrium after baseline biatrial CFE maps were complete, with the map turned off. Antral \textit{pulmonary vein isolation} was performed typically as ipsilateral pairs, although on some occasions intervenous/carina ablation was necessary to achieve the immediate endpoint of PV \textit{entrance block} (Figure 4-2). Once block was confirmed, a repeat CFE map was recorded in the LA. Note that pulmonary vein
isolation was rechecked at every stage of the procedure, and if recurrent conduction was detected, then repeat ablation was performed at conducting gaps until complete isolation was achieved. CFE maps were only recorded at each subsequent stage only after adequate pulmonary vein isolation had been sufficiently (re)established.

*Linear ablation* was then performed at the LA roof between the ipsilateral venous isolation lines, and then at the lateral mitral isthmus between the anterior isolation line at the left inferior pulmonary vein and the mitral valve annulus (MVI), with the immediate endpoint of local electrogram attenuation by >50% and a maximum of 30 seconds ablation at a single site. Following completion of both lines to this standard (endocardially only), a further LA CFE map was performed.

The LA CFE map after the linear ablation stage was used to guide ablation of CFE, with an endpoint of abolition or organisation of local electrograms at all annotated CFE sites except at the LAA (note that under this protocol, ablation within the LAA was electively avoided to minimise the risk of perforation, and ablation at the anterior aspect of the LAA ostium similarly avoided but in order to obviate the risk of inadvertent electrical isolation of the appendage which might increase the subsequent risk of thromboembolism).

Finally, if AF persisted, CFE mapping was again performed in both atria, following which DC cardioversion was used to restore sinus rhythm. A minimal biphasic energy of 150J was used, and 200-360J when required.
Figure 4-2  Pulmonary vein isolation during atrial fibrillation

After antral circumferential ablation ring has been created, there is residual conduction to the right upper pulmonary vein, with earliest activation at electrode 5,6 of the spiral catheter (labelled Lasso). *Entrance block* is created during ablation at this site (note electrical artefact at ablation onset and at the spiral bipole). The last activation of the pulmonary vein is arrowed. Atrial fibrillation continues (see coronary sinus recording in blue)

If *atrial tachycardia* ensued at any point, the mapping and AF ablation protocol (after a minimum of complete pulmonary vein isolation) was terminated and the tachycardia mapped and ablated using conventional methods. In brief, the intracardiac recordings were assessed for stability of activation sequence and regularity, and if possible a P wave identified on the surface ECG. A suitable timing reference was used in the coronary sinus or left atrial appendage. Following this, direction of activation was evaluated at the anterior, posterior and inferior LA to establish the likelihood of a macroreentrant tachycardia. If a focal arrhythmia was suggested, then 3-dimensional local activation mapping was performed with either the AFocusII or mapping/ablation catheter. If macroreentry was suggested, the mechanism was confirmed by pacing manoeuvres to prove concealed entrainment within or near a critical isthmus, and ablation applied as appropriate in order to achieve termination to sinus rhythm. Such macroreentry was confined to the site of the left atrial roof, mitral isthmus, or the cavo-tricuspid isthmus.
Confirmation of linear lesion block

In this example from a patient (S59) immediately after restoration of sinus rhythm, the left panel shows pacing from the AFocusII catheter (labelled Lasso) positioned in the left atrial appendage. Two decapole catheters are placed within the coronary sinus, distally (blue) and more proximally (red). The mapping (ABLd) signal from the roof is shown. The upper orange arrow highlights the conduction time from the stimulus until the latest potential detected in the coronary sinus catheter. Note that the CS catheter (blue) is positioned distally enough to ‘straddle’ the mitral isthmus line at CS 5,6, with the distal (CSD and CS3,4) part recording a signal on the LAA side of the line. **Primary mitral isthmus block is therefore present.** Below, the ablation catheter records a signal on the posterior aspect of the roof line, which is not blocked. The right panel shows achievement of roof block after further ablation then achieves roof block, depicted in the right panel, where there has been a split of potentials between early and late, showing that the ablation catheter is sitting exactly at the roof line, block of which means the impulse now takes 140ms to reach the other side of the roof line from the left atrial appendage.

In sinus rhythm, pulmonary vein isolation was reassessed using the AFocusII catheter and multisite pacing to show the endpoint of entrance (PVI endpoint) and exit block. Exit block was proven when possible during pacing from the pulmonary vein when ipsilateral pulmonary vein capture was demonstrated without atrial capture, however in general was presumed in the presence of high-output pacing and no atrial capture. Entrance block was further clarified, when necessary, by assessment of differential pacing and sensing in the right atrium (for right PV) and left atrial appendage or CS (for left PV).
Similarly, bidirectional mitral and roof-line integrity was assessed by differential pacing and sensing from the LAA, CS and posterior wall. The presence of a blocked line immediately after cardioversion was defined as primary block for purposes of subsequent analysis; further ablation was performed at incomplete lines (Figure 4-3). For the mitral isthmus, this could include ablation within the coronary sinus opposite the endocardial lesions.

A linear lesion was then performed at the cavotricuspid isthmus during proximal coronary sinus pacing, using the same principles as above ensure bidirectional linear block.

4.3.5 Data analysis

Complete study data was recorded on to optical disc (recordable DVD media) and stored under the patient’s study code. For analysis each study was loaded on to an Ensite Laptop Review Station (St Jude Medical).

Prior to formal analysis, the CFE mapping data for each map was manually reviewed and cleaned up. This process involved the following steps, following which each map was re-saved:

i. Display of all acquisitions in order of CFE-mean

ii. Removal of acquisitions with high frequency electrical or mechanical artefact, or adjustment within the beat buffer if sufficient retrospective 5-second recording available

iii. Adjustment of peak-peak voltage/amplitude threshold for CFE detection in order to account for unavoidable background noise, which varied by patient and atrium. For standardisation of measurement, this threshold was then fixed for subsequent maps within the same atrium during the same study
4.3.5.1 CFE area assessment

In the left atrium, in order to assess the remote effect of i) pulmonary vein isolation and ii) linear lesions on left atrial CFE, areas excluded by or involved in these lesions were excluded from subsequent area analysis. Thus the saved geometry, with its associated ablation points, that was recorded immediately after ablation of the roof and mitral lines was used as the basis for calculation of the left atrial ‘denominator’ area, and all CFE map data, stored separately from the geometry, was loaded (superimposed) on to this.

Using the standardised projection and interpolation settings as defined above, and with the NavX field-scaling algorithm applied, the NavX surface marker tool (Figure 4-4) was then used to demarcate areas as follows:

i. The area of left atrium remaining after excluding to within 5mm of the PVI encircling lesions and linear lesions, and excluding the mitral valve annulus

ii. The excluded area of pulmonary vein and linear lesions on each side. Thus i+ii equalled total baseline LA surface area to drawn around the whole remaining LA.

iii. All regions with CFE-mean ≤120ms, i.e. all areas within (i) displayed with white-blue colour annotation, the sum of which was defined as left atrial CFE-area

This method was designed to permit assessment of remote impact of PVI then linear lesions on the remote parts of the left atrium, here defined as all left atrium >5mm from the annotated ablation lesions. Note that the fourth left atrial CFE map, performed after map-guided ablation of CFE from the third (post-linear lesion) map, served 2 separate purposes i) validation of the impact of direct ablation of CFE sites, also permitting investigation of whether new or temporally unstable sites of CFE arose despite targeting the residual CFE
after linear ablation, and ii) to provide the denominator map for final right atrial CFE assessment (see next paragraph).

![Image](image.png)

**Figure 4-4 Surface marker annotation of CFE**
Anterior (left) and modified posterior (right) view of the left atrium: the geometry and CFE map, taken after linear lesions, is displayed. The *surface marker* tool of NavX has been used to annotate CFE areas from baseline (red), post-PVI (amber), and post-linear lesions (green), which have been left projected on the map surface. A degree of temporal stability of the anterior CFE region is noted, but the posterior and peri-right PV regions have disappeared after (remote) ablation. Note: only areas not enclosed or affected by PVI and linear lesions have been counted towards CFE-area.

Any example of sequential left atrial CFE maps, projected on to the lesion-set/ geometry recorded immediately after linear ablation, is shown in Figure 4-5.
Figure 4-5  Sequential LA CFE maps

High-density CFE-mean maps are shown at baseline and after stepwise ablation. Example electrograms and their sites are arrowed: yellow marks show annotation of electrograms contributing to the CFE-mean over 5 seconds.

In the right atrium, the same principles were applied but adapted for the difference in anatomy, location, and relationship to ablation sites. In order to assess the remote effect of all left atrial ablation (PVI, linear lesions, and CFE ablation) on the right atrium, the saved geometry, with its associated ablation points, that was recorded immediately after final (left atrial) CFE ablation was used as the basis for calculation of the right atrial ‘denominator’ area. Any left atrial (septal) lesions within 10mm of the right atrial geometry were projected on to its surface, to allow exclusion of these areas – which might otherwise confound the true remote impact of LA lesions. After field scaling, the following were performed:
i. The area of right atrium remaining after excluding (to within 5mm) any projected left atrial (septal) lesions, and excluding the tricuspid valve annulus, and the ostia of the coronary sinus and superior and inferior caval veins

ii. All regions with CFE-mean ≤ 120ms, i.e. all areas within (i) displayed with white-blue colour annotation, the sum of which was defined as right atrial CFE-area

An example of right atrial CFE mapping at baseline and after all LA ablation, projected on to the final RA lesion-set/geometry (including projected lesions from the LA) taken prior to DC cardioversion, is shown in Figure 4-6.

**Figure 4-6 Sequential RA CFE maps**
High-density CFE maps are shown in the RA at baseline and after all LA ablation. LA ablation lesions projecting within 10mm of the RA surface have been displayed and the area excluded from analysis (black outline top right). Electrograms are shown from the lateral wall pre and post ablation, displaying marked organisation of a prior CFE site.
4.3.5.2 Atrial segmentation

In order to categorise CFE distribution, the LA was divided into 3 segments as previously described, namely anterior, posterior, and appendage (Figure 4-7). The RA was similarly segmented into lateral, septal, and appendage (Figure 4-8).

![Diagram of atrial segmentation](image)

**Figure 4-7 Left atrial segmentation**

The anterior and posterior walls were defined superiorly by the roof line between the left superior pulmonary vein (LSPV) and right superior pulmonary vein (RSPV), and laterally by the mitral valve isthmus (MVI) line in AP and PA views respectively. The appendage was defined by protrusion from the LA geometry as above. The method of segmentation is based on that of Singh et al.\textsuperscript{276}
In order to assess differential impact of ablation on CFE-area in regions of the right atrium, it was segmented into 3 zones: lateral, septal and appendage. The tricuspid valve annulus (TVA) served as the anterior border for both lateral and septal, with division between the two at its midline in en-face projection. The right atrial appendage (RAA) was defined by protrusion from the RA anatomy in a typical anatomical location superior to the tricuspid annulus. On the left, right anterior oblique projection shows the lateral RA, and on the right, a left posterior oblique view shows the septal RA. SVC = superior vena cava; IVC = inferior vena cava

4.3.6 Statistical analysis

Continuous data are presented as mean ± standard deviation, and categorical data as frequency/percentage. Change in CFE-area was analysed by absolute and percentage coverage of atrial surface area, and compared by paired t-tests. Linear regression was additionally performed to assess factors associated with baseline CFE areas (age, gender, baseline appendage CL, HF aetiology, amiodarone, LA diameter, AF duration, and LVEF), reduction of remote RA CFE area (adding RF duration), reduction of remote LA CFE area by
PVI and linear lesions (adding primary linear block). Arrhythmia-free survival was assessed by Kaplan-Meier technique, and Cox regression used to assess influencing factors. Analysis was performed within SPSS for Mac. P-values of <0.05 were regarded as significant.

4.3.7 Follow-up

All antiarrhythmic drugs except non-sotalol beta-blockers were discontinued post-ablation, unless indicated for ventricular arrhythmia. Patients were followed up at 3, 6, and 12 months, and routinely 6 monthly thereafter, with additional review for symptomatic recurrence. 48h Holter recording or equivalent device interrogation was performed at 6 and 12 months, and ECG at subsequent follow-ups. Arrhythmia recurrence was defined as AF or atrial tachycardia lasting more than 30 seconds after a 2-month blanking period.
4.4 Results

4.4.1 Catheter ablation procedure

Total procedural duration was 331±55 min, fluoroscopy time 79±18 min, and total radiofrequency ablation time 82±19 min (PVI 46±17 min; roof line 3.3±1.7 min, mitral isthmus line 4.0±2.3 min, CFE 12.1±7.7 min). After cardioversion, primary roof block was present in 26/30 patients, the remaining 4 being blocked after further ablation (2.3±1.4 min). There was primary mitral block in 11/30 patients, and further ablation (6.6±3.5 min) in the remainder (including epicardially via the coronary sinus in 15) achieved block in 28/30 (93%) patients. CTI ablation was performed in 28/30 patients (in 2 cases not performed due to long procedural duration), achieving bidirectional block in 27/28 (96%).

4.4.2 Mapping procedure

A total of 168 CFE maps were acquired (Figure 4-1), constituting 114 LA maps (479±99 points per map) and 54 RA maps (373 ± 96 points per map). The total number of points per map did not differ significantly between the baseline and subsequent LA (ANOVA p=0.22) and RA (p=0.89) maps. The total surface area included for sequential CFE-area analysis was 117±24cm² in the LA (after exclusion of 96±25 cm² area from PV isolation and linear lesions) and 136±33cm² in the RA.

4.4.2.1 Impact of catheter ablation on CFE-area

At baseline LA CFE-area was 18.3±12.0cm² (16.2±10.6% of LA surface) comprising 7.9±6.0cm² (6.8±5.1%) anteriorly, 6.6±5.8cm² (5.9±5.3%) posteriorly, and 3.8±4.1cm² (3.5±3.8%) in the LAA. After PVI there was a reduction in CFE-area to 10.2±7.1cm² (9.0±6.6%, p<0.001 versus baseline), comprising 4.5±4.0cm² (3.8±3.2%) anteriorly
(p<0.001), 2.8±3.2cm$^2$ (2.6±3.0%, p<0.001) posteriorly, and 2.8±2.5cm$^2$ (2.5±2.3%, p=0.11) in the LAA. After addition of linear lesions and compared with post-PVI analysis, total LA CFE-area had further reduced to 7.7±6.5cm$^2$ (6.9±5.9%, p=0.002), comprising 4.2±4.2cm$^2$ (3.7±3.7%, p=0.96) anteriorly, 1.7±2.8cm$^2$ (1.6±2.6%, p=0.008) posteriorly, and 1.7±1.8cm$^2$ (1.6±1.7%, p=0.01) in the LAA (Figure 4-9). As expected, direct CFE ablation significantly reduced final LA CFE-area, compared with post-linear lesion analysis, to 3.1±3.5 cm$^2$ (2.8±3.0%, p<0.001), comprising 1.4±2.0cm$^2$ (1.1±1.6%, p<0.001) anteriorly, 0.2±0.9cm$^2$ (0.2±0.8%, p=0.004) posteriorly, and 1.6±2.1cm$^2$ (1.5±2.1%, p=0.92) in the LAA.

**Figure 4-9  Impact of stepwise ablation on left atrial CFE-area**

The percentage (mean±SD) of atrial surface (excluding PVI and linear lesion sites) covered by CFE is shown, segmented as per Figure 4-7, at baseline and following stepwise PVI, then linear lesions (LL) and finally CFE ablation. Note that the region of the left atrial appendage was not targeted with ablation (see text) during CFE ablation. P values are shown for comparisons between steps of ablation, and denoted * <0.05, ** <0.01, and *** <0.001
The percentage (mean±SD) of atrial surface (excluding sites with projected LA lesions) covered by CFE is shown, segmented as per Figure 4-8, showing baseline (pre) and after all LA ablation (post).

P values are denoted *<0.05, **<0.01, ***<0.001

At baseline, RA CFE-area was 25.9±14.1 cm² (19.2±10.3% of the total RA surface), comprising 9.6±6.8 cm² (7.2±4.9%) laterally, 10.1±7.2 cm² (7.7±5.9%) septally, and 6.2±5.8 cm² (4.3±3.8%) in RAA. Final RA CFE-area after LA ablation was reduced to 12.9±11.8 cm² (9.9±7.8%, p<0.001), comprising 7.0±7.1 cm² (5.6±5.3%, p=0.03) laterally, 2.5±2.8 cm² (2.0±2.1%, p<0.001) septally, and 3.6±3.9 cm² (2.5±2.6%, p=0.01) in the RAA (Figure 4-10).

4.4.2.2 Impact of catheter ablation on AF cycle length

LAA CL at baseline was 161±28 ms, prolonging to 170±37 ms after PVI (p=0.003). LAA CL after linear ablation was 174±34 ms (compared with post-PVI p=0.15), and 180±42 ms (p=0.01, versus post-linear) after LA CFE ablation. RAA baseline CL was 167±33 ms, and 175±33 ms after PVI (p=0.006). It was 174±30 ms (p=0.29) after linear ablation, prolonging to

![Graph showing impact of stepwise ablation on right atrial CFE-area](image)
179±41ms (p=0.01, versus post-linear) after completion of LA ablation. Hence in both atria CL prolonged significantly after PVI and CFE ablation, but was not impacted independently by linear ablation. Change in CL did not significantly correlate with change in CFE-area (R=0.21 in RA, p=0.35, for sequential LA maps R =0.08-0.29, p=0.12-0.91).

4.4.2.3 Predictors of baseline CFE-area

Non-ischaemic HF aetiology, shorter RAA baseline CL, female gender, and lower LA diameter were associated with greater baseline RA CFE-area (as percentage of total surface area). In multivariate analysis only non-ischaemic aetiology remained a significant factor (p=0.002, 11.2cm², 95% CI 4.5 to 17.9). LA CFE percentage coverage was associated with non-ischaemic HF aetiology and shorter baseline LAA CL, although only LAA CL was significant in multivariate analysis, with a small effect (p=0.03, coefficient -0.084, 95% CI -0.161 to -0.008).

4.4.2.4 Predictors of CFE-area reduction after PVI and linear lesions

Non-ischaemic HF aetiology, longer baseline LAA CL, and higher EF were associated with greater reduction in CFE by PVI alone, although after correction for baseline remote CFE-area, the reduction in CFE by PVI was independent of any identifiable independent variable. However, the reduction of CFE-area after linear lesions was significantly greater in those with primary mitral block (p=0.009, -3.43cm², 95% CI -5.91 to -0.94), but not primary roof block. This factor persisted after adjustment for pre-linear lesion remote CFE-area (p=0.02, coefficient -2.90cm², 95% CI -5.30 to -0.49).

4.4.2.5 Atrial Fibrillation Termination

Termination of AF was observed in 6 cases. In 2 patients this occurred just prior to CFE ablation (after post-linear lesion mapping), and in both a roof-dependent atrial tachycardia was mapped and ablated to sinus rhythm. In the other 4, termination of AF occurred during
CFE ablation, 2 via sustained atrial tachycardia (peri-mitral and focal – both successfully ablated), and in 2 cases via transient organisation then sinus rhythm. Hence 24/30 patients had sequential RA maps for comparison, whereas all patients had sequential post-PVI and linear lesion LA maps for the above analysis (Figure 4-1). Considering baseline CL, overall AFCL prolongation, CFE-area, LA size, primary linear lesion block, RF time, age, and AF duration, there were no statistically significant predictors of AF termination.

4.4.3 Clinical outcome

After a single ablation procedure, at 494±223 days follow-up, 19/30 patients (63%) were free of atrial arrhythmias. Of the 11 patients with arrhythmia recurrence, 3 had AF and 8 atrial tachycardia. Kaplan-Meier arrhythmia-free survival estimation (Figure 4-11) was 71.8% at 1 year, off antiarrhythmic drugs, after a single ablation procedure. Three patients died of progressive HF during follow up at 1, 11 and 14 months: none had documented recurrent atrial arrhythmia, including two confirmed via device interrogation.

4.4.3.1 Repeat ablation procedures

Those with recurrent arrhythmia presented at a median of 206 (range 67-705) days. Repeat ablation procedures were performed in 9 patients (7 for atrial tachycardia and 2 for AF) of whom 8 required re-isolation of ≥1 pulmonary vein. In 2 cases atrial tachycardia was focally emanating with presumed microreentrant mechanism, all previous lines remaining blocked. Of the remaining 7 cases, linear lesion sites were involved in macroreentrant tachycardia circuits in 5 patients (including 3 roof-dependent and 4 peri-mitral tachycardias), of whom 3 additionally had separate focally-emanating tachycardias near prior CFE ablation sites. Two patients underwent a third ablation procedure, 1 for focally-emanating atrial tachycardias near prior CFE ablation sites, and 1 for recurrent AF. Overall, at last follow-up, 28/30 patients (93%) remained in sinus rhythm after 1.4±0.6 procedures.
4.4.3.2 Factors influencing arrhythmia-free survival after one procedure

Age, gender, LA size, heart failure aetiology, ejection fraction, AF duration, baseline CFE-areas, baseline CL, total change in CL, total change in LA CFE, procedural AF termination, radiofrequency duration (total and CFE), and incompleteness of linear lesions at the index procedure were analysed as possible risk factors for recurrence: the presence of unblocked linear lesions was the only predictor of arrhythmia recurrence in multivariate analysis (Table 4-2). Survival curves comparing complete linear block in all lines (roof, mitral, cavotricuspid) with presence of any unblocked lines are shown in Figure 4-12 (Log Rank test p=0.002). No patient with procedural AF termination had recurrence within the follow up period (Log Rank test p=0.058, Figure 4-13).

![Cumulative Survival vs Follow up (days) for All patients](image.png)

**Figure 4-11 Atrial arrhythmia-free survival**

Kaplan-Meier estimation of arrhythmia-free survival after a single ablation procedure. Vertical tick marks show the points at which patients were censored (last follow-up) and vertical steps show events.
Table 4-2  Cox regression analysis model

Cox regression for atrial arrhythmia-free survival after a single ablation procedure

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.93-1.06</td>
<td>0.77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>0.60</td>
<td>0.16-2.31</td>
<td>0.46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA size</td>
<td>1.12</td>
<td>1.02-1.24</td>
<td>0.022</td>
<td>1.11</td>
<td>0.99-1.24</td>
<td>0.09</td>
</tr>
<tr>
<td>Ischaemic HF</td>
<td>2.02</td>
<td>0.61-6.69</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.98</td>
<td>0.91-1.05</td>
<td>0.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF duration</td>
<td>1.01</td>
<td>0.98-1.04</td>
<td>0.41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline LA CFE-area</td>
<td>1.01</td>
<td>0.96-1.07</td>
<td>0.62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline RA CFE-area</td>
<td>1.00</td>
<td>0.96-1.05</td>
<td>0.85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in LAA CL</td>
<td>1.02</td>
<td>0.98-1.07</td>
<td>0.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in LA CFE</td>
<td>0.92</td>
<td>0.09-9.80</td>
<td>0.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF termination</td>
<td>0.03</td>
<td>0.00-11.44</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF duration</td>
<td>1.00</td>
<td>1.00-1.00</td>
<td>0.91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unblocked LL</td>
<td>7.49</td>
<td>1.74-32.16</td>
<td>0.007</td>
<td>4.69</td>
<td>1.05-21.06</td>
<td>0.04</td>
</tr>
</tbody>
</table>

HR = Hazard Ratio, CI = confidence interval, p = p value
AF = atrial fibrillation, CFE = complex fractionated electrogram, CL = cycle length, HF = heart failure, LA = left atrial, LL = linear lesion, LV = left ventricular, RA = right atrial, RF = radiofrequency ablation
Figure 4-12 Unblocked linear lesions: impact on success
Kaplan-Meier survival estimation for atrial arrhythmia-free survival after a single ablation procedure, comparing those with and without *complete linear lesion block* at the index procedure.

Figure 4-13 AF termination: impact on success
Kaplan-Meier survival estimation for atrial arrhythmia-free survival after a single ablation procedure, comparing those with and without *AF termination* at the index procedure.
4.5 Discussion

The main finding of this study are that in this human model of advanced atrial substrate, persistent AF and heart failure, CFE-area is reduced at remote sites following PVI and linear ablation. Within the LA, CFE-area was reduced sequentially following PVI and linear lesions. Furthermore, CFE-area in the RA was also reduced after ablation only within the LA. Primary block of the mitral isthmus line produced greater reduction of CFE-area compared with an unblocked mitral isthmus line. Additionally, the stepwise ablation approach employed resulted in a high freedom from atrial arrhythmia following a single procedure, with atrial tachycardia (both macroreentrant and ‘focal’) the usual mode of recurrence, and the presence of unblocked linear lesions at the end of the index procedure was the only independent predictor of arrhythmia recurrence.

4.5.1 Ablation of complex fractionated electrograms

Since the initial data supporting CFE ablation to eradicate AF,127 investigators have targeted CFE alone,200 in conjunction with PVI,201, 204 or within a stepwise strategy incorporating linear lesions.202, 203 However, studies randomising persistent AF patients to CFE ablation have produced sharply differing results.244, 256, 277 A recent clinical trial reported that algorithm-guided CFE ablation combined with PVI significantly improved procedural success.277 In contrast, another study showed that up to 2 hours of conventional CFE mapping and ablation after PVI provided no additional clinical benefit.256 Such discrepancies might relate to the heterogeneity of CFE mapping, including use of operator-identification versus semi-automated algorithms, and variable mapping density (point-to-point mapping pragmatically achieving a resolution approximately 25% of multipolar mapping).204 However, CFEs also have incompletely understood and heterogeneous aetiologies. They may
be a consequence of slow conduction\textsuperscript{192, 193, 196} or anisotropy-related behaviour,\textsuperscript{196, 197} or represent endo-epicardial breakthrough,\textsuperscript{278} localised reentry, wavelet collision,\textsuperscript{192} or wavebreak adjacent to high-frequency drivers,\textsuperscript{279} or could relate to acetylcholine release at locations of epicardial ganglionated plexi.\textsuperscript{198} Notably, some of these mechanisms suggest source activity responsible for maintaining fibrillation, while others suggest passive bystander activation: a crucial distinction when judging their relevance as targets for catheter ablation.

Other investigators have shown that PVI reduces fractionation at non-PV sites.\textsuperscript{274, 275} More recently Matsuo et al showed that, in patients with mostly lone AF, linear lesions combined with PVI also reduced CFE at remote sites.\textsuperscript{280} However, in contrast to the current study, these studies examined patients without significant structural heart disease and minimal atrial dilatation (mean 40-45mm). Our study examined a model of more advanced atrial disease (LA dilatation and LV dysfunction) and uniquely also examined the impact of left atrial lesion sets on CFE in the RA, finding a significant reduction of CFE-area not only in the LA but also in the RA.

If CFE represent sites of reentrant activity responsible for maintaining AF elsewhere - rather than simply bystander wavefront collision - then while reduction of remote CFEs by ablation in a lone-AF model might be explained by acute electrophysiological remodelling, it is perhaps surprising that biatrial CFE can be reduced by remote ablation in an advanced atrial substrate associated with chronic stretch and fibrosis.\textsuperscript{28, 58, 59, 65} However, it is possible, as described above, that the mechanisms underlying CFE are heterogenous and, thus, the CFE which are abolished by remote ablation are only those which are caused by bystander activation.
4.5.2 Linear lesions

Although placement of complete linear lesions can be challenging and incompleteness is proarrhythmic,\textsuperscript{167} they can help achieve long-term freedom from atrial arrhythmias.\textsuperscript{171, 176, 178} In addition to preventing macroreentrant tachycardia, compartmentalisation by linear lesions may reduce both initiation and maintenance of AF.\textsuperscript{281} Allessie \textit{et al} have recently performed high-density epicardial mapping of persistent AF in humans\textsuperscript{282} showing that, rather than rotors or foci maintaining AF, the substrate was based on lines of block within the atrial musculature, with longitudinal dissociation facilitating multiple wavefronts. Our observed reduction in CFE-area with linear ablation, particularly the greater reduction seen with complete lines (primary block), would fit a hypothesis that ‘iatrogenic’ creation of lines could alter the propagating route for AF wavefronts and hence affect fractionation observed at remote sites, particularly when it is due to incident activation. Additionally, if some CFE represent sites of endo-epicardial breakthrough,\textsuperscript{278} placement of linear lesions in the vicinity of such sites might reduce non-uniform anisotropy and the probability of slow epicardial-breakthrough.

Our data additionally shows that a stepwise strategy incorporating linear lesions is associated with favourable clinical outcome in this cohort, and reaffirms the importance of robust linear ablation, given that unblocked lesions predicted arrhythmia recurrence and participated in the offending arrhythmia mechanism in approximately 50% of atrial tachycardia recurrences. However, AF recurrence was low, and in those having repeat procedures all atrial tachycardias were successfully ablated.
4.5.3 Sequence of ablation in a stepwise approach

The ideal ablation strategy for persistent AF remains uncertain. Stepwise ablation, including PVI, targeting of CFE, and linear lesions, can lead to favourable outcomes. Some CFE may facilitate ongoing AF, and indeed in our study ablation of residual CFE after linear ablation both prolonged AF cycle length and terminated AF in a handful of cases. Although several investigators have attempted to categorise and stratify potential CFE ablation sites, identification of active versus bystander CFE sites remains challenging.

One potentially important clinical implication of our data stems from the finding that many CFE sites can be rendered ‘normal’ by remote PVI and linear ablation, and thus would be themselves unsuitable targets for ablation as they may result from bystander activation. If one intends to pursue CFE ablation, but suspects heterogeneity of CFE mechanisms, then our data would support a strategy involving initial application of PVI, then linear lesions – which are potentially needed anyway for long term arrhythmia-free success in longstanding persistent AF – in order to minimise unnecessary subsequent ablation of CFE, which may itself be proarrhythmic. This is in keeping with the conclusions of prior studies into remote impact of ablation on CFE in lone AF, and our data would suggest this also applies in the case of non-lone AF. In addition, our finding of significant remote CFE reduction in the RA – also suggesting passive bystander activation – may in part explain the previously reported lack of benefit of adding routine right atrial CFE ablation to a left sided procedure.

Our relatively high single-procedure success mirrors that reported with a similarly extensive ablation strategy by other centres. Interestingly, a smaller proportion of our patients had AF termination. Although AF termination showed a trend towards predicting improved outcome in our cohort, termination was not necessary for long-term success in the majority, and this would suggest that ablating to an endpoint of termination may involve unnecessary
destruction of atrial tissue. Notably, we did not use ‘facilitation’ with antiarrhythmic drugs peri-procedure, and only a small number of patients were on these agents, which may explain a lower termination rate than other series. The long procedure times inherent to our mapping and ablation protocol effectively provided a long ‘waiting time’ after PVI and linear lesions, with additional ablation when necessary, a factor that possibly contributed to the improved outcome.\textsuperscript{287}

### 4.5.4 Limitations

The present study has several limitations. Firstly, as it did not randomise to different treatment strategies, the relative contributions of different lesions towards outcome are uncertain. We elected to apply all contemporary ablation strategies in this clinical trial cohort to minimise arrhythmia recurrence.\textsuperscript{202} Secondly, incomplete linear block as a predictor of recurrence could have arguably been confounded by a more difficult or lengthy procedure: however, in regression analysis, procedure and radiofrequency duration were not significant risk factors. Finally, to minimise procedural duration in this cohort of patients with heart failure, we did not acquire RA CFE maps at every stage of the procedure, hence we cannot comment on the component effects of stepwise ablation on the RA CFE-area.
4.6 Conclusion

In patients with persistent AF associated with LV systolic dysfunction, high-density contact mapping revealed that both PVI and subsequent linear lesions each had a significant effect in reducing LA fractionation at sites remote from ablation. LA ablation also led to a reduction in RA fractionation. A significant proportion of the CFE seen in the untreated atrium in this model of advanced atrial substrate were thus abolished by ablation at remote sites, which could suggest the CFE are functional or that the substrate is acutely amenable to modification by ablation. Completeness of linear lesions was associated with both greater CFE reduction and improved medium-term procedural outcome. Our study would suggest that targeting CFE after PVI and linear lesions could minimise unnecessary collateral damage to atrial myocardium, and that such a strategy is associated with a high level of sinus rhythm maintenance at follow up.

Acknowledgement

This work was presented in part at the Heart Rhythm Society Annual Scientific Sessions, May 2012, Boston USA, in an oral abstract session entitled *AF Ablation: New Insights*.288
5 The ARC-HF trial results

5.1 Abstract

5.1.1 Background

The optimal therapy for atrial fibrillation (AF) associated with heart failure (HF) is unclear. Drug-based rhythm-control has not proved clinically beneficial. Catheter ablation improves cardiac function in patients with HF, but impact on physiological performance has not been formally evaluated in a randomized trial.

5.1.2 Methods

Adults with symptomatic HF, radionuclide left ventricular ejection fraction (EF) 35% or less, and persistent AF were randomly assigned to undergo catheter ablation or rate-control. Primary outcome was 12-month change in peak oxygen consumption (VO$_2$). Secondary endpoints were quality-of-life, BNP, 6-minute walk distance (6MWd) and EF. Results were analysed by intention-to-treat.

5.1.3 Results

52 patients (63±9 years, EF 24±8%, median 36 months AF) were randomized, 26 each to ablation and rate-control. At 12 months, 88% of ablation patients maintained sinus rhythm (single-procedure success 68%). In the rate-control group, rate criteria were achieved in 96%. The primary endpoint, peak VO$_2$ significantly increased in the ablation arm compared with rate-control (difference +3.07ml/kg/min, 95% CI 0.56-5.59, p=0.018). The change was not evident at 3 months (+0.79ml/kg/min, 95% CI -1.01 to 2.60, p=0.38). Ablation improved
Minnesota score (p=0.019) and BNP (p=0.045), but showed only non-significant trends toward improved 6MWd (p=0.095) and EF (p=0.055).

5.1.4 Conclusions

This first randomized controlled trial of ablation versus rate-control to focus on objective exercise performance in AF in HF shows significant benefit from ablation, a strategy which also improves symptoms and neurohormonal status. The effects are not instant but develop over 12 months, consistent with progressive amelioration of the heart failure syndrome.
5.2 Background

See Chapter 1

5.3 Methods

See Chapter 2

5.4 Results

A total of 101 patients were referred for participation, and 75 attended for baseline assessment. 52 patients were randomised, 26 patients to each arm (Figure 5-1).

Baseline characteristics are summarized in Table 5-1

One patient in the ablation arm withdrew consent for ablation and continued existing therapy.
One patient in the rate-control arm requested and underwent ablation after 4 months. Both patients attended for all follow-up investigations and were analysed by intention-to-treat.

One patient in the ablation arm died 11 months post-ablation, due to progressive cardio-renal failure. He had chronic lung disease, dilated cardiomyopathy, and a biventricular pacemaker-defibrillator in-situ for 2 years. Device interrogation showed no AF recurrence.
Figure 5-1  CONSORT diagram for ARC-HF

AF = atrial fibrillation; GA = general anaesthesia; ITT = intention-to-treat; LVEF = left ventricular ejection fraction.

*no 6 or 12-month data for 1 patient who died before final review
Table 5-1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Rate-control (n=26)</th>
<th>Catheter Ablation (n=26)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%) / mean±SD</td>
<td>N (%) / mean±SD</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>62±9</td>
<td>64±10</td>
<td>0.38</td>
</tr>
<tr>
<td>Male</td>
<td>24 (92)</td>
<td>21 (81)</td>
<td>0.22</td>
</tr>
<tr>
<td>HF aetiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>7 (27)</td>
<td>10 (38)</td>
<td>0.38</td>
</tr>
<tr>
<td>Non-ischaemic</td>
<td>19 (73)</td>
<td>16 (62)</td>
<td></td>
</tr>
<tr>
<td>Time since HF diagnosis (months)</td>
<td>48±57</td>
<td>68±62</td>
<td>0.22</td>
</tr>
<tr>
<td>Time since AF diagnosis (months)</td>
<td>51±76</td>
<td>51±39</td>
<td>0.98</td>
</tr>
<tr>
<td>Duration of continuous AF (months)</td>
<td>24±29</td>
<td>23±22</td>
<td>0.95</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA II</td>
<td>13 (50)</td>
<td>14 (54)</td>
<td>0.79</td>
</tr>
<tr>
<td>NYHA III</td>
<td>13 (50)</td>
<td>12 (46)</td>
<td></td>
</tr>
<tr>
<td>Recent HF hospitalisation (&lt;1year)</td>
<td>7 (27)</td>
<td>10 (38)</td>
<td>0.38</td>
</tr>
<tr>
<td>Minnesota LHFQ score (/105)</td>
<td>49±21</td>
<td>42±23</td>
<td>0.23</td>
</tr>
<tr>
<td>Peak VO₂ (ml/kg/min)</td>
<td>18.2±4.8</td>
<td>16.3±5.3</td>
<td>0.19</td>
</tr>
<tr>
<td>Radionuclide LVEF (%)</td>
<td>25±7</td>
<td>22±8</td>
<td>0.13</td>
</tr>
<tr>
<td>LA diameter (M-mode, mm)</td>
<td>46±7</td>
<td>50±6</td>
<td>0.07</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>283±285</td>
<td>412±324</td>
<td>0.13</td>
</tr>
<tr>
<td>Creatinine</td>
<td>102±28</td>
<td>96±24</td>
<td>0.42</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>411±109</td>
<td>416±78</td>
<td>0.84</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>81±12</td>
<td>77±9</td>
<td>0.18</td>
</tr>
<tr>
<td>Exercise HR (bpm)</td>
<td>109±18</td>
<td>108±15</td>
<td>0.88</td>
</tr>
<tr>
<td>Rate-controlled at baseline (≤80/≤110 at 6MW)</td>
<td>14 (54)</td>
<td>17 (65)</td>
<td>0.40</td>
</tr>
<tr>
<td>QRS duration (ms) non-paced only</td>
<td>113±21</td>
<td>119±19</td>
<td>0.37</td>
</tr>
<tr>
<td>Pre-existing ICD; of which CRT</td>
<td>4 (15); 3 (12)</td>
<td>10 (38); 8 (31)</td>
<td>0.06; 0.09</td>
</tr>
<tr>
<td>Ventricular pacing dependent</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>24 (92)</td>
<td>24 (92)</td>
<td>1.0</td>
</tr>
<tr>
<td>ACE or ARB</td>
<td>26 (100)</td>
<td>25 (96)</td>
<td>0.31</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>6 (23)</td>
<td>13 (50)</td>
<td>0.04</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>3 (12)</td>
<td>3 (12)</td>
<td>1.0</td>
</tr>
<tr>
<td>Digoxin</td>
<td>12 (46)</td>
<td>16 (62)</td>
<td>0.27</td>
</tr>
<tr>
<td>≥1 prior class I/ III antiarrhythmic</td>
<td>9 (36)</td>
<td>9 (36)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

ACE = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, ARB = angiotensin receptor blocker, BNP= B-type natriuretic peptide, CRT = cardiac resynchronization therapy, HF = heart failure, HR = heart rate, ICD = implantable cardioverter defibrillator, LA = left atrial, LHFQ = Minnesota Living with Heart Failure Questionnaire, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, 6MW = 6-minute walk.
5.4.1 Primary end-point

At 12 months peak VO₂ had increased by 2.13 (-0.10 to +4.36) ml/kg/min in the ablation arm, compared with a decrease (-0.94, -2.21 to +0.32 ml/kg/min) in the rate-control arm. The mean difference between the groups (primary endpoint) was +3.07 ml/kg/min (95% CI 0.56 to 5.59, p=0.018; Figure 5-2). At 3 months there had been a non-significant increase of VO₂ in the ablation arm (mean difference +0.79ml/kg/min, -1.01 to +2.60, p=0.38).

Figure 5-2  Change in peak oxygen consumption (primary endpoint)
By intention-to-treat, change (Δ) in peak VO₂ (mean±95%CI) from baseline, comparing ablation (shown as solid dot/line) versus rate-control (shown as open dot/dashed line) at 3 (p=0.38) and 12 month (p=0.018) follow-up. Statistical significance shown between groups at each time point: * if p<0.05.
Individual responses of VO$_2$ are shown in the graphs below. Note that the patient who died A20 had missing data at 12 months. Imputation was not performed for calculation of the primary endpoint, although sensitivity analyses are discussed in the limitations section.

Figure 5-3  Individual patient responses in peak VO$_2$ – rate control group
Line graphs showing absolute peak VO$_2$ (ml/kg/min) recorded at each time point for each patient randomised to the rate control group
Figure 5-4  Individual patient responses in peak VO$_2$ – ablation group

Line graphs showing absolute peak VO$_2$ (ml/kg/min) recorded at each time point for each patient randomised to the rate control group.
5.4.2 Secondary endpoints

Minnesota LHFQ score (Figure 5-5) improved (reduced) in the ablation arm, non-significantly at 3 months (p=0.196) but significantly at 6 (p=0.015) and 12 months: median -15.5 (IQR -26.75 to -7.25) compared with -5 (-16 to +9) under rate-control (p=0.019). The change in score was normally distributed and was additionally analysed by (parametric) t-test. The mean reduction in LHFQ score with ablation was -19.6 (95% CI -29.0 to -10.0) compared with -5.4 (95% CI -11.7 to +1.0) for rate control, which corresponded to mean treatment effect (difference) of -14.2 points (95% CI -25.1 to -3.3, p=0.012).

![Figure 5-5 Change in Minnesota LHFQ score (secondary endpoint)](image)

By intention-to-treat, change (Δ) from baseline, displayed as median and interquartile range, for Minnesota Living with Heart Failure Questionnaire (LHFQ) score. Ablation shown as solid dots/lines, rate-control as open dots/dashed lines. Statistical significance* shown between at 6 months (p=0.015) and 12 months (0.019) by Mann Whitney U-test.
**Figure 5-6 Change in plasma BNP (secondary endpoint)**

By intention-to-treat, change (Δ) from baseline, displayed as median and interquartile range, for plasma B-type natriuretic peptide (BNP) levels. Ablation shown as solid dots/lines, rate-control as open dots/dashed lines. Statistical significance* shown between at 6 months (p=0.038) and 12 months (0.045) by Mann Whitney U-test.

*BNP* similarly showed non-significant decrease at 3 months (p=0.132) but significant reduction at 6 (p=0.038) and 12 months (p=0.045) in the ablation arm: median -124(-284 to 0) pg/ml, compared with -18(-86 to +31) pg/ml for rate-control (Figure 5-6).
Six-minute walk distance (Figure 5-7) tended to increase in both groups towards 6 months. At 12 months, ablation produced a non-significant increase (p=0.095) (median +21 metres, -51 to +89) compared with a decrease under rate-control (median -10 metres, -73 to +15). Left ventricular EF, as measured by radionuclide ventriculography, showed a non-significant trend towards improvement in the ablation arm (mean difference +5.6%, CI -0.1 to +11.3, p=0.055) – see chapter 6 for further information.

Figure 5-7  Change in 6-minute walk distance (6MWd, secondary endpoint)
By intention-to-treat, change (Δ) from baseline in 6MWd, median and interquartile range. Ablation shown as solid dots and lines, rate-control as open dots and dashed lines. Non-significant trend^ shown for difference at 12 months (p=0.095).
5.4.3 Other parameters

*Exercise time* mirrored peak VO2 with non-significant change at 3 months in the ablation arm (mean difference +54s, -31 to 139, p=0.205) with significant improvement at 12 months (mean difference +133s, 19 to 246, p=0.023).

*VE/VCO2 slope* showed a non-significant reduction from ablation at 3 months (mean difference -3.45, -7.33 to 0.44, p=0.081) and 12 months (mean difference -1.68, -6.50 to 3.14, =0.49). The proportion of ablation patients with VE/VCO2 >34 was 19/26 (73%) at baseline and 13/25 (52%) at 12 months, compared with 14/26 (54%) and 11/25 (44%) in the rate control arm. These findings would suggest a trend towards improvement in alveolar gas exchange but with no statistically significant difference between groups.

The proportion of patients achieving satisfactory ventilator anaerobic threshold was analysed as a method to compare effort between groups at follow-up. Using a respiratory exchange ratio (RER) of 1.05 as a cut off, this was 17/26 ablation vs. 16/26 rate control at baseline (p=0.77) and 16/25 vs. 15/26 at 12 months (p=0.77). Additionally, the change in RER was calculated for each patient. In the rate control arm, change in peak RER was +0.03±0.07 at 3 months and +0.3±0.12 at 12 months. By comparison, in the catheter ablation arm the change was +0.01±0.12 at 3 months (p=0.39) and 0.01±0.14 at 12 months (p=0.50). Overall there was no evidence of increased motivation in the ablation arm to explain the difference in peak VO2 observed in analysis of the primary endpoint.

*NYHA class* was assigned by the investigators thus was unblended as was not included as one of the pre-specified secondary endpoints, however it collected at every time-point and was included in post-hoc analysis given its relevance to clinical practice. At 12 months, there was median reduction of 1 NYHA class in the ablation arm, compared with no change in the rate control arm (Mann-Whitney U test p=0.004): more meaningful in this context is perhaps the
mean change of -0.8 (95% CI -1.2 to -0.4) in the ablation arm compared with -0.2 (95% CI -0.5 to +0.1) for rate control, representing a difference of -0.57 (95% CI -1.01 to -0.12, p=0.013). To put this in perspective, NYHA class changed from 2.5±0.5 to 1.6±0.7 in the ablation arm, and 2.5±0.5 to 2.3±0.6 over 12 months in the rate control arm; 13 patients in the ablation arm were classified as NYHA I (including 1 patient in sustained but rate-controlled atrial flutter), compared with only 1 in the rate control arm.

**Figure 5-8  Change in left atrial (LA) size**

By intention-to-treat, change (Δ) from baseline in LA size as assessed by 2-dimensional LA area in the echocardiographic apical 4 chamber view. Ablation shown as solid dots and lines, rate-control as open dots and dashed lines. Statistical significance** shown between at 6 months (p=0.001) and 12 months (0.001) by t-test.
LA area markedly decreased in the ablation arm at both 6 months (mean difference -4.96 cm², -7.23 to -2.68, p=0.001) and 12 months (mean difference -6.22 cm², -9.17 to -3.27, p=0.001; Figure 5-8). RA area showed similar decrease at 6 months (-5.44 cm², -8.33 to -2.61, p<0.001) but not at 12 months (-2.62 cm², -5.99 to 0.74, p=0.124). For further information see chapter 6.

The pre-specified combined endpoint, analysed by individual t-tests of components, for change in LVEF, 6 minute walk, and LHFQ was rendered positive by the change in LHFQ score (p=0.012).*

5.4.4 Rate-control

At baseline, rate-control criteria – as defined by 6-minute walk and clinical heart rate assessment – were met in 14/26 (54%) patients. Rate-control drugs were changed in 12: 2 were started on beta-blockers, 9 had beta-blockers increased, 4 were commenced on digoxin, and 1 had digoxin increased. By 3 months, 23/26 (88%) were rate-controlled. At 12 months, 2 were in sinus rhythm (1 after defibrillation at 9 months; 1 after undergoing ablation); of the remainder 23/24 (96%) were rate-controlled.

An increase in beta-blockade did not itself have an impact on (e.g. reduced) VO₂ either at 3m (p=0.65) or 12m (p=0.66). The presence of rate control at baseline also did not significantly influence change in VO₂ (p=0.41 at 12 months) across the entire cohort.

Holter mean heart rate was 83±14 bpm in the rate control arm at baseline versus 84±9 in the ablation arm, 78±11 vs. 74±11 at 6 months (p=0.16) and 78±16 vs. 71±8 at 12 months (p=0.07). Maximum heart rate (1 minute average) was 128±22 vs. 126±23 at baseline (p=0.8), 124±25 vs. 101±23 at 6 months (p=0.003) and 116±35 vs. 100±21 at 12 months

* i.e. single p-value <0.017 – see Chapter 2 for discussion of Bonferroni principle.
Minimum heart rate (1 minute average) was 65±13 vs. 68±23 at baseline (p=0.59), 60±15 vs. 67±24 (p=0.24) at 6 months, and 61±22 vs. 62±14 at 12 months (p=0.97). Therefore there was an expected trend towards reduction in range of heart rate with ablation (mostly sinus rhythm) versus rate control (mostly AF). There was no significant difference in the level of ventricular ectopic burden compared between time points or groups at baseline or during follow up (e.g. at 12 months 54±80 vs. 67±71 ectopics per hour, p=0.58).

5.4.5 Catheter Ablation

Of 26 patients randomized, 25 underwent catheter ablation after 1 withdrew consent (patient A1). Procedure duration was 333±61 minutes, fluoroscopy 80±19 minutes, and ablation 82±20 minutes. Ablation comprised 47±17 minutes for pulmonary vein isolation, 187±75 seconds of ablation at the roof ablation (and additional 140±84 seconds in the 4 patients requiring additional roof ablation after cardioversion to achieve block), 240±150 seconds ablation at the mitral isthmus (plus 364±209 seconds in the 14 patients requiring additional ablation), and 719±474 seconds (12±8 minutes) ablation of CFE in the 23/25 patients who remained in AF after linear lesions. All patients had conduction block of the pulmonary veins and roof; 24/25 (96%) had mitral isthmus block; 22/25 (88%) had cavotricuspid isthmus block (not attempted in 2 due to concern regarding prolonged anaesthetic).

AF terminated during the ablation procedure in 5 patients, in all cases via some form of atrial tachycardia. This occurred after linear lesions and prior to CFE ablation in 2 patients (A16 and A21), in both cases being roof-dependent macroreentrant atrial tachycardia. In 3 others transformation occurred during CFE ablation: subsequent atrial tachycardia terminated to sinus rhythm spontaneously in 1 patient (A25), and after ablation of ‘focal’ (microreentrant) atrial tachycardia in 2 patients (A6 and A26).
DC cardioversion was required during the blanking period in 8 patients (5 for AF, 3 for atrial tachycardia), 3 of whom remained arrhythmia-free (2 AF and 1 atrial tachycardia).

During follow-up 5 patients had additional ablation procedures for recurrent arrhythmia: 4 for atrial tachycardia, and 1 for AF (followed by a 3rd procedure for atrial tachycardia). One patient had asymptomatic flutter at final follow-up after a single procedure, having been in sinus rhythm at previous follow-ups (A3). Another reverted to AF by 6 months, but declined further ablation given prior complications (A7). Mean time to first atrial arrhythmia recurrence (including patient A1 – no ablation – blanked to 2 months and without cardioversion) was 168 (CI 62-248) days (median 158.5, IQR 87.75 to 221.75 days). For the randomised patients that underwent ablation (excluding A1), this was mean 183 days (95% CI 62 to 248) and median 206 days (IQR 101.5 to 234.5).

By intention-to-treat, Kaplan-Meier 1-year arrhythmia-free survival was 69% after a single ablation, off antiarrhythmic drugs (Figure 5-9). Mean arrhythmia-free survival time was 304 (CI 264-345) days. Following all procedures, 22/25 (88%) were in sinus rhythm without further atrial arrhythmias, 1 of whom was on sotalol and amiodarone for ventricular arrhythmias. Excluding the patient who declined ablation, single-procedure success was 72%, and multi-procedural success 92%.
Figure 5-9  Single-procedure arrhythmia-free survival at 1 year
Intention-to-treat Kaplan-Meier atrial arrhythmia-free survival estimation, after a single ablation procedure. The blanking period was set at 2 months, after which occurrence of documented atrial tachyarrhythmia constituted procedural failure.

5.4.5.1 Complications

There was one serious procedural complication: a steam-pop caused tamponade during cavo-tricuspid-isthmus ablation, requiring emergency pericardiocentesis and sternotomy to repair a perforation at the atrioventricular groove. This patient (A7) required a prolonged period of treatment on the intensive care unit, requiring cardiorespiratory and renal support, followed by rehabilitation for a ‘critical-care’ peripheral neuro-myopathy. He was unable to undergo formal follow up investigations at 3 and 6 months but attended at 12 months and was able to complete cardiopulmonary exercise testing despite still requiring a tri-frame for support – his results were included in the primary analysis. He was found to be in AF during
device follow up at 7 months post-ablation: a repeat catheter ablation procedure was not deemed appropriate in view of the previous complication and protracted physical recovery. Other complications, delaying discharge from hospital or requiring readmission, were: one groin haematoma, one chest infection 2 weeks post-ablation, and one patient with post-procedural pulmonary oedema which resolved within 24 hours. All these patients made a full recovery and completed follow-up.

For all patients, the median stay in hospital was 2 days (IQR 2-3, full range 2 to 100 – the latter being the patient who had tamponade).

5.4.6 Composite Endpoint for Major Adverse Clinical Events

The composite endpoint for event-free survival is shown in Figure 5-10.

The events in the ablation arm were:

- *lower respiratory tract infection* in patient A11 (intensive care admission) within the first month after ablation, thought to be related to post-anaesthesia atelectasis

- *unplanned heart failure admissions* in 3 patients
  - 25 days after ablation, due to occurrence of atrial tachycardia which required cardioversion (within blanking period); this patient (A19) had post-blanking recurrence of atrial tachycardia at 206 days post-ablation, which was successfully ablated
  - 78 days after ablation, with gastroparesis in the context of worsening right-sided heart failure. This patient (A20) had heart failure medication optimised but despite optimal care was deemed end-stage and entered a palliative management strategy 4 months after entry into the study, and died at 11 months
339 days after ablation, with worsening dyspnoea despite maximal medical therapy. A biventricular pacemaker-defibrillator (CRT-D) was inserted (A13).

Figure 5-10 MACE-free survival by treatment group
Kaplan-Meier Major Adverse Clinical Event (MACE)-free survival according to treatment group: ablation (solid) versus rate-control (dashed), Log-Rank p=0.76.

The events in the rate-control arm were:

- cerebrovascular transient ischaemic attack 28 days after enrolment, in the context of a subtherapeutic INR, with full recovery (patient RC8)
- non-ST elevation myocardial infarction, ventricular fibrillatory cardiac arrest, and biventricular defibrillator insertion 315 days after enrolment (patient RC21).
Defibrillation restored sinus rhythm which was still present at the final follow-up 2 months later

- *unplanned heart failure admissions* in 3 patients
  
  o 174 days (patient RC2) and 261 days (patient RC3) after enrolment – admitted from clinic due to progressive fluid overload and dyspnoea, for additional diuresis

  o 182 days after enrolment (RC9) having withdrawn from the rate-control arm and undergone catheter ablation: he presented with rapid atrial tachycardia necessitating cardioversion and then repeat ablation on 2 occasions (for atrial tachycardias not AF). Sinus rhythm was maintained at final follow up.

### 5.5 Discussion

*See Chapter 8 for discussion of the ARC-HF trial results*

### Acknowledgements

The ARC-HF investigators were: DG Jones, SK Haldar, R Sharma, SL Rahman-Haley, TA McDonagh, R Underwood, V Markides, and T Wong.

The primary investigator was Dr Tom Wong (registered on ClinicalTrials.gov), who had the original idea for the study. The clinical trial was designed and coordinated by me, with input from Drs Sharma (heart failure), McDonagh (heart failure and biomarkers), Rahman-Haley (echocardiography), Markides and Wong (electrophysiology), and Professor Underwood (nuclear imaging). Dr Haldar assisted in recruitment and follow-up of patients from October 2010 to June 2012.
I am grateful to the late Professor Philip Poole-Wilson for his expert guidance in the design of this study; to the data and safety monitoring board (Professor Kim Fox, Dr Paul Oldershaw, Professor Peter Collins); Winston Banya and the Clinical Trials and Evaluation Unit at Royal Brompton Hospital for their assistance with randomization and statistical analysis; Mr Matthew Ockendon for assistance in plotting of graphical data; and our patients for their participation.

Both Dr Haldar and I were supported by an educational grant from St Jude Medical, UK. The trial was sponsored by the Royal Brompton & Harefield NHS Foundation Trust, and supported by the NIHR Cardiovascular Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London

The ARC-HF trial was accepted as part of the Late-Breaking Clinical Trials submission by the American Heart Association, for presentation in the Annual Scientific Sessions November 2012, Los Angeles, USA. The abstract* was presented Monday 5th November 2012 in a special session entitled Clinical Science: Special Reports: New Insights into Management of Common Cardiovascular Disorders


Dr Hussain provided clinical input to patients within the study, and contributed to editing of the trial manuscript. Dr Francis contributed to editing of the trial manuscript and provided expertise in cardiopulmonary exercise testing. Dr Wala Mattar assisted Dr Rahman-Haley in analysis of the echocardiographic data.
6 Imaging in atrial fibrillation and heart failure

6.1 Abstract

This chapter examines the impact of the strategies of rate control and catheter ablation upon cardiac function as assessed by the imaging modalities of echocardiography and radionuclide ventriculography.

6.2 Background

Assessment of cardiac function includes not only clinical and physiological assessment, but also relies upon the use of imaging techniques. The various modalities employed in this process can assess cardiac chamber size, volumes, contractile or ‘systolic’ function, relaxation or ‘diastolic function’, and valve structure and function. Imaging parameters of left ventricular function, in particular, have significant diagnostic and prognostic utility in patients with heart disease. \(2^{89-293}\)

Indeed, this has led to *left ventricular ejection fraction* (LVEF) being used as a marker of disease severity and an inclusion criterion for heart failure studies, such as those examining pharmacological interventions, \(\text{2}^{23, 90}\) and more recently for cardiac implantable electronic devices such as automatic implantable cardioverter-defibrillators (ICDs) \(\text{2}^{94}\) or cardiac resynchronisation therapy (CRT) \(\text{2}^{50, 295}\) and thus these measurements are pivotal to patient selection in the clinical application of these therapies. The change in LVEF over time has also been shown to be a powerful prognostic marker, as demonstrated in the V-HeFT studies. \(\text{2}^{91}\)

Imaging ventricular function is however challenging in patients with atrial fibrillation (AF), due to the beat-to-beat variability impacting upon both diastolic filling and to a lesser extent systolic contraction. Indeed, averaging of several cardiac cycles can be required to give reproducible results, \(\text{2}^{96, 297}\) and still it remains challenging to know the true accuracy of any individual
measurement of LVEF given the effective lack of a gold standard for what is a variable measurement. However this does not mean that LVEF measurement does not have utility in patients with atrial fibrillation. On the contrary, many clinical trials and investigations of AF and its therapeutic intervention have utilised ejection fraction measurement by echocardiographic, radionuclide, or magnetic resonance techniques, and improvements in LVEF has been shown to parallel improvement in a broad range of outcomes. Also, most large-scale clinical trials into optimal heart failure management have included patients with atrial fibrillation, which may be present in 10-50% of patients with heart failure, depending upon severity. Importantly, adequate assessment of left ventricular function is vital to allow appropriate thromboembolic risk stratification.

Cardiac imaging can also investigate chamber size and valve function. *Left atrial enlargement* is present in many patients with AF, and may predispose to or be a consequence of the condition. Its severity correlates with the chance of successfully restoring sinus rhythm with cardioversion. Left atrial dilatation has also been demonstrated as an independent prognostic marker in patients with ventricular dysfunction. *Mitral regurgitation* is present to varying degrees in patients with AF and is a recognised aetiologic factor. It has also recently been shown it may be a consequence of persistent AF.

Hence, although imaging parameters cardiac function may not in isolation be robust as a surrogate primary endpoint for investigation of therapies targeted at atrial fibrillation, they provide additional information regarding the impact of different therapies, which can help guide clinical decision-making. Radionuclide ventriculography and echocardiography were therefore performed as part of the baseline and follow-up assessment of patients undergoing treatment with rate-control or catheter ablation within the ARC-HF study, constituting a sub-section of the secondary endpoints. Radionuclide ventriculography was chosen as the principle measure of ejection fraction for both

159
inclusion criteria and for secondary endpoint analysis within the clinical trial as registered on ClinicalTrials.gov (NCT00878384).

6.3 Methods

Subjects were patients enrolled within the ARC-HF study, comprising 52 patients with 26 randomly allocated each to catheter ablation and rate control. Patients underwent baseline radionuclide ventriculography and echocardiography prior to enrolment, with a follow up scan at 1 year. Additionally, subjects underwent additional an echocardiogram at 6 months.

6.3.1 Radionuclide ventriculography (RNV)

6.3.1.1 Acquisition Technique

In vivo red blood cells were labelled with 800 MBq of $^{99m}$Tc. A dual-headed gamma camera with a high-resolution low-energy collimator was employed. For ECG gating an R-R window width was set at 20%, but widened up to 50% on each side in case of markedly irregular heart rate. Wider window allows inclusion of beats with variable lengths, which may reduce image quality but is a better representation of the cardiac haemodynamics in arrhythmias. This avoids an otherwise long acquisition time, which may not be practicable for HF patients or can lead to patient motion and resultant low quality images. For planar imaging, using a single detector, a planar oblique acquisition with the best septal separation angle was selected. R-R interval was gated into 16-32 frames with matrix size of 64×64 pixel size of 0.39 cm. A total of nine million counts was acquired.

Where available (25/52 patients), 3-dimensional single-photon emission computed tomography (SPECT) imaging was acquired. 180° acquisition was performed from right-anterior oblique 45° to left posterior oblique 45° in noncircular orbit with heads at 90° by step and shoot method. 32 steps
(16 steps/head) of 30 seconds each were acquired in a $64\times64$ matrix with pixel size of 0.59 cm. Each cardiac cycle was gated into 16 frames. Follow up scans were performed with the same equipment and imaging sequence.

### 6.3.1.2 Image Analysis

Image analysis was performed in a blinded manner by nuclear medicine technicians and all results reviewed and confirmed by nuclear medicine physicians. On planar imaging, a semi-automated region of interest was selected around the left ventricular blood pool on both end-systolic and end-diastolic planar images. A further region of interest over a background area (usually the mediastinum) was also selected and used to background-correct counts within the blood pool regions of interest. Left ventricular ejection fraction was calculated as the difference between corrected end-diastolic and end-systolic counts divided by the corrected end-diastolic counts. The planar EF was used for inclusion criterion purposes.

### 6.3.2 Transthoracic echocardiography

A standardized protocol was used to acquire images on Vivid 7 or Vividi echocardiograph machines for subsequent analysis on EchoPAC software (GE Healthcare Milwaukee, WI, USA). Standard 2D images and colour/pulsed/continuous Doppler were acquired. Atrial size and method-of-discs LV volumes and ejection fraction (average 3 cycles) was calculated by 2 observers for final results analysis, both of whom were blinded to the prior randomisation. At follow up scans in sinus rhythm, presence of atrial contraction was assessed by mitral A-wave Doppler, and where possible the A’ tissue Doppler component. Other parameters measured were LV wall thickness, LA diameter, LV and right ventricular (RV) pre-ejection period, mitral E/A, lateral mitral annular E’ (tissue Doppler), mitral regurgitation severity,* left ventricular outflow tract (LVOT) velocity time

* Mitral regurgitation graded absent/trivial, mild, moderate, severe: for mild and above, the MR was graded using standard colour Doppler and proximal isovelocity surface area (PISA) – effective regurgitant orifice (ERO)
integral (VTI), estimated cardiac output*, tricuspid annular plane systolic excursion (TAPSE) and tricuspid regurgitation pressure gradient as an estimate of pulmonary artery pressure.

### 6.3.3 Statistical analysis

See chapter 2 (Methods) for further information. Assessment of normality, parametric and non-parametric testing, and correlation measurements were performed in SPSS Statistics for Mac version 20. Bland-Altman plots were created within Excel for Mac. All results were analysed on an intention-to-treat basis, i.e. by allocation to undergo rate control or catheter ablation. Follow-up results were analysed as absolute change from baseline, and then compared between groups. Other than for pre-specified secondary endpoints (LVEF and LA size), further analyses were exploratory with no adjustment made for multiple comparisons (e.g. Bonferroni).

### 6.4 Results

For patient characteristics see Chapter 5, Table 5-1.

#### 6.4.1 Radionuclide ventriculography

Planar RNV data was available for all 52 patients at baseline, and 50 patients at follow up (1 death; 1 image quality insufficient and patient unable to tolerate a repeat scan due to back discomfort). 3D SPECT data was available in 25 patients, with follow-up data available in 24 (1 death). Baseline planar LVEF was 23±8 (median 23, IQR 18 to 29.25). In the subgroup of patients with 3D SPECT, baseline LVEF was 29±11 (median 29; IQR 19 to 38).

The impact of the treatment strategies is shown in Table 6-1.

---

* = heart rate x stroke volume [= π(LVOTdiameter/2)^2 x VTI_{LVOT}]
Figure 6-1  Radionuclide ventriculography - example 1

The upper panels show the output from planar radionuclide ventriculography at baseline (left) and after 12 months follow up (right) in a patient (S11) in the rate-control arm. The lower panels show the corresponding 3D SPECT data. In this case, there has been a decrease of 2% in the measured planar LVEF, but an increase in the measured SPECT LVEF. This patient had a 16% rise in peak VO2 at 12 months follow-up.
Figure 6-2  Radionuclide ventriculography – example 2

The upper panels show the output from planar radionuclide ventriculography at baseline (left) and after 12 months follow up (right) in a patient (S24) in the catheter-ablation arm, who maintained sinus rhythm after a single ablation procedure. The lower panels show the corresponding 3D SPECT data. In this case, there has been an increase of 23% in the measured planar LVEF (18% to 41%), compared with an increase of 12% in the measured SPECT LVEF (22% to 34%). This corresponded with an increase of 26% in peak VO$_2$ at 12 months follow-up.
<table>
<thead>
<tr>
<th></th>
<th>Rate control (RC)</th>
<th>Catheter ablation (CA)</th>
<th>RC versus CA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=26 planar, n=13 SPECT)</td>
<td>(n=26 planar, n=12 SPECT*)</td>
<td>p values</td>
</tr>
<tr>
<td>Base</td>
<td>Base</td>
<td>Base</td>
<td></td>
</tr>
<tr>
<td>12m change</td>
<td>12m change</td>
<td>12m change</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>p</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Planar EF %</td>
<td>24.9 (7.2) +5.4 (8.5) 0.003</td>
<td>21.5 (8.3) +11.0 (11.5) &lt;0.001</td>
<td>0.13 0.055</td>
</tr>
<tr>
<td>SPECT EF %</td>
<td>31.5 (11.5) +5.1 (8.4) 0.047</td>
<td>26.7 (9.1) +6.3 (10.5) 0.08</td>
<td>0.26 0.78</td>
</tr>
<tr>
<td>SPECT EDV ml</td>
<td>200.5 (68.6) -6.2 (39.8) 0.58</td>
<td>208.6 (60.8) +28.5 (44.1) 0.06</td>
<td>0.76 0.055</td>
</tr>
<tr>
<td>SPECT ESV ml</td>
<td>140.1 (65.3) -11.7 (36.1) 0.27</td>
<td>156.5 (59.3) +4.36 (46.9) 0.76</td>
<td>0.52 0.35</td>
</tr>
</tbody>
</table>

Planar EF significantly increased from baseline in both arms. In the rate control arm, this was from 24.9±7.2 to 30.2±9.4 (p=0.003), an increase of 5.4±8.5%. In the catheter ablation arm, EF increased from 21.5±8.3 to 32.8±14.3 (p<0.001), an increase of 11.0±11.5%. However, when comparing the change from baseline between groups (defined as the secondary endpoint), there was only a non-significant/borderline trend towards a greater improvement in the ablation arm (mean increase over rate control: +5.6%, CI -0.1 to +11.3, p=0.055). The differential impact on 3D SPECT was even less marked, increasing by 6.3±10.5% under ablation versus 5.1±8.4% with rate control, p=0.78. There was an apparent trend towards increase in end-diastolic volume (EDV) and decrease in end-systolic volume (ESV) in both groups although this did not approach statistical significance.
Planar EF increased in 19/26 (73%) rate control (p=0.003 compared with baseline) and 19/24 (79%) catheter ablation (p<0.001) patients, whereas SPECT EF increased in 9/13 (69%, p=0.047 compared with baseline) and 8/11 (73%, p=0.08) respectively. 10/24 (42%) of catheter ablation patients showed >10% improvement in planar EF, compared with 6/26 under rate control (23%) (Fisher exact p=0.13).

Figure 6-3  Left ventricular ejection fraction: impact of ablation vs. rate control

Change in left ventricular ejection fraction (LVEF) from baseline, as assessed by planar radionuclide ventriculography (left) and echocardiography by biplane method-of-discs (right). The intention-to-treat data are presented showing the ablation group as solid dots/lines and rate-control group as open dots/dashed lines. 2-sided p-values for intergroup comparison (independent t-test) are shown at follow-up.

6.4.2 Echocardiography

Echocardiographic data is presented in Table 6-2. Echocardiographic LVEF was shown to be different between the groups at baseline, being significantly lower in the catheter ablation arm despite randomisation. When examining change, there was an overall increase in EF in both groups, although this was less marked than for RNV (Figure 6-3). In the catheter ablation arm, LVEF was 26.2±8.8% at baseline, increasing to 33.2±11.1% at 6 months (p=0.004) reflecting a change of +6.5±10.3%, and 33.5±9.4% at 12 months (p<0.001 compared with baseline), reflecting a total change of +6.8±8.9%. By comparison, the change in the rate control arm, although
positive, was of lower magnitude: baseline EF was 33.7±12.2%, increasing to 34.6±9.4 at 6 months (p=0.65), reflecting a change of +1.0±10.8%, and 35.4±10.2% at 12 months (p=0.49 compared with baseline), a change of +1.7±12.6%.

When comparing the change between groups, as pre-specified for secondary endpoint analysis, the increase in the ablation arm was shown to be a statistical trend rather than reaching significance. At 6 months, the increase in the catheter ablation arm was 5.6% greater than the rate control arm (95% CI -0.4 to +11.5%, p=0.066) and at 12 months was 5.1% greater (95% CI -1.1 to 11.2%, p=0.104).

Of the other parameters, the most striking change was in left atrial (LA) size, a pre-specified secondary endpoint parameter. LA diameter was shown to have a marginal increase in the rate-control arm at 6 (+0.1±3.4mm, p=0.87) and 12 months (+0.5±5.2mm, p=0.63), but a significant decrease in the catheter ablation arm at 6 months (-4.8±4.6mm, p<0.001) and 12 months (-5.7±5.3mm, p<0.001) reflecting a change from 49.9±6.4mm to 44.0±8.3mm.

**Figure 6-4**  **Atrial size: impact of ablation vs. rate control**

Change from baseline in left atrial area (left) and right atrial area (right), as measured in apical 4-chamber view. Ablation group shown as solid dots/lines, rate-control as open dots/dashed lines.
### Table 6-2  Echocardiographic data

<table>
<thead>
<tr>
<th></th>
<th>Rate control</th>
<th>Catheter ablation</th>
<th>Rate Control vs. Catheter Ablation (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=26</td>
<td>n=26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Base</td>
<td>6m change</td>
<td>12m change</td>
</tr>
<tr>
<td><strong>IVSd mm</strong></td>
<td>11.2 (1.9)</td>
<td>-0.3 (2.5)</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>PWd mm</strong></td>
<td>10.5 (1.8)</td>
<td>-0.3 (2.1)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>LVEDD mm</strong></td>
<td>61.4 (8.5)</td>
<td>-0.9 (5.2)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>LVESD mm</strong></td>
<td>53.4 (9.6)</td>
<td>-2.3 (5.4)</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td><strong>LVEDV ml</strong></td>
<td>141 (53)</td>
<td>-4 (30)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>LVESV ml</strong></td>
<td>96 (45)</td>
<td>-3 (25)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>LVEF %</strong></td>
<td>33.7 (12.2)</td>
<td>+1.0 (10.8)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>LA diameter mm</strong></td>
<td>46.4 (7.2)</td>
<td>+0.1 (3.4)</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>LA area cm$^2$</strong></td>
<td>27.2 (6.9)</td>
<td>+1.5 (6.2)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>RA area cm$^2$</strong></td>
<td>21.3 (4.5)</td>
<td>+1.9 (4.9)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>TAPSE mm</strong></td>
<td>17.2 (3.9)</td>
<td>+1.0 (4.3)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>LVPEP ms</strong></td>
<td>111 (28)</td>
<td>+1 (24)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>RVPEP ms</strong></td>
<td>94 (23)</td>
<td>+7 (22)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Mitral E ms$^{-1}$</strong></td>
<td>0.94 (0.19)</td>
<td>+0.06 (0.14)</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td><strong>E’ ms$^{-1}$</strong></td>
<td>0.11 (0.03)</td>
<td>+0.01 (0.03)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>E/E’ ratio</strong></td>
<td>8.9 (3.9)</td>
<td>0.0 (3.1)</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>LVOT VTI cm</strong></td>
<td>12.9 (3.5)</td>
<td>+2.3 (3.2)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td><strong>Est. CO l/min</strong></td>
<td>3.3 (0.7)</td>
<td>+0.2 (0.9)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Est. CO = estimated cardiac output (from LVOT VTI – see text), E(E’) = mitral (tissue) Doppler E wave, EDD/V = end-diastolic diameter/volume, EF = ejection fraction, ESV = end-systolic diameter/volume, IVSd = interventricular septum diastole, LA = left atrium, LV = left ventricle, LVOT = LV outflow tract, PWd = posterior wall diastole, RV= right ventricle, TAPSE = tricuspid annular plane systolic excursion. *no follow-up data available for patient who died, therefore n=25 for change data
2-dimensional LA area, which is a more robust measure than M-mode diameter,\textsuperscript{309} was shown to have a similar profile (Figure 6-4): under catheter ablation, there was a change from 29.5±5.8cm\textsuperscript{2} at baseline to 24.7±6.5cm\textsuperscript{2} at 6 months (change -4.9±6.5, p<0.001) with a area of 25.0±8.1cm\textsuperscript{2} at 12 months (change from baseline -4.7±7.1, p=0.003); with rate control LA area was 27.2±6.9cm\textsuperscript{2} at baseline, 28.3±8.6cm\textsuperscript{2} at 6 months(+1.5±6.2, p=0.40), and 29.2±8.2cm\textsuperscript{2} at 12 months (+2±7, p=0.16). Comparing change between groups, at 6 months LA area was 6.4cm\textsuperscript{2} lower in the catheter ablation arm (95% CI -10.0 to -2.8, p=0.001), and at 12 months 6.7cm\textsuperscript{2} lower (95% CI -10.7 to -2.7, p=0.001). Right atrial area showed similar magnitude change at 6 months (-5.4cm\textsuperscript{2}, 95% CI -8.3 to -2.6, p<0.001), although at 12 months the difference between groups was non-significant (-2.6cm\textsuperscript{2}, 95% CI -6.0 to +0.7, p=0.12).

All patients who underwent catheter ablation and had sinus rhythm at follow up had a recordable mitral Doppler A wave and lateral mitral tissue Doppler atrial component (A'). At 6 months 22/25 (88%) patients at 6 months were in sinus rhythm and had A wave amplitude 0.46±0.14ms\textsuperscript{-1}, and A' amplitude 0.05±0.02ms\textsuperscript{-1}. At 12 months, the same proportion were in sinus rhythm, with A 0.44±0.13ms\textsuperscript{-1} and A' 0.05±0.02ms\textsuperscript{-1}.* Unsurprisingly, this recovery of mechanical left atrial systolic function was reflected in the mitral E waveforms, which may be due to the change in proportion of ventricular filling occurring passively during early ventricular diastole: whilst amplitude of the E wave had increased in the rate-control arm at 6 and 12 months, there had been a significant decrease in the catheter ablation arm at follow-up. The difference between the groups was highly significant at both 6 (p<0.001) and 12 months (0.003). However, there was no significant change in the E/E' ratio.

* Not included are the two patients in the rate-control arm: the patient (RC9) who underwent catheter ablation at 4 months, with subsequent repeat procedures for atrial tachycardia, had a recorded A amplitude of 0.35ms\textsuperscript{-1} and A' of 0.04ms\textsuperscript{-1} at 12 months; the patient (RC21) who was defibrillated at 10 months had A amplitude 0.4ms\textsuperscript{-1} and A' 0.03ms\textsuperscript{-1}.
Although there was an increase in LVOT VTI in the catheter ablation arm, this was not reflected in overall cardiac output estimation. This appears to be at least partly explained by the difference in heart rate seen in the two groups: at baseline heart rate (at the time of echocardiography, average over 30 seconds) was 81.4±14.1bpm in the rate control arm, and 83.9±13.5bpm in the ablation arm (p=0.53); at 6 months, heart rate was 77.6±16.0bpm and 69.2±13.8bpm (p=0.051) respectively, and 77±18.6bpm and 67.5±10.7 bpm (p=0.03). Therefore, there was a small but statistically significant reduction in heart rate with catheter ablation (and predominantly sinus rhythm) compared with rate control (where patients were predominantly in atrial fibrillation), which would offset – and may indeed have been responsible for – the increase in LVOT VTI.

*TAPSE* increased in the ablation arm at 6 (p=0.02) and 12 (p=0.01) months, with no significant change in the rate control arm, suggesting an improvement in right ventricular systolic function. However, when comparing the change at follow-up this was not significant (12 month difference +1.21mm, 95% CI -1.5 to +4.0, p=0.38). *Mitral regurgitation* (defined as >trivial and quantifiable by PISA-ERO) was present in 15/26 ablation arm patients, and 11/26 (p=0.27) rate-control patients at baseline, the majority mild or mild-moderate, with PISA-ERO 0.06±0.07cm$^2$ and 0.06±0.05 respectively (p=0.97). At follow up, there was a trend towards a small reduction in the ablation arm (-0.05±0.08) compared with the rate control arm at 6 months (+0.03±0.10, p=0.15) which reached significance at 12 months (mean difference in ablation arm -0.15cm$^2$, 95% CI -2.7 to -.03); the number of patients with quantifiable MR was 8/26 and 5/26 respectively (p=0.26).

### 6.4.3 Reliability and co-relation of estimates of LV function

In order to assess reliability and comparability of the three modalities (planar, SPECT, echo) used to assess LVEF, correlation estimations (Pearson unless otherwise stated) and Bland-Altman plots were created to compare values at baseline (Figure 6-5) and follow-up (Figure 6-6).
Figure 6-5  Reliability and correlation of LV parameters – baseline data

Left: Bland-Altman plots for echo and radionuclide ventriculographic (RNV) measurements, at baseline. The solid line represents the mean difference, and dashed lines 2 standard deviations either side. Right: Scatter-plots with regression lines and square of the Pearson correlation coefficient \( R^2 \) displayed for each.
Figure 6-6  Reliability and correlation of LV parameters – 12-month follow-up data

Left: Bland-Altman plots for echocardiographic and radionuclide ventriculographic (RNV) measurements, at 12 month follow-up. The solid line represents the mean difference, and dashed lines 2 standard deviations either side. Right: Scatter-plots with regression lines and square of the Pearson correlation coefficient (R²) displayed for each. See text for discussion.
Figure 6-7  Scatter plots and correlation: atrial fibrillation and sinus rhythm
Scatter plots for 12-month follow up echocardiographic and radionuclide ejection fraction measurements, with lines of best fit and square of the Pearson correlation coefficient (R²).

Additionally, LVEF measurements at follow-up were compared between sinus rhythm and atrial fibrillation/tachycardia (Figure 6-7).

Echocardiographic and SPECT LVEF was generally higher than planar radionuclide LVEF. Echo LVEF % was 6.8±8.9 higher than radionuclide at baseline, with modest correlation (p<0.001, R²=0.37). SPECT LVEF % was 5.1±6.2 higher than planar RNV, with better
correlation (p<0.001, R²= 0.67). Echo end-diastolic volume (EDV) was generally lower than SPECT EDV, by 63.3±34.7ml (correlation p<0.001, R²=0.73), and similarly for end-systolic volume (ESV) by 50.3±35ml (correlation p<0.001, R²=0.72). There was a clear proportional difference in the volume assessments, with greater difference at higher volumes.

At 12-month follow-up, similar relationships were present. Echo gave LVEF % values that were 3.0±8.1 higher than planar RNV (correlation p<0.001, R²=0.55), and SPECT was 3.8±8.0 higher than planar (correlation p<0.001, R²=0.49). Echo EDV was 70.3±37.4ml lower than SPECT EDV (correlation p<0.001, R²=0.75) and echo ESV was 44.6±33.3ml lower than SPECT ESV (correlation p<0.001, R²=0.78).

At follow-up, there appeared to be a marginally closer relationship between echocardiographic and planar RNV values in those patients in sinus rhythm (correlation p<0.001, R²=0.69), compared with those in AF (correlation p<0.001, R²=0.47). In sinus rhythm, echo LVEF % was 2.0±8.6 higher than planar RNV LVEF, and SPECT LVEF % was 3.9±9.1 higher than RNV. In atrial fibrillation, echo LVEF % was 4.0±7.6 higher than RNV, and SPECT LVEF % was 3.7±7.5 higher than RNV.

Change in LVEF from baseline to 12 months correlated between echo and planar LVEF (p=0.002, R²=0.19), whereas change in LVEF did not significantly correlate between SPECT and planar EF (p=0.105, R²=0.15) or echo LVEF (p=0.18, R²=0.08).

6.4.4 Correlation with physiological outcomes/biomarkers

The change in LVEF by different modalities was compared with the change in the ARC-HF study endpoints, namely change in peak VO₂ by Pearson correlation, and change in Minnesota Living with Heart Failure Questionnaire (LHFQ) score and plasma B-type natriuretic peptide (BNP) by Spearman rank correlation (Table 6-3).
Planar radionuclide ventriculography correlated best with all three endpoints. SPECT correlated poorly, although the smaller sample size may have impacted upon this.

**Table 6-3** Correlation of LVEF measurements with other ARC-HF endpoints

For each modality of LVEF assessment, correlation estimations were performed using Pearson (comparing change in VO\(_2\)) and Spearman Rank correlations (comparing change in LHFQ score and BNP) against change (\(\Delta\)) in LVEF, from baseline to 12 months follow-up. Correlation coefficient values (R) are shown with corresponding 2-sided p-values.

<table>
<thead>
<tr>
<th></th>
<th>(\Delta) Planar LVEF</th>
<th>(\Delta) Echo LVEF</th>
<th>(\Delta) SPECT LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(p)</td>
<td>(p)</td>
<td>(p)</td>
</tr>
<tr>
<td>(\Delta) VO(_2)</td>
<td>0.54</td>
<td>&lt;0.001</td>
<td>0.35 (0.01)</td>
</tr>
<tr>
<td>(\Delta) LHFQ score</td>
<td>-0.41 (0.003)</td>
<td>-0.22 (0.13)</td>
<td>-0.32 (0.13)</td>
</tr>
<tr>
<td>(\Delta) BNP</td>
<td>-0.52 (&lt;0.001)</td>
<td>-0.28 (0.05)</td>
<td>-0.23 (0.28)</td>
</tr>
</tbody>
</table>

*BNP = B-type natriuretic peptide, LHFQ = Minnesota Living with Heart Failure Questionnaire score, LVEF = left ventricular ejection fraction, VO\(_2\) = peak oxygen consumption at treadmill exercise testing*
6.5 Discussion

In this clinical trial, the strategies of catheter ablation-based rhythm control and robust protocol-guided rate control were compared by assessment of cardiopulmonary exercise capacity, symptomatic status, neurohormonal activation, and imaging parameters of cardiac function. The modalities of radionuclide ventriculography and 2-dimensional echocardiography were used to assess the latter.

The principal measure of left ventricular function in this study was planar radionuclide LVEF, which increased significantly in both arms (Figure 6-3), although with greater magnitude in those randomised to undergo catheter ablation. Although this increase, when compared between treatment groups, showed a statistical trend (p=0.055) rather than significance, change in planar RNV LVEF positively correlated well with the positive endpoint of peak oxygen consumption, and also with quality-of-life score and plasma BNP where a reduction (improvement) in these values was associated with increased LVEF (negative correlation). Echocardiographic LVEF increased significantly in the catheter ablation arm, with only slight (non-significant) change in the rate-control arm, although inter-group comparison showed again only a weak trend towards greater increase in LVEF at follow-up. Echo LVEF correlated less well than RNV with the other positive endpoint outcomes. Interestingly, although the magnitude and vector of change was different between RNV and LVEF, the relative improvement in the ablation arm was remarkably similar at 12 months (5.6 vs. 5.1% for RNV and Echo respectively; Figure 6-3). SPECT LVEF was evaluated only in a subset of patients, and thus was likely to be underpowered for endpoint analysis and comparison. However, this relatively novel technique, performed at the same sitting as standard planar ventriculography, was shown to record left ventricular volumes with some correlation to
echocardiographic measures, albeit with evidence of a proportional difference producing larger differential error at higher LV systolic and diastolic volumes.

Consistent with prior studies, the data showed a relative overestimation of LVEF using SPECT compared with planar RNV, and of echo (biplane Simpson’s) versus planar RNV. The modalities used showed a moderate of correlation in LVEF, although with marked variability in agreement when assessed by Bland-Altman method, as previously reported. Cardiovascular magnetic resonance imaging has been reported as a more accurate and reliable technique than echo and radionuclide ventriculography, and has been proposed as the preferred modality in heart failure patients. However, in the modern era, a significant proportion of patients with heart failure are managed with implanted devices such as CRT and ICDs, which render MRI contra-indicated – although compatible devices are on the horizon. Hence, in designing ARC-HF, cardiovascular magnetic resonance was not chosen as an imaging modality: inclusion would have meant either its use only in a small sub-group, or recruiting for a heart failure study from a population of patients which would not reflect a realistic clinical cohort. Indeed, in ARC-HF, 27% of patients had implanted devices at study enrolment.

Planar radionuclide ventriculography is known to be highly reproducible, and RNV LVEF is thus often used as an inclusion criterion and/or endpoint in heart failure clinical trials, and was chosen as the principal measure of LVEF in the ARC-HF study given its ability to cope with arrhythmias without the user-dependency of echocardiography. However, as with any measure of ejection fraction there is a degree of variability in results that is increased by the presence of atrial fibrillation. The lack of clear positivity in the endpoint of LVEF from either planar RNV or echo may relate to this high variability in measurement of EF. Additionally, there was a small but significant improvement observed in LVEF in the rate-control arm, reducing the differential change when comparing treatment
arms. Both of these effects would reduce the *effect size*, the first by increasing the standard deviation of the group means, and the second by reducing the treatment effect (mean difference), leaving the current study marginally underpowered to detect a statistical difference in the endpoint of LVEF.

Previous non-randomised observational studies examining the impact of heart failure found significant increases in LVEF after catheter ablation. The Bordeaux group reported a significant increase of 21±13% in LVEF and a reduction in systolic and diastolic diameters by 8±7 and 6±6mm respectively,\(^\text{133}\) compared with a non-significant increase of 5% (7.2±3% in ‘responders’) as reported by the Cleveland group.\(^\text{134}\) The profound increase in the former should be seen in the context of a non-randomised cohort of patients undergoing catheter ablation in its first few years of application for AF, and as such may have been a highly-selected group. Additionally, the duration of heart failure was not specified, and it is possible that some of these patients had a form of tachycardia or other reversible cause of cardiomyopathy: in the case of the former, subgroup analysis showed a greater improvement in those without rate control at baseline.\(^\text{133}\) Indeed in our study, there was a trend for those with adequate rate control at enrolment to have a less marked increase in planar RNV LVEF than those with inadequate control (-5.2%, 95% CI -11.0 to 0.66 %, p=0.08). Also, the patients in our study had a median duration of heart failure 48 months (IQR 12-81) compared with AF duration 36 months (IQR 12-63) reflecting a cohort that, on the whole, had well-established chronic heart failure and persistent AF. Finally, the use of echocardiographic LVEF in the above non-blinded studies would open up the possibility of bias, which could influence the baseline LVEF during AF by choice of shorter cycle lengths (faster heart rate) with near-inevitable reduction of ejection fraction, and the potential for error in biplane estimation of LVEF during follow-up regardless of rhythm. Radionuclide ventriculography LVEF estimation is less open to bias by its semi-automatic calculation, and in ARC-HF
investigators reporting both this and echocardiographic LVEF were blinded to the treatment allocation group.

There was evidence of return of left atrial mechanical function in patients who underwent catheter ablation. Although this has been reported previously in patients after AF ablation without significant structural heart disease,\textsuperscript{233} this has not previously been reported in the context of severe LV dysfunction and longstanding AF. Despite a prolonged history of AF and extensive left atrial ablation in many cases, contractile function is able to return, which may contribute towards improved haemodynamics through atrial primer pump function and atrioventricular synchrony. Furthermore, a marked reduction in biatrial size was seen by 6 months, with a maintained significant reduction of LA size in the ablation arm compared with an increase in the rate control arm at 12 months. The had been a reduction in RA size in the ablation arm by 6 months but by 12 months this effect appeared to have reversed, with the implication that the longer lasting impact of ablation, which itself was mostly confined to the left atrium, was mainly on that side. A reduction in left atrial size has previously been reported in patients with lone AF,\textsuperscript{316-319} but a recent randomised study of patients with heart failure showed no impact on left atrial end-diastolic area.\textsuperscript{300} However, regression of atrial dilatation has been demonstrated in the setting of structural heart disease, for instance after mitral valve surgery,\textsuperscript{320} and in patients with diastolic dysfunction administered an angiotensin-converting enzyme inhibitor.\textsuperscript{321} The data from the present study would suggest that catheter ablation, if associated with a high rate of sinus rhythm maintenance, can lead to a regression in atrial dilatation. Whether this, itself, could be beneficially protective against recurrent atrial arrhythmias remains uncertain, given that prior studies – in patients without significant structural heart disease – have provided conflicting data.\textsuperscript{316, 322} In the present study, change in LA size was predictive of recurrence of (any) atrial arrhythmia in those randomised to and who underwent ablation (excluding patient A1), with Cox regression
statistically significant at 6 months (Hazard ratio 1.19/cm², 95% CI 1.01-1.40, p=0.037) and showed a trend at 12 months (Hazard ratio 1.10/cm², 95% CI 0.99-1.22, p=0.07).

Although there were some statistically significant changes in TAPSE, suggesting an improvement in right ventricular function, and quantitative mitral regurgitation, these results – although potentially interesting and consistent with the overall group data – should be interpreted with caution as these were not prospectively designated endpoints, the subgroup size was small and thus open to random effects, and correction for multiple tests of significance was not incorporated into the study design.

6.6 Conclusion

Imaging of ventricular function in patients with AF is challenging and methods all have pitfalls – including test reproducibility and variability, which can be exaggerated further in the presence of irregular and rapid arrhythmia. In the context of a clinical trial examining the relative impact of two strategies to treat AF in heart failure, namely catheter ablation and medical rate control, the outcome of change in LVEF from baseline showed overall improvements in both treatment arms, with a trend towards a greater increase in LVEF under assignment to catheter ablation. A study with a larger sample size might be expected to show a significant difference in this outcome. Change in planar radionuclide LVEF correlated well with changes in cardiopulmonary exercise performance, quality of life score, and B-type natriuretic peptide levels. There is evidence of a regression in left atrial dysfunction after catheter ablation and restoration of sinus rhythm, despite often-longstanding persistent atrial fibrillation and heart failure, which may contribute towards maintenance of sinus rhythm and favourable haemodynamics.
Biomarkers in atrial fibrillation and heart failure

7.1 Abstract

The optimal therapy for AF in heart failure remains unclear: drug-based 'rhythm-control' has been shown to have no clear advantage over drug-based ‘rate-control’. The newer therapy of radiofrequency catheter ablation has been shown to be feasible in achieving sinus rhythm in patients with heart failure and to confer clinical benefits. Outcomes from long-term, large scale clinical trials are awaited to assess whether this newer therapy confers an advantage to patients, however trials based around event endpoints can be limited by low event rates and the need for prolonged follow-up. Biomarkers may act as surrogate markers of prognosis and allow earlier assessment of prognostic impact in this patient population.

This chapter examines the impact of rate control and catheter ablation upon neurohormonal status in patients with atrial fibrillation and heart failure. Using a per-protocol analysis, the impact of each therapy upon novel and established cardiac biomarkers is presented.

7.2 Background

Biomarkers, in particular B-type natriuretic peptide (BNP), have become key elements in the diagnosis of heart failure. BNP is secreted primarily from the left ventricle in response to changes in left-ventricular wall stretch, thus levels may be influenced by a number of factors including heart rate/rhythm, blood pressure/afterload, fluid status, and co-existing conditions like left ventricular hypertrophy or coronary artery disease. BNP is the best predictor of prognosis we have to date, improves outcomes when used as a guide to heart failure therapy, and it is now well established that improvements in the heart failure
syndrome are associated with a reduction in BNP concentrations.\textsuperscript{231,232} BNP levels have been shown to fall after catheter ablation for paroxysmal and persistent AF in patients without ventricular dysfunction.\textsuperscript{233,234} It has been shown that BNP and N-terminal pro-BNP levels are not independently affected by AF in advanced heart failure,\textsuperscript{325,326} thus BNP is well placed for assessing serial change in cardiac function, in parallel with imaging modalities, in comparison of rate and rhythm-control.

The novel peptide \textit{apelin} is an endogenous peptide ligand for the angiotensin-like 1 (APJ) receptor,\textsuperscript{327} and is known to have potent inotropic effects – alongside reduction in preload and afterload – in animal models.\textsuperscript{328,329} Plasma concentrations of apelin have been shown to be decreased in patients with chronic heart failure when compared with controls\textsuperscript{330} and its concentration shown to be increased after CRT.\textsuperscript{331} However, data are contrasting, with evidence that plasma concentrations are significantly increased in mild-moderate heart failure, and decrease back towards control levels in severe heart failure.\textsuperscript{332} It is uncertain whether the changes in plasma apelin are due to increased myocardial apelin production or enhanced production from the peripheries as a consequence of improved haemodynamics.\textsuperscript{333} Tissue concentrations are increased after ventricular off-loading by left ventricular assist device (LVAD) therapy.\textsuperscript{332} Thus apelin seems have potential as a novel biomarker for reverse remodelling in heart failure. However, the effect of sinus rhythm restoration on plasma apelin levels, in the context of persistent atrial fibrillation, is presently unknown.

\textit{Atrial natriuretic peptide} (ANP) is secreted by atrial myocytes under conditions of atrial stretch. Several hormones and neurotransmitters, such as endothelin, vasopressin, and catecholamines, directly stimulate its secretion.\textsuperscript{334} It has diuretic, vasodilating, and renin/angiotensin inhibitory effects. Plasma levels of ANP are known to be increased in patients with heart failure and sinus rhythm,\textsuperscript{335} and are known to be further increased in patients with atrial fibrillation,\textsuperscript{336} a finding which has been shown to be independent of LV
dysfunction. Studies have shown that longer duration of AF is associated with lower ANP levels, perhaps reflecting some form of ‘atrial insufficiency’ and there may be subsequent interplay between two competing mechanisms: the haemodynamic burden of heart failure (increasing ANP) and progression atrial degeneration (decreasing ANP). Both DC cardioversion and AF ablation are known to decrease ANP levels by restoration of sinus rhythm in those without structural heart disease. In heart failure, ANP proved to be inferior to BNP in terms of its diagnostic and prognostic potential, largely due to lack of reproducibility. However, recently an assay of the midregional segment of the more stable precursor pro-ANP - mid regional pro-ANP (MR-proANP) – has been shown to have similar accuracy to BNP as a diagnostic test, and may be a stronger prognostic marker. It may also give more direct information about atrial remodelling than other biomarkers which relate to ventricular remodelling.

**Interleukin-6 (IL-6)** an inflammatory cytokine, has multiple endocrine and metabolic actions including haematologic, immune, and hepatic effects. It is secreted during stress and is positively controlled by catecholamines. IL-6 is known to be increased in patients with AF, and may contribute to the pro-thrombotic state in this condition. In patients with coronary artery disease, raised IL-6 levels were independently associated with AF. Furthermore, raised levels of IL-6 and C-reactive protein have recently been associated with increased likelihood of AF recurrence in patients after radiofrequency catheter ablation. There also appears to be a link between IL-6 gene polymorphisms, level of IL-6 expression, and the propensity to AF after cardiac surgery. IL-6 is well known to be raised in patients with chronic heart failure, particularly in those requiring left-ventricular assist devices.

In this study we explored, for the first time, the effects of AF ablation on plasma apelin and MR-ANP in a population of patients with heart failure. Changes in these novel biomarkers
were assessed alongside those in the established biomarkers BNP and IL-6, and the compared with the effect of rate control over the same time period.

7.3 Methods

7.3.1 Study population

Blood samples were acquired from patients enrolled in a randomized clinical trial (see chapters 2, 5, and 6) which was seeking to test the hypothesis that ablation-based rhythm-control improves outcomes compared to a conventional rate-control strategy, using exercise, questionnaire and image-based assessment of cardiovascular function as outcomes. The trial population consisted of patients with persistent (documented AF >7 days in duration) or permanent (persistent AF >1 year) atrial fibrillation and chronic heart failure NYHA class ≥II; LVEF ≤ 35 %. The strategies of rate control and catheter ablation were compared in a 1:1 randomised fashion, with primary endpoint of peak oxygen consumption at exercise testing, and secondary endpoints including ejection fraction, 6 minute walk, and Minnesota quality of life score.

7.3.2 Sample acquisition

Prior to exercise testing (and radionuclide ventriculography when applicable), peripheral venous blood was collected from patients in the resting state (prior to exercise testing), into tubes containing 7ml ethylene-diamine-tetra-acetic acid. Centrifugation was performed at 1000G for 5 minutes, within 1 hour of sample acquisition, and plasma was extracted via manual pipette into cryo-tubes for freezer storage of 2ml plasma aliquots at -70 degrees C. Samples were acquired at enrolment into the trial, and at subsequent follow-up visits at 3, 6 and 12 months, after randomisation to either rate or rhythm control.
**7.3.3 Laboratory assays**

Laboratory analyses were performed blinded to the randomisation group, using coded pseudo-anonymised labelling of samples.

*BNP* was measured by immunoassay on the Beckman Access 2 Immunoassay analyser (Beckman Coulter, High Wycombe, UK) using the Alere Triage BNP reagents. (analytical range 25-5000ng/L).

*Apelin* was measured by ELISA (Phoenix Europe GmbH, Karlsruhe, Germany); an extraction-free protocol was followed. The antibody used in this apelin assay cross-reacts 100% with Apelin-12, 13 and 36. The assay therefore includes all of the above peptides if present in the plasma (analytical range 0.01-100 ng/ml).

*MR-pro-ANP* was measured by immunofluorescent assay on the Brahms Kryptor analyser (Thermo scientific, BRAHMS GmbH, Henningsdorf, Berlin, Germany; analytical range 2.1-10000 pmol/L).

*IL-6* was measured by immunoassay on the Beckman Access 2 Immunoassay analyser (Beckman Coulter, High Wycombe, UK; analytical range 2.5-1500 pg/ml).

*CRP* was measured by an immunoturbidimetric method on the Beckman DxC600 autoanalyser (Beckman Coulter, High Wycombe, UK; analytical range 1.0 - 500mg/L).

**7.3.4 Statistical analysis**

Although the main clinical trial outcomes (including BNP) were analysed on an intention-to-treat basis, the biomarker sub-study of ARC-HF was designed to examine the impact of undergoing ablation thus a *per-protocol analysis* was used, with censorship of results after any breach of protocol.
The sample size was calculated for the primary endpoint of the pre-existing clinical trial, requiring 25 patients in each group to detect a 10% (SD 12.5%) change in peak oxygen consumption at exercise testing (see chapter 5). The magnitude of possible effect on Apelin and MR-ANP was unknown, however previous observational studies have examined changes in BNP after ablation in similar size populations. If similar variability is assumed (SD 25pmol/L), our study population would be sufficient to detect a 20pmol/L reduction in BNP at 80% power, alpha 0.05, for a two-sample t-test method.

Baseline values are expressed as mean+/−SD or frequency/percentage. The primary endpoint was change in biomarker plasma level at 12 months, and secondary endpoints were change at 3 and 6 months. Change was assessed by independent group comparison of individual absolute differences from baseline. Data were assessed for normality by histogram, skewness, and Kruskal-Wallis test within SPSS for Mac version 20 (IBM). Based upon this, normally distributed data were analysed by independent (two-sample) t-test (adjusted for presence/absence of equal variances by Levene’s test) and presented as mean±SD, whilst non-parametric data were analysed by Mann Whitney U (Wilcoxon rank-sum) test and summarised as median and interquartile range (IQR = 25th to 75th percentiles). Paired t or Wilcoxon tests were used to analyse individual responses. Correlation analyses were performed using Pearson (parametric) or Spearman Rank (non-parametric) methods. P values of less than 0.05 were regarded as statistically significant, and a p-value less than 0.1 was used as an indication of a non-significant trend.
7.4 Results

A total of 52 patients were investigated. Plasma samples for biomarkers were acquired at all available time points. One patient withdrew consent for ablation and continued on normal medical therapy, and was excluded from the per-protocol analysis. Two patients had baseline and 3 month assays only: one entered palliative care for end stage heart failure post 3 month follow up, was unable to attend 6 month follow-up and died prior to the final 12 month follow up; another patient requested catheter ablation at 4 months and results were censored after 3 month follow up.

Baseline characteristics are shown in (Table 7-1). All randomised patients are included, 26 in each group. The groups were well-matched for age, gender, heart failure aetiology and clinical characteristics. The only significant difference was in frequency of aldosterone usage, however this would be an acceptable finding in a randomised population (26 parameters subjected to statistical testing).

A flow-chart illustrating the study protocol and reasons for patient/result censoring is shown in Figure 7-1.

Results are presented for each biomarker by section below. Based upon normality testing as above, results (change) showed non-parametric distribution in at least one arm in at least 2/3 of all time points for all assessed biomarkers. Hence all outcomes are shown as median (IQR) change and the groups were compared with Mann Whitney U test.
# Table 7-1  Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Rate control n=26</th>
<th>Catheter Ablation n=26</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%) / mean±SD</td>
<td>N (%) / mean±SD</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>62±9</td>
<td>64±10</td>
<td>0.38</td>
</tr>
<tr>
<td>Male</td>
<td>24 (92)</td>
<td>21 (81)</td>
<td>0.22</td>
</tr>
<tr>
<td>HF aetiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>7 (27)</td>
<td>10 (38)</td>
<td>0.38</td>
</tr>
<tr>
<td>Non-ischaemic</td>
<td>19 (73)</td>
<td>16 (62)</td>
<td>0.38</td>
</tr>
<tr>
<td>Time since HF diagnosis (months)</td>
<td>48±57</td>
<td>68±62</td>
<td>0.22</td>
</tr>
<tr>
<td>Time since AF diagnosis (months)</td>
<td>51±76</td>
<td>51±39</td>
<td>0.98</td>
</tr>
<tr>
<td>Duration of continuous AF (months)</td>
<td>24±29</td>
<td>23±22</td>
<td>0.95</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA II</td>
<td>13 (50)</td>
<td>14 (54)</td>
<td>0.79</td>
</tr>
<tr>
<td>NYHA III</td>
<td>13 (50)</td>
<td>12 (46)</td>
<td></td>
</tr>
<tr>
<td>Recent HF hospitalisation (&lt;1year)</td>
<td>7 (27)</td>
<td>10 (38)</td>
<td>0.38</td>
</tr>
<tr>
<td>Minnesota LHFQ score (/105)</td>
<td>49±21</td>
<td>42±23</td>
<td>0.38</td>
</tr>
<tr>
<td>Creatinine</td>
<td>102±28</td>
<td>96±24</td>
<td>0.42</td>
</tr>
<tr>
<td>Peak VO₂ (ml/kg/min)</td>
<td>18.2±4.8</td>
<td>16.3±5.3</td>
<td>0.19</td>
</tr>
<tr>
<td>QRS duration (ms) non-paced only</td>
<td>113±21</td>
<td>119±19</td>
<td>0.37</td>
</tr>
<tr>
<td>Radionuclide LVEF (%)</td>
<td>25±7</td>
<td>22±8</td>
<td>0.13</td>
</tr>
<tr>
<td>LA diameter (M-mode, mm)</td>
<td>46±7</td>
<td>50±6</td>
<td>0.07</td>
</tr>
<tr>
<td>Apelin (pg/ml)</td>
<td>881±423</td>
<td>794±288</td>
<td>0.39</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>283±285</td>
<td>412±324</td>
<td>0.13</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>3.3±3.2</td>
<td>10.0±16.5</td>
<td>0.052</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>4.4±3.0</td>
<td>5.7±6.8</td>
<td>0.39</td>
</tr>
<tr>
<td>MR-proANP (pmol/L)</td>
<td>353±196</td>
<td>372±142</td>
<td>0.70</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>411±109</td>
<td>416±78</td>
<td>0.84</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>81±12</td>
<td>77±9</td>
<td>0.18</td>
</tr>
<tr>
<td>Exercise HR (bpm)</td>
<td>109±18</td>
<td>108±15</td>
<td>0.88</td>
</tr>
<tr>
<td>Proportion rate-controlled at baseline (≤80 rest, ≤110 at 6MW)</td>
<td>14 (54)</td>
<td>17 (65)</td>
<td>0.40</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>24 (92)</td>
<td>24 (92)</td>
<td>1.0</td>
</tr>
<tr>
<td>ACE or ARB</td>
<td>26 (100)</td>
<td>25 (96)</td>
<td>0.31</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>6 (23)</td>
<td>13 (50)</td>
<td>0.04</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>3 (12)</td>
<td>3 (12)</td>
<td>1.0</td>
</tr>
<tr>
<td>Digoxin</td>
<td>12 (46)</td>
<td>16 (62)</td>
<td>0.27</td>
</tr>
<tr>
<td>Preexisting ICD; of which CRT</td>
<td>4 (15); 3 (12)</td>
<td>10 (38); 8 (31)</td>
<td>0.06 ; 0.09</td>
</tr>
<tr>
<td>Ventricular pacing dependent</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

ACE = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, ARB = angiotensin receptor blocker, BNP= B-type natriuretic peptide, CRP = C-reactive protein, CRT = cardiac resynchronization therapy, HF = heart failure, HR = heart rate, ICD = implantable cardioverter defibrillator, IL-6 = Interleukin-6, LA = left atrial, LHFQ = Minnesota Living with Heart Failure Questionnaire, LVEF = left ventricular ejection fraction, MR-proANP = Mid-Regional proAtrial Natriuretic Peptide, NYHA = New York Heart Association, 6MWD = 6-minute walk distance.
Figure 7-1  ARCHF biomarker sub-study flowchart.

Number of patients included for per-protocol analysis shown at each time point
7.4.1 Mid-regional atrial natriuretic peptide (MR-proANP)

Sequential results for change in baseline of MR-proANP are shown graphically in Figure 7-2.

In the ablation arm, there was a median change of -79.6 pmol/L (IQR -186.2 to -12.7) at 3 months, -123.1 pmol/L (-231.1 to -13.6) at 6 months, and -106.0 (-228.2 to -60.6) at 12 months. In the rate-control arm, there was median change of -39.6 pmol/L (IQR -77.4 to -0.6) at 3 months, -31.1 (-112.9 to +0.3) at 6 months, and -28.7 (-69 to +9.5) at 12 months. By Mann Whitney U test, reductions in the ablation arm were non-significant at 3 months (0.277) and 6 months (0.119) but reached statistical significance by 12 months (p=0.028).

Figure 7-2 Mid-Regional proAtrial Natriuretic Peptide (MR-proANP)

Change (Δ) in mid-regional proANP (MR-proANP) from baseline at follow-up, represented as median with error bars showing 25th and 75th percentiles (IQR): catheter ablation (solid line) vs. rate control (dashed line). Statistical significance* is shown at 12 months between groups (p=0.028)
7.4.2 Apelin

The sequential changes in plasma apelin are displayed graphically in Figure 7-3.

In the ablation arm, median change was -27 pg/ml (IQR -250.25 to +161.5) at 3 months, -89.5 pg/ml (-238.5 to +52.5) at 6 months, and +9.5 pg/ml (-153.5 to +139.75) at 12 months. By comparison, in the rate control arm, median change was +74.5 (IQR -65 to 205.25) at 3 months, +133 pg/ml (-40 to +240) at 6 months, and +120 pg/ml (-9 to +294) at 12 months.

**Figure 7-3  Apelin**

Change (Δ) in Apelin from baseline at follow-up time points, represented as median with error bars showing IQR: catheter ablation (solid line) vs. rate control (dashed line). ** indicates p=0.002 at 6 months, whereas the difference between groups was not statistically significant at 12 months.
The difference in groups was non-significant at 3 months (p=0.22), although there was further change reaching significance at 6 months (p=0.002). However, due to an overall increase in Apelin level in the final 6 months, comparison at 1 year was non-significant (p=0.134).

7.4.3 B-type natriuretic peptide (BNP)

![Figure 7-4 B-type Natriuretic Peptide (BNP)](image)

Change (Δ) in BNP from baseline at follow-up time points, represented as median with error bars showing IQR: catheter ablation (solid line) vs. rate control (dashed line). The change at 6 (p=0.052) and 12 months (0.051) was borderline, showing a statistical trend^ rather than meeting significance criteria.

The sequential change for plasma BNP is presented in Figure 7-4

For patients randomised to catheter ablation, BNP showed a change of -90 pg/ml (IQR -270 to +8) at 3 months, -112 pg/ml (-380 to -3) at 6 months, and -120 pg/ml (-285 to +8) at 12
months. Under rate control, the changes were -26 pg/ml (IQR -74 to +22) at 3 months, -24 pg/ml (-84 to +56) at 6 months, and -16 pg/ml (-88 to +36) at 12 months.

Comparing the groups, the reduction in BNP in the ablation arm did not reach any significance at 3 months (p=0.17) however showed a strong non-significant trend at 6 (p=0.052) and 12 months (p=0.051). It is noted that, under the original intention-to-treat protocol, the outcome for BNP did reach significance for a reduction with ablation over rate-control (p=0.038 at 6 months and p=0.045 at 12 months – see chapter 5) and the borderline shift of significance level is likely to reflect borderline sufficient power of the sample size (reduced in the per-protocol analysis) and/or assay variability rather than a lack of clinical effect, when taken in the context of the other outcomes.

### 7.4.4 Interleukin-6 (IL-6)

Results for change in IL-6 from baseline are shown graphically in Figure 7-5. Overall the changes were small, and did not significantly vary between groups. Again, due to outliers and skewed distribution, non-parametric analysis is presented.

In the catheter ablation group, IL-6 showed a median change of +0.07 pg/mL (IQR -0.45 to +0.76) at 3 months, +0.06 pg/mL (IQR -0.52 to +1.38) at 6 months, and -0.06 pg/mL (IQR -0.64 to +1.69) at 12 months. In the rate control group, the change was -0.1 pg/mL (IQR -0.89 to 0.51) at 3 months, +0.11 pg/mL (IQR -0.78 to +0.88) at 6 months, and +0.34 pg/mL (IQR -0.47 to +0.87) at 12 months.

Comparing the groups, there was no significant difference at 3 (p=0.93), 6 (p=0.32) or 12 months (p=0.68).
7.4.5 Correlation of biomarkers with ARC-HF endpoints

The trends in change for MR-proANP and BNP were visually remarkably similar to the observed change in peak VO2 (primary endpoint for the ARC-HF clinical trial) and quality of life score (see chapter 5) and left ventricular ejection fraction (LVEF, see chapter 6). Correlation analysis showed that MR-proANP correlated best with all 3 endpoints, and was the closest correlated with peak VO2. BNP was most closely correlated with change in LVEF (Table 7-2).
MR-proANP and BNP also correlated well together (change at 12 months R=0.63, p<0.001). MR-proANP also correlated moderately with change in left atrial (area) size (R=0.39, p=0.006).

Table 7-2  Correlation of biomarker measurements with other ARC-HF endpoints
For each biomarker, correlation estimations were performed using Spearman Rank correlations against change (Δ) from baseline to 12 months follow-up, based on the per-protocol analysis (see methods). Correlation coefficient values (R) are shown with corresponding 2-sided p-values; n = number of patients samples available for analysis.

<table>
<thead>
<tr>
<th>ΔMRANP</th>
<th>p</th>
<th>ΔApelin</th>
<th>p</th>
<th>ΔBNP</th>
<th>p</th>
<th>ΔIL-6</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=49</td>
<td></td>
<td>n=49</td>
<td></td>
<td>n=48</td>
<td></td>
<td>n=49</td>
</tr>
<tr>
<td>ΔVO₂</td>
<td>0.13</td>
<td>0.36</td>
<td>-0.63</td>
<td>&lt;0.001</td>
<td>-0.12</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>ΔLHFQ</td>
<td>0.14</td>
<td>0.30</td>
<td>0.22</td>
<td>0.14</td>
<td>-0.04</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>ΔLVEF</td>
<td>0.16</td>
<td>0.28</td>
<td>-0.53</td>
<td>&lt;0.001</td>
<td>-0.03</td>
<td>0.85</td>
<td></td>
</tr>
</tbody>
</table>

BNP = B-type natriuretic peptide, IL-6 = Interleukin 6, LHFQ = Minnesota Living with Heart Failure Questionnaire score, LVEF = left ventricular ejection fraction, MRANP = Mid-Regional proAtrial Natriuretic Peptide, VO₂ = peak oxygen consumption at treadmill exercise testing.
7.5 Discussion

This study investigated the impact on cardiac biomarker of alternative management strategies, namely catheter ablation and medical rate-control, for persistent atrial fibrillation in patients with systolic heart failure. The most significant impact was on MR-proANP, which showed an overall trend towards reduction in both groups, but which was significantly greater in the ablation arm by 12 months.

MR-proANP has recently been identified as an important biomarker, with several studies indicating its potential role as a predictor or morbidity and mortality.\textsuperscript{340, 341} Additionally it may be superior to BNP for detecting and managing high-risk patients.\textsuperscript{350} Increases of $\geq 30\%$ have appeared to define patients at highest risk of events, although more modest changes also have an impact.\textsuperscript{350} In the current study, the reduction in MR-proANP after ablation was (median) 28\%, compared with (median) 7\% for rate control at 12 months. It could be hypothesised that such reductions in MR-proANP may have prognostic implications based on the recent studies. Although, in the current study, this is purely speculative, the finding that changes in MR-proANP correlate strongly with changes in VO$_2$ (and moderately well with changes in LVEF and quality of life score) would lend further weight to the emerging evidence that this biomarker could be a useful indicator in assessing the impact of treatment and providing information to assist in risk stratification of patients with heart failure.\textsuperscript{350}

The changes in BNP showed remarkably similar trends to MR-proANP, and indeed the two measures were highly correlated. Furthermore, BNP correlated best with LVEF, which is perhaps to be expected given its relationship with ventricular strain and failure. However, in the context of this biomarker sub-study, the reduction in BNP did not quite reach statistical significance despite the observed trends and this, in the face of the above data and emerging
evidence, might suggest it is inferior to MR-proANP for detecting changes in cardiovascular performance and perhaps in its ability to predict outcome.

IL-6 did not show a significant change, either from baseline or between groups, in the present study. Another marker of inflammation, C-reactive protein (CRP) was measured at baseline and during follow-up in all patients within the ARC-HF study. CRP was 10±16 mg/L in the ablation arm and 3±3 mg/L in the rate control arm at baseline (apparently skewed by patient A8, who was on stable therapy for a chronic inflammatory arthritis): at follow up, the change in CRP trended towards a reduction in the ablation arm (3 month p=0.029, 6 months p=0.074 and 12 months p=0.062), however with a very small magnitude of change (median -1, IQR -3 to +1 mg/L in the ablation arm compared with median 0, IQR -1 to +3 mg/L in the rate control arm). Although the CRP data should be interpreted with caution, due to the baseline differences and the post-hoc analysis, taken together with the IL-6 results these findings indicate that ablation, versus rate-control, has an overall small and probably neutral effect on markers of inflammation in the context of pre-existing persistent atrial fibrillation and heart failure.

Apelin is perhaps the most difficult of the biomarkers to interpret, both in terms of the results of this study and their clinical and physiological relevance. It has been demonstrated that the changes in circulating Apelin levels are not linearly related to severity of heart failure. Whilst plasma levels of Apelin were shown to be raised in patients with early heart failure and to fall in severe disease, other studies have shown that Apelin levels are reduced from normal in varying severities of heart failure, and are raised by intervention such as biventricular pacing. In the presence of the former pattern of behaviour, a varied response to restoration of improved haemodynamics might be expected, with patients starting from different positions on the scale. Plasma Apelin itself may be an insufficient marker in isolation, without considering its binding interaction with the APJ receptor at the cardiac level, which
appears to be down-regulated in heart failure and up-regulated during reverse ventricular remodelling.\textsuperscript{332}

7.5.1 Limitations

This study used a per-protocol analysis, thus the treatment arms could in absolute terms be regarded as ‘case-control’ and the study ‘observational’ rather than randomised. However, this protocol was pre-specified, and sought to examine the real impact of catheter ablation rather than using an intention-to-treat analysis as was appropriate for the main clinical trial outcomes. Data was therefore ‘missing’ for the two patients who ‘crossed-over’ (A1, after baseline; RC9, after 3 months) patient who died (A20) and for the patient who spent a prolonged period in rehabilitation (A7). No imputation or sensitivity analysis was used, as this could lead to multiple alternative virtual results and potential bias. The limitation resulting from all this therefore largely relates to sample size and (probable) lack of power, particularly relating to BNP, where a borderline increase in the p-value rendered the analysis non-significant.

None of the biomarker data-sets were normally distributed, and therefore non-parametric testing was used. This limits conclusive comments to be made about the magnitude of change when comparing the treatment arms, although the graphical trends are informative. Furthermore, serial measures analysis by summary measures including area-under-curve\textsuperscript{351} is not pragmatically feasible without application of parametric testing. An alternative method to deal with outliers is logarithmic transformation. However, using this for change data has significant pitfalls: i) the need to add a constant to negative values to render them >0, and ii) difficulty in interpretation of a meaningful clinical effect based upon geometric means in this
context. A further strategy would be outlier exclusion: however this can lead to significant bias. In this study, it was clear that some data was outlying – e.g. interquartile range of 12m BNP values was -208 to +26 (median -34pg/ml), and only one patient had a change >1500: patient A13 who died of progressive heart failure 2 months after completion of follow-up. Exclusion of this data point was tested: changes remained non-normally distributed, although BNP was significantly reduced in the ablation arm by parametric and non-parametric testing (Mann Whitney p=0.023, t-test p=0.048). However, such observations should be interpreted with caution and such techniques were not used during the presented analysis of the study data.
7.6 Conclusion

Catheter ablation-based rhythm control, when compared with rate control, led to a significant reduction in MR-proANP, which appeared progressive during follow up, and which may be a prognostically relevant marker of improved cardiac function. There was a similar reduction in BNP although this was a non-significant trend. An ablation strategy was associated with a marked reduction of the novel peptide Apelin after 6 months, although by 12 months the two groups were converging again.

The correlation of reduced MR-proANP with improved cardiopulmonary, symptomatic and imaging indices was striking. This novel assay may have a role in surveillance and prognostication for patients with heart failure, and its reduction appears to lend further weight to the finding that catheter ablation-based rhythm control confers an advantage over optimally managed rate control.

Acknowledgments

I am most grateful to Jackie Donovan and Helen Berry in the department of Clinical Biochemistry at Royal Brompton Hospital for their assistance in performing and analysing the assays; to the Heart Function office at Royal Brompton, and the Heart Science Centre at Harefield, who provided me with access to centrifuges and freezers; to Professor Theresa McDonagh, who had the original idea to include MR-proANP and Apelin and in this study; to Dr Shouvik Haldar who assisted in the processing and storage of plasma samples; and finally to St Jude Medical (UK) who provided an educational/scientific grant towards the cost of the assays.
8 Discussion

8.1 The ARC-HF trial

Atrial fibrillation (AF) and heart failure are increasingly common conditions in clinical practice, management is challenging, and the search for optimal therapy has an ongoing area of research for several years. Up until 2008, when the ARC-HF trial was designed, no randomised trial had examined a non-paroxysmal atrial fibrillation (AF) population, nor compared catheter ablation with medical rate control, in those with heart failure. Even in 2012, this is the first randomised clinical trial of ablation-based rhythm-control, versus rate-control, of persistent AF in heart failure to focus on objective cardiopulmonary exercise capacity.

A strategy of catheter ablation as a form of rhythm control, when compared with a rigorous rate-control strategy, was associated with improvement in the primary endpoint of peak VO2, as well as the secondary endpoints of quality-of-life score and neurohormonal status. Left atrial size was reduced by ablation and was associated with evidence of mechanical atrial recovery. Left ventricular ejection fraction (LVEF), which has greater natural variability in AF, showed only a non-significant increase when compared with the rate-control arm, although the changes in baseline were highly significant for the catheter ablation arm. It should be noted that, for LVEF and several other parameters, improvement trends were seen in the rate control arm also – providing evidence that these patients were well-managed, and in many cases benefited significantly from well-adjusted rate control and medical therapy within the clinical trial environment. Overall these results suggest that rhythm-control by ablation, maintaining sinus rhythm in the vast majority at 1 year, is a more effective strategy than medical rate-control.
8.1.1 Management of AF

In general populations with AF, previous studies found no advantage from drug-based rhythm-control over rate-control.\textsuperscript{82, 120} Although sub-group AFFIRM data showed a trend towards favourability of rhythm-control in those with heart failure,\textsuperscript{82} the results from AF-CHF subsequently showed no benefit over rate-control.\textsuperscript{122} The possible reasons for the negative outcomes from drug-based rhythm control include the adverse effects of antiarrhythmic drugs and the relatively poor efficacy in maintaining sinus rhythm.\textsuperscript{123} Secondly, when paroxysmal patients were included, many patients in the rate control arm would spontaneously return to sinus rhythm. Third, some studies had significant cross-over rates: for instance, in AF-CHF, more than 20% of patients crossed over to rate control from rhythm control, and 10% in the opposite direction. These phenomena reduce the potential for, and the ability to detect, a benefit of rhythm control therapy.

There is evidence that sinus rhythm is beneficial, if it can be maintained.\textsuperscript{35, 352} Whilst this might reflect self-selecting cohorts, a role has been argued for a therapy that can maintain sinus rhythm with minimal side effects. As catheter ablation may be able to achieve both these goals and had shown promise in non-randomised studies in the heart failure population,\textsuperscript{133, 134} the next logical step was to prospectively compare an ablation-based rhythm-control strategy directly against medical rate-control,\textsuperscript{122, 208} in a well-defined cohort with non-paroxysmal AF and systolic heart failure, which formed the basis for ARC-HF.

8.1.2 Objective exercise performance

The primary endpoint, peak VO\textsubscript{2}, is well established as a prognostic indicator in heart failure,\textsuperscript{214-216} and as an endpoint in clinical trials.\textsuperscript{295, 353} Recently, Swank \textit{et al} have shown that modest increases in peak VO\textsubscript{2} were associated with reduced mortality and
hospitalization. For every 6% increase in VO2 at repeat cardiopulmonary exercise testing after 3 months, there was a 7% reduction in all-cause mortality. The distinct beneficial impact of catheter ablation on cardiopulmonary exercise performance found in our study – of the magnitude of 20% (mean 19.9% higher than rate control, 95% CI 3.9 to 35.9%, p=0.016) – has potential to have favourable prognostic implications for catheter ablation in persistent AF in heart failure. Although analysing the individual changes from baseline between groups could underestimate the real benefit of treatment (based on divergent outcomes), if we include the patient who died (A20) before final follow-up and assume his peak VO2 would have fallen (see also 8.1.7), then 50% of the catheter ablation arm had a >6% rise in peak VO2, compared with 23% in the rate-control arm (p=0.04). The numbers are almost identical for an increase of ≥1 ml/kg/min (50% vs. 19%, p=0.020): this latter value was used as a threshold for significance by the investigators in the RethinQ study on cardiac resynchronisation therapy (CRT) in patients with QRS ≤130ms, which found no benefit from CRT in this population (which excluded patients with persistent AF). However, the subgroup with QRS≥120ms, the population where there is evidence of mortality (and morbidity) benefit from CRT, did show a significant increase in VO2, consistent with prior studies. Hence, there is direct and indirect evidence of the importance of changes in VO2 in patients with heart failure, with an increasing body of evidence to suggest positive changes are associated with reduced morbidity and mortality.

Whilst some caution might be exercised in extrapolating these data to patients with persistent AF, as studies have only had relatively small proportions of these patients or in fact excluded them, much of the improvement in exercise capacity seen in the rhythm-control arm of ARC-HF was seen after sinus rhythm had already been restored. Indeed, the observed changes at interim stages of several measured parameters, particularly quality of life score and biomarkers, would suggest progressive development of the effects. The effect of catheter-
ablation based rhythm control on exercise capacity, visible clearly at the trial end time of 12 months was very much smaller at 3 months. Previous studies have shown that restoration of sinus rhythm by cardioversion can increase peak VO2\(^{224}\) and that continued maintenance of sinus rhythm leads to later improvement after 1-2 years,\(^{225}\) although the studies were not specifically in patients with heart failure. It is unlikely that the exercise capacity advantage of catheter ablation arises solely from being in sinus rhythm during the exercise test alone, because the same high proportion of patients were in sinus rhythm at 3 months and 12 months, yet \(\sim\frac{3}{4}\) of the 12-month advantage developed only in those intervening 9 months: an additional increment of 2.55 ml/kg/min (95% CI 0.71 to 4.39, \(p=0.008\)). The most likely explanation for this is progressive systemic improvement in cardiovascular physiology during the year, largely occurring long after sinus rhythm was restored.

### 8.1.3 Secondary endpoints

In the secondary endpoints, the numerical trends were in the same direction for all four (see chapter 5 and 6). Minnesota LHFQ score and BNP improved in the ablation arm, which became more visible as follow-up progressed. LHFQ score, a validated measure of therapeutic efficacy,\(^{357}\) was improved by a similar magnitude to that previously associated with favourable prognostic outcomes.\(^{358}\) The reduction in BNP, previously demonstrated in a non-heart failure population,\(^{233}\) may also have prognostic implications. BNP levels appear not to be independently affected by rhythm itself in heart failure and remain prognostically important.\(^{326, 359}\)

Our study did not show significant differences in the 6-minute walk test, rather a trend towards improvement. However this, being self-paced, is open to an additional degree of variation which is not present on formal cardiopulmonary exercise testing, the latter being the variable with more extensively-documented relationship to long-term survival.\(^{213-216}\)
Additionally, several patients were limited in performing this test without walking aids at follow up (3 in the ablation arm and 1 in the rate control arm at 12 months) whereas they could support themselves on treadmill; another possible reason is that the 6 minute walk was always performed at the end of the assessment visit, and fatigue may have been relevant in some patients. LVEF showed a numerical trend to improvement but had sufficient variability to make it not possible to distinguish confidently a genuine sizeable improvement from chance alone. Nevertheless in head-to-head comparisons objective cardiopulmonary exercise capacity shows stronger prognostic power in heart failure than ejection fraction.\textsuperscript{215, 360}

8.1.4 The left atrium

Regression of left atrial size occurred with catheter ablation. Although this has been reported in patients without left ventricular dysfunction,\textsuperscript{316, 317} this is the first such observation in a heart failure cohort where atrial dilatation might be expected to be less reversible. The effect was already detectable at 6 months. Atrial size is likely to be a dynamic consequence of multiple influences including medium term remodelling. Thus despite the advanced substrate of heart failure and baseline atrial dilatation, given time the atrium has some potential to recover partially. It is conceivable this may contribute to reduction of future arrhythmia recurrence although previous studies, albeit in non-heart failure populations, have provided conflicting data.\textsuperscript{316, 317, 322, 361}

8.1.5 Procedural outcome

For catheter ablation, both single procedure and multi-procedure success was higher than initially expected in our cohort of patients with mostly long-standing persistent AF and heart failure. Maintenance of sinus rhythm was achieved at 1 year in 92% of the patients who underwent ablation, with single procedure success, off antiarrhythmic medication, of 72%.
The success rate may reflect the increasing efficacy that modern equipment and protocols are now achieving, building upon the initial multi-procedural success of 78% (69% off drugs), with 50% requiring a redo ablation procedure, as reported by the Bordeaux group when treating a similar population in 2004 with pulmonary vein isolation (PVI) and linear lesions. More recently, the PABA-CHF study achieved 71% freedom from AF off antiarrhythmic drugs (and 88% on drugs) at 6 months, although half of the patients were paroxysmal rather than persistent. A recent international consensus recommends that clinical trials should enrol patients with only one type of AF, to avoid such ‘mixed bags’ cohorts and enable clinicians to understand the true impact of therapy. Also, the aim should be restoration and maintenance of sinus rhythm without the need of antiarrhythmic drugs, which was not often reported in earlier studies, and is still sometimes not reported in the headline results: for example the high success rates of the Cox-Maze surgical procedure are well known, but it should be noted that almost a third of patients from the original Cox-Maze III cohort were taking antiarrhythmic drugs at latest follow up. In ARC-HF, antiarrhythmic drugs were stopped in all patients (except patient A18 who was on sotalol and amiodarone for ventricular arrhythmias, and also required repeat ablation for atrial tachycardia) prior to the end of the post-ablation blanking period, and in most cases at the point of the ablation procedure. Only standard beta-blockers were continued, along with other appropriate heart failure medications. Hence, importantly, the single-procedure success (69 or 72% depending on whether patient A1 – who withdrew consent for ablation – was included in the analysis) was reported in patients entirely free of antiarrhythmics for at least 1 year.

In comparison with these studies, our protocol involved the addition of a lesion at the cavo-tricuspid isthmus, and in most patients the addition of lesions targeting complex fractionated electrogram (CFE) sites, in line with more contemporary approaches to longstanding persistent AF ablation. Perhaps most importantly, our procedures were long,
involving mapping steps that have not been routine in previous eras, and probably resulted in extensive debulking of left atrial tissue, which in turn may explain why AT was far more common than AF during follow up. The long procedure times inherent to performing and confirming block in multiple linear lesions, together with repeat high-density mapping of the LA and PV antra at each stage of the procedure, provided a very long waiting time after initial PVI during which loss of isolation could be identified and corrected, which might be an additional avenue that improved outcome.\textsuperscript{287,363}

Since commencement of ARC-HF, a randomised trial with a different ablation protocol that delivered only 50\% maintenance of sinus rhythm, and with a shorter follow up of 6 months,\textsuperscript{300} has reported no significant difference in the primary endpoint of magnetic resonance left ventricular EF (p=0.6), N-terminal pro-BNP (0.45) and quality of life (p=0.65). As the investigators themselves commented, a strategy that delivered only 50\% maintenance of sinus rhythm in the ablation arm greatly reduced the power of the study, requiring (for example) 4 times as many patients to detect an effect as would a study that maintained all intervened patients in sinus rhythm. A second concern is whether ejection fraction is a sufficiently comprehensive marker of physiological state, considering the greater prognostic power of integrated markers such as objective exercise capacity.\textsuperscript{214} A third concern is whether 6 months would be sufficient for the effect of restoration of sinus rhythm to fully manifest. This duration of follow-up was also a limitation identified by the authors of the PABA-CHF trial in their own study.\textsuperscript{240} ARC-HF helps put the Macdonald et al\textsuperscript{300} study in context: the difference in headline results between the studies may be not a contradiction but merely a manifestation of the markedly different number of patients required to detect an effect.
8.1.6 Clinical Implications

These data suggest that amongst patients with heart failure and persistent AF, a benefit can be expected from catheter ablation on symptoms, neurohormonal status and objective exercise capacity. They do, however, suggest that the effect takes many months to develop. In the context of other studies, it seems that an extensive and robust protocol of ablation - to give high efficacy in maintenance of sinus rhythm – may be worthwhile.

8.1.7 Study limitations

ARC-HF was a physiological study and was not designed to evaluate event endpoints. Studies specifically designed to evaluate prognostic impact of AF ablation are now underway and are scheduled to complete in 3 or 4 years including CASTLE-AF (NCT00643188) with primary outcomes of mortality and heart failure hospitalisation, and RAFT AF (NCT01420393) with the primary endpoint of cardiovascular mortality.

Although an intention-to-treat protocol was used, the inevitable consequence of patient death prior to final follow up is missing data for the endpoints. We did not impute any values for this analysis, although sensitivity analyses have been performed post-hoc: imputation of a ‘worst case scenario’ group-lowest resting VO₂ as his final peak VO₂ result still produced a statistically significant primary endpoint (mean benefit of catheter ablation +2.63 ml/kg/min, 95% CI 0.03-5.23, p=0.048).

There were some minor imbalances in the baseline characteristics of patients, which would be expected in approximately 5% of such characteristics in any randomised study. For instance, aldosterone antagonist prescription rate was higher at baseline in the ablation arm, and there was a trend towards more patients with CRT in-situ. However, in regression analysis, neither
of these had a significant impact on the studied endpoints (e.g. for change in peak VO$_2$, aldosterone antagonist p=0.14, CRT p =0.56).

Finally, although the trial complied with the minimal monitoring for persistent AF ablation suggested by the international consensus statements of both 2007$^{128}$ and 2012$^{272}$, it is possible that silent episodes of paroxysmal AF were missed during the remainder of follow up. However, in a population of patients with (mostly longstanding) persistent AF, the presence of sinus rhythm at multiple time points is highly suggestive of a major impact on and reduction of arrhythmia burden. Silent AF or atrial tachycardia episodes >30 seconds were not seen in the patients with implanted devices; however, 4 patients had atrial arrhythmias picked up when they attended for review with progressive symptoms and were appropriately included as rhythm failures, subsequently undergoing ablation in 3 cases (fourth was patient A7 – see chapter 5.4.5.1). In addition, it should be noted that the primary outcome was not freedom from AF, but rather a prognostically relevant physiological endpoint, and assessed the strategy of AF ablation rather than its success. Nevertheless, the strategy appeared highly successful in maintaining sinus rhythm, and the longer-term follow-up presented in chapter 4 is consistent with this.

8.1.8 The ARC-HF trial: conclusions

ARC-HF, a randomised controlled trial of patients with persistent atrial fibrillation and heart failure, indicates that a catheter ablation protocol which achieves maintenance of sinus rhythm in the majority produces, after 1 year, improvements in symptoms, neurohormonal status and objective physiological exercise capacity. Progressive improvement from 3 to 12 months implies that the effects reflect more than just restoration of sinus rhythm and this method of rhythm control therapy allows a period of beneficial cardiac remodelling. Large-scale trials have now been begun of the prognostic impact of catheter ablation-based rhythm
control of atrial fibrillation in heart failure: the encouraging pointers for now is that, under randomised controlled conditions, two powerful prognostic markers (VO₂ and BNP) respond favourably.

8.2 Impact of catheter ablation on biomarkers

Previous data has suggested that there is a significant fall in plasma levels of BNP and ANP in the first few days after catheter ablation, and essentially this is maintained out to 3 months. In patients without significant structural heart disease, this is associated with a significant reduction in left atrial diameter, a recovery of atrial mechanical function and increased LVEF. Similar findings have been found in BNP after cardioversion, if sinus rhythm is maintained, including a reduction of plasma apelin. The present study would appear to suggest that, although there is indeed an early reduction in the first few months, when compared in a randomised study with a robust strategy of rate-control, the improvements in the ‘control’ arm mean it takes much longer to detect an effect and, indeed, there is progressive ‘improvement’ out towards 6-12 months, at least in MR-proANP and BNP. This is in keeping with the results of the main ARC-HF trial which showed that the improvement in VO₂ predominantly occurred from 3 to 12 months, and was not i) just a reflection of being in sinus rhythm at 3 months testing or ii) an improvement which occurred during the early phase after sinus rhythm. The overall picture is of a progressive amelioration of the heart failure syndrome – by a process (catheter ablation) associated with a high degree of maintenance of sinus rhythm – the data suggesting such amelioration involves gradual atrial and ventricular remodelling. Interestingly, most of the change in LVEF and LA size had occurred by 6 months, whereas the most significant differences in MR-proANP and BNP were seen at 12 months. Although 6 month VO₂ data was not collected, both VO₂ and the trend in 6-minute walk tended towards improvement at 12 months, and this might suggest that
the early phase of restoration of sinus rhythm (in the majority) with catheter ablation leads to a form of mechanical remodelling, whereas the later improvements may reflect overall systemic amelioration, with improved symptoms and exercise performance along with neuroendocrine ‘stabilisation’.

8.3 Mapping and catheter ablation for persistent AF

The data presented in chapter 4 prompts further discussion. Whilst the study did not prospectively seek to compare strategies of ablation, the high single (and multiple) procedural success at 1 year, in this cohort with persistent AF, heart failure and dilated atria, would suggest that there was something different in the methods used in this cohort compared with the lower single procedure success seen in relatively contemporary series of ablation in patients with and without structural heart disease.

The first question is whether linear lesions could be a beneficial component of AF ablation, in this and other cohorts. Recent evidence in a dog model suggests the roof may play a more important role than the pulmonary vein antrum in the persistent AF substrate. Also, earlier work by our group has shown that the roof may participate in the mechanisms present at the onset of paroxysmal AF. In the present study on the cohort of patients from ARC-HF (chapter 4 and 5), completion of all linear lesions – including the left atrial roof, mitral valve isthmus, and cavo-tricuspid isthmus – was shown to be superior to leaving any one of these lines incomplete, although strong conclusions cannot be drawn given only small numbers (3 out of 30 patients). More importantly, approximately 50% of the atrial tachycardia recurrences were related in some way to gaps in these linear lesions.

It is often unclear in multicentre clinical trials exactly what went on in terms of ablation lesion sets, when studies focus on pulmonary vein isolation and leave the rest to operator discretion – a case in point being the PABA-CHF study. Even worse, many studies enrol...
‘mixed bags’ of patients in AF (persistently) and predominantly sinus rhythm (paroxysmal AF). Nevertheless, several studies have addressed the question of which ablation strategies are optimal, as outlined in Chapter 1. Linear lesions have been shown to be antiarrhythmic\textsuperscript{133, 170, 171, 175, 176, 178, 180, 202, 367-370} and yet are well recognised to have proarrhythmic potential through incomplete or recovered conduction block.\textsuperscript{167, 179, 180, 368, 371, 372} These apparently contradictory observations have, not infrequently, come from the same investigatory groups.\textsuperscript{171, 180, 367, 368} It appears that it depends whether one is examining single procedure success or the entire journey towards sinus rhythm, which may indeed include atrial tachycardia on the way.\textsuperscript{171, 180, 367, 368} Taking the pro-arrhythmia (for atrial tachycardia) aside, the vast majority of the above series have shown a benefit of adding linear lesions in some form or other, although this is not a completely universal finding.\textsuperscript{373} This, together with the desire to maximise procedural success (maintenance of sinus rhythm) and minimise the risk of regular, often persistent, macroreentrant atrial tachycardias (which may be poorly tolerated in, or indeed worsen, pre-existing cardiac failure), and the fact that ARC-HF patients were likely to have an ‘advanced’ substrate with dilated and/or hypertrophied atria capable of sustaining multiple macroreentrant drivers (see below), formed the basis for an ablation protocol design which included these lesions in the first place.

Some of the mechanistic possibilities to explain the benefit of linear lesions on the atrial substrate in AF were discussed in Chapter 4. In addition to this, a recent study examined the impact of linear lesions on the atrial substrate based upon the change in spectral components seen at frequency analysis. It was found that neither PVI, the undisputed cornerstone of all AF ablation procedures, nor CFE ablation had a significant impact, but (complete) linear lesions led to reduction and elimination of spectral components separate from – and typically lower than – the dominant frequency.\textsuperscript{374} The findings of that study would support the concept that some components of AF are lower frequency, simultaneous atrial tachycardias which
respond to linear ablation presumably by interruption of a critical isthmus in the potential macroreentrant circuit. Hence targeting CFE or PVI alone may miss such components: this may explain why linear lesions are additionally required in a high proportion of patients in order to achieve termination of longstanding persistent atrial fibrillation. However, with extra ablation may come a price – not only that of proarrhythmia should the lines of block recover – but the potential for collateral damage to adjacent structures, for instance the circumflex artery when ablating the mitral isthmus. In our study, the only major life-threatening complication was tamponade: whilst a recognised complication of ablation procedures, the investigators involved in ARC-HF have never otherwise this complication occurring during a ‘routine’ cavotricuspid isthmus ablation, and it serves as a reminder that ablation of any type is associated with a small but significant risk of complications.

*Complex fractionated electrograms* remain another controversy in AF ablation. There did not appear to be any advantage, in terms of long term freedom from AF, of adding routine CFE ablation to PVI in patients with paroxysmal AF, or in a cohort of patients with mixed paroxysmal and persistent AF. Another recent randomised study showed that up to 2 hours of conventional CFE mapping and ablation after PVI provided no additional clinical benefit. In contrast, one multicentre trial did show a benefit of CFE ablation, guided by the same semi-automated computer algorithm as used within ARC-HF, compared with PVI alone, for high-burden paroxysmal and persistent AF.

Addition of CFE ablation in the right atrium and coronary sinus was shown not to be routinely beneficial, whereas a strategy guided by AF cycle length – as a marker of the location predominantly driving AF (which may however oversimplify the underlying mechanisms involved) – showed that the RA was implicated in approximately 20% of persistent AF cases, and ablation in this chamber could terminate AF in more than half such patients. Redo ablations in our study largely focussed on the left atrium: ablation was
however performed in the right atrium of 2 patients, one of whom had an atrial septal defect identified at pre-procedural imaging (patient A4) and in whom the second procedure included intercaval and right peri-septal ablation as well as superior vena cava isolation, which then rendered him free of AF, and another in whom giant atria were associated with remarkably few CFE but rather apparent slow drivers with long cycle length almost like an atrial ‘torsades’ (in the presence of sotalol and amiodarone for ventricular arrhythmia; patient A18), but who was also rendered free of AF by the second procedure. So the right atrium certainly has a role, but it appears this is in a minority of patients. Furthermore, evidence from the high-density biatrial mapping study (see Figure 4-10) would suggest that fractionation seen at baseline within the right atrium can be eliminated or significantly reduced by left atrial ablation alone, which would suggest a strategy of targeting the right atrium early during an ablation procedure should be avoided, particularly to minimise the risk of collateral damage to the phrenic nerve and nodal structures.

In turn, another controversy is the acute endpoint for AF ablation. As discussed in chapter 4, AF termination is used as procedural endpoint for persistent AF ablation by some centres, but the evidence from ARC-HF, albeit in a relatively small cohort, would suggest highly favourable outcomes can be achieved in the majority without aiming for this endpoint. Indeed, some form of electrical and/or structural remodelling, induced by the combination of extensive trigger/substrate ablation, a prolonged period of sinus rhythm, and regression of atrial dilatation, may bridge the gap between an endpoint as defined by the ARC-HF protocol (complete PVI, linear lesions, and map-guided left atrial CFE ablation) and one which seeks to terminate AF, which almost inevitably would require ablation of more (potentially viable) atrial tissue. Such atrial tissue may play an important role in both mechanical recovery, but also in electrical interatrial and atrioventricular synchrony. Excessive ablation in the anterior wall may lead to excessive delay to, and even isolation of, the lateral components including
the left atrial appendage, which may have a negative impact on long-term mechanical recovery and thromboembolic risk. A notable finding of the present study was that linear ablation, even more when complete, led to reduction of fractionation within the left atrium and thus reduced the target area for CFE ablation (chapter 4): this may be a further avenue to minimise collateral damage, that is, perform PVI, then linear ablation, and then reassess the atria for presence of CFE. The finding that linear ablation did not prolong cycle length is consistent with the findings and mechanistic implications of the study by Yokohawa et al\textsuperscript{374}, and the fact that cycle length did then prolong with residual CFE ablation provides some support for the notion that these sites contributed as drivers of ongoing AF, indeed apparently leading to termination of fibrillation in several patients.

So, what is the optimal AF ablation strategy in heart failure patients? The data from the present study may suggest that this question is not the one that requires answering. Perhaps heart failure itself does not lead to a particularly irreversible substrate, and it is perhaps the optimal ablation strategy for longstanding persistent AF that remains elusive. Indeed, it has recent been shown that LV dysfunction itself does not independently influence the outcome of AF ablation, whereas left atrial size does,\textsuperscript{380} and our outcomes are at least as good as series treating persistent AF in the general (non-heart failure) population.

A new technique may however have promise in optimising AF ablation procedures, which currently employ – at best – a stepwise approach to dealing with an otherwise unknown substrate for AF in the individual patient. Targeting focal impulses and performing rotor modulation (FIRM) is a recently reported technique aimed at tailoring the ablation towards each patient, by attempting to find the unique drivers of AF in that individual. In 92 patients undergoing ablation for AF (72% persistent) a computer algorithm was used to analyse data from a 64-pole basket catheter inserted in the left, and in some cases right, atrium. Localised rotors or focal impulses were detected in 97% of examined cases, and an endpoint of
termination or ‘slowing’ (≥10% prolongation of AF cycle length) was achieved in 86% where FIRM ablation (initially alone) was applied; more impressively, AF terminated in 56% (20 of 36 cases). Although its application may be limited in dilated atria due to the structure/size of the basket catheter and requirement for electrical contact, the reporting of this new technique is currently attracting the attention of many arrhythmologists. This could possibly be because it remains so mysterious (the computer algorithm used is proprietary, and the work has yet to be validated and reproduced by other investigators), but it could also provide a way to terminate and maintain sinus rhythm without excessive destruction of atrial tissue, and may allow a reduction in the long procedure times associated with ablation of longstanding persistent atrial fibrillation. Further investigation of this novel technique is awaited.
8.4 Conclusion

The results of the ARC-HF trial and its sub-studies would support the stated hypothesis that “a strategy of rhythm control by catheter ablation, compared with rate-control, for management of persistent atrial fibrillation in patients with heart failure, improves cardiovascular performance, symptoms, and neuroendocrine status”.

Overall, this research makes a case to support a change in the contemporary clinical practice, of many physicians, from a position of accepting so-called ‘chronic’ atrial fibrillation when it occurs in patients with heart failure, to the alternative approach of aiming to pursue restoration and maintenance of sinus rhythm, which can be achieved with high levels of success via catheter ablation without the need of antiarrhythmic drug therapies. It appears that this strategy can expose the underlying benefit that is already known to exist for being in sinus rhythm compared with atrial fibrillation.

The high-density mapping studies (chapters 3-4) provided insights into both the atrial substrate and the basis for a rationale stepwise approach in treating patients with relatively advanced syndrome of (often longstanding) persistent atrial fibrillation, systolic heart failure, and associated atrial dilatation. The ablation strategy devised was shown to confer a remarkably high level of arrhythmia freedom even after a single procedure, when compared with pre-existing studies. However, with similar protocols, there is no obvious reason why these results should not be applicable to other centres, as long as sufficient time and resource is given to performing the procedures. Such resources may be limited, but cost burdens are likely to be offset by the improvement in morbidity resulting from the procedure, although longer term data is awaited regarding the impact of an ablation strategy upon hospitalisation and mortality in patients with persistent atrial fibrillation and advanced heart failure.
Catheter ablation for persistent atrial fibrillation continues to evolve, as the strategies become more refined, and as new evidence comes to light regarding how best to eradicate this rhythm that was once thought untreatable. Newer techniques of mapping may yet allow further minimisation of collateral damage with unnecessary ablative destruction of atrial tissue. Based upon the evidence gathered in chapters 5-7, this could in turn maximise the potential recovery of both atrial and ventricular mechanical, electrical, and neuroendocrine function. Furthermore, there is increasing evidence that the surrogate endpoints examined in these investigations carry powerful prognostic information. Hence, for patients with the combined conditions of atrial fibrillation and heart failure, catheter ablation-based rhythm control may offer not only improved quality of life but also, when coupled with optimal pharmacological and device-based therapy, an amelioration of the heart failure syndrome and an improved prognosis.
References


34. Saxon LA. Does cardiac resynchronization therapy reduce the incidence of atrial fibrillation, and does atrial fibrillation compromise the cardiac resynchronization therapy effect? *Heart Rhythm*. 2007; 4: S31-3.


175. Fassini G, Riva S, Chiodelli R, Trevisi N, Berti M, Carbucicchio C, Maccabelli G, Giraldi F and Bella PD. Left mitral isthmus ablation associated with PV Isolation: long-


257


320. Westenberg JJ, van der Geest RJ, Lamb HJ, Versteegh MI, Braun J, Doornbos J, de Roos A, van der Wall EE, Dion RA, Reiber JH and Bax JJ. MRI to evaluate left atrial


10 Appendix

10.1 Minnesota Questionnaire

<table>
<thead>
<tr>
<th>Study number</th>
<th>Visit</th>
<th>B</th>
<th>3M</th>
<th>6M</th>
<th>12M</th>
<th>Date</th>
</tr>
</thead>
</table>

MINNESOTA LIVING WITH HEART FAILURE QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

<table>
<thead>
<tr>
<th>Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -</th>
<th>No</th>
<th>Very Little</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. causing swelling in your ankles or legs?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. making you sit or lie down to rest during the day?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3. making your walking about or climbing stairs difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4. making your working around the house or yard difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5. making your going places away from home difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6. making your sleeping well at night difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>7. making your relating to or doing things with your friends or family difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>8. making your working to earn a living difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>9. making your recreational pastimes, sports or hobbies difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10. making your sexual activities difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>11. making you eat less of the foods you like?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>12. making you short of breath?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>13. making you tired, fatigued, or low on energy?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>14. making you stay in a hospital?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>15. costing you money for medical care?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>16. giving you side effects from treatments?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>17. making you feel you are a burden to your family or friends?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>18. making you feel a loss of self-control in your life?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>19. making you worry?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>20. making it difficult for you to concentrate or remember things?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>21. making you feel depressed?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

©1986 Regents of the University of Minnesota. All rights reserved. Do not copy or reproduce without permission. LIVING WITH HEART FAILURE® is a registered trademark of the Regents of the University of Minnesota. 11/10/04
10.2 Case report form for ARC-HF

Patient Study ID number ________________

Name
Hosp no.
DOB
Sex  Male  Female

Date of Enrolment  ________________
Date of Randomisation  ________________

RANDOMISATION GROUP

RATE CONTROL  CATHETER ABLATION

Index date for follow up ________________
Date of 3M follow-up ________________
Date of 6M follow-up ________________
Date of 12M follow-up ________________
### PAST MEDICAL HISTORY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Y/N</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention (PCI)</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>Valve operation</td>
<td></td>
<td>none, MV repair, MVR, AVR, other</td>
</tr>
<tr>
<td>Implantable Device in-situ</td>
<td>Y/N</td>
<td>PPM, CRT-P, CRT-D, ICD Inserted <strong>date</strong> date inserted _<strong>date</strong></td>
</tr>
<tr>
<td>COPD/asthma</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>Insulin / tablet /diet / N</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>Current / ex- (&gt;3months) / never</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td></td>
<td>Hyper / Hypo/ N</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>CVA</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>Comments/Other (free text)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### HEART FAILURE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Y/N</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>Unknown DCM</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>Viral DCM</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>Valvular</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>Other (free text)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Date of HF onset/diagnosis

Recent unplanned hospitalisation (<1y) Y/N

### ARRHYTHMIA CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>First known AF</td>
<td>___________ Persistent ; Long-standing persistent (&gt;1 year)</td>
</tr>
<tr>
<td>Duration of AF</td>
<td>___________ Persistent ; Long-standing persistent (&gt;1 year)</td>
</tr>
<tr>
<td>Past DC cardioversion?</td>
<td>N/ Y - number: 1,2,3, &gt;3</td>
</tr>
<tr>
<td>Previous SVT</td>
<td>Y/N</td>
</tr>
<tr>
<td>Previous typical flutter</td>
<td>Y/N</td>
</tr>
<tr>
<td>Prior AV node ablation</td>
<td>Y/N</td>
</tr>
<tr>
<td>Prior other (non-AF) ablation</td>
<td>Y/N</td>
</tr>
<tr>
<td>If Y details</td>
<td>___________</td>
</tr>
</tbody>
</table>
Patient Study ID number ________________

SYMPTOMS

Palpitation Y/N
Syncope Y/N
Angina Y/N
Breathlessness Y/N
Comments __________________

Orthopnoea (no. pillows) (n=____)
PND Y/N
Ankle swelling Y/N
Fatigue Y/N

Other ____________________________

MEDICATION

Allergies Y/N If Y: ________
ACEi cough Y/N
BB wheeze Y/N

Warfarin dose (mg) ____________

Y/N (for each) Drug Name Dose in 24h (mg)

ACEi Y/N ____________
ARB Y/N ____________
B-blocker Y/N ____________
Aldosterone ant. Y/N ____________
Loop diuretic Y/N ____________
Other diuretic Y/N ____________
Statin Y/N ____________
Aspirin Y/N ____________
Amiodarone Y/N ____________
Digoxin Y/N ____________
Diltiazem Y/N ____________

Other ___________________________

Previous/failed AADs: None
Amiodarone
Sotalol
class I
other

Comments ________________________________
CLINICAL EXAMINATION

DATE

Height _______ m  Weight _______ kg
BP (mmHg) _______/______
Heart rate: (see 6MW) _______ bpm
ECG: rhythm AF SR Flutter other (______)
      QRSd _______ ms

JVP: normal raised markedly raised (>10cm)
Murmur none systolic diastolic ________________
3rd HS Y/N  4th HS Y/N
Chest normal
crepitations wheeze
      reduced breath sounds dull to percussion
P. oedema: none mild (ankle) moderate (knee) severe (thigh-sacral)
Comments: ____________________

BASELINE INVESTIGATIONS

Date
Comments (free text) ___________________________________________________________

NYHA class □

   I   II   III   IV

Quality of Life questionnaire. □

Score ______/105 ENDPOINT

Blood tests. □

BNP (pmol/L) _______________________ ENDPOINT
Apelin ____________________________ ENDPOINT
Patient Study ID number ________________

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td></td>
</tr>
<tr>
<td>Pts (x10⁹/L)</td>
<td></td>
</tr>
<tr>
<td>WCC (x10⁹/L)</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td></td>
</tr>
<tr>
<td>Na (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Creat (µmol/L)</td>
<td></td>
</tr>
<tr>
<td>Bili (µmol/L)</td>
<td></td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td></td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td></td>
</tr>
<tr>
<td>fT4 (pmol/L)</td>
<td></td>
</tr>
<tr>
<td>TSH (IU/L)</td>
<td></td>
</tr>
<tr>
<td>Urate (µmol/L)</td>
<td></td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td></td>
</tr>
<tr>
<td>B12 (ng/L)</td>
<td></td>
</tr>
<tr>
<td>Folate (µg/L)</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td></td>
</tr>
<tr>
<td>QRS rate (bpm)</td>
<td></td>
</tr>
<tr>
<td>Rhythm at evaluation:</td>
<td>sinus, AF, AT, other</td>
</tr>
<tr>
<td>QRSd (ms)</td>
<td></td>
</tr>
<tr>
<td>Axis (degrees)</td>
<td></td>
</tr>
<tr>
<td>LBBB/RBBB</td>
<td>no, LBBB, RBBB, other</td>
</tr>
<tr>
<td>EXERCISE TREADMILL TEST (MVO2)</td>
<td></td>
</tr>
<tr>
<td>ECHOCARDIOGRAM</td>
<td></td>
</tr>
<tr>
<td>RADIONUCLIDE VENTRICULOGRAPHY</td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td></td>
</tr>
<tr>
<td>ENDPOINT</td>
<td></td>
</tr>
<tr>
<td>SIX MINUTE WALK TEST. (6MW)</td>
<td></td>
</tr>
<tr>
<td>HRpre (bpm)</td>
<td></td>
</tr>
<tr>
<td>HRend (bpm)</td>
<td></td>
</tr>
<tr>
<td>6MWD (metres)</td>
<td></td>
</tr>
<tr>
<td>HOLTER</td>
<td></td>
</tr>
</tbody>
</table>
RATE CONTROL GROUP

BASELINE

Date __________
Resting HR (bpm) __________
6MWD peak HR (30sec average) __________

Medication change necessary (tick)?

None
Addition of beta blocker
Increased dose of beta blocker
Decreased dose of beta blocker
Addition of digoxin
Increased dose of digoxin
Decreased dose of digoxin

Other __________

If no changes START FOLLOW-UP PERIOD (to 3, 6, and 12 months)

Otherwise arrange further visit at 4 weeks:

4 WEEK CHECK

Date __________
Resting HR (bpm) _____
Ambulant HR (bpm) _____
Comments __________
Medication change necessary?

If no changes START FOLLOW-UP PERIOD (to 3, 6, and 12 months)

Otherwise arrange further visit at 8 weeks:

8 WEEK CHECK

Date __________
Resting HR (bpm) _____
Ambulant HR (bpm) _____
Comments __________
Medication change necessary?

START FOLLOW-UP PERIOD (to 3, 6, and 12 months)

Rate control achieved? Y/N
Follow-up 3 MONTHS

Major adverse event: Y/N
(tick one or more – with date where relevant)

Unplanned HF admission
Unstable angina
MI
Stroke
TIA
Pulmonary embolism
Cardiac Transplantation
Death

Any unplanned hospital admission? Y/N ______________________
Significant clinical event? Y/N ______________________

3 month CLINICAL EXAMINATION

DATE_________

Height _______ m Weight _______ kg
BP (mmHg) _______/_______
Heart rate: (see 6MW) _______ bpm
ECG: rhythm AF SR Flutter other (______)
QRSd _______ ms

JVP: normal raised markedly raised (>10cm)
Murmur none systolic diastolic ________________
3rd HS Y/N 4th HS Y/N

Chest normal
crepitations wheeze
reduced breath sounds dull to percussion

P. oedema: none mild (ankle) moderate (knee) severe (thigh-sacral)

Comments: ____________________
### 3 month INVESTIGATIONS

**Date**

**Comments (free text)**

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
</table>

Quality of Life questionnaire.

Score ______/105 ENDPOINT

**Blood tests.**

- BNP (pmol/L) __________ ENDPOINT
- Apelin __________ ENDPOINT

**ECG**

QRS rate (bpm) _______

Rhythm at evaluation: sinus, AF, AT, other _______

**EXERCISE TREADMILL TEST (MVO2)**

**SIX MINUTE WALK TEST. (6MW)**

- HRpre (bpm) _______
- HRend (bpm) _______
- 6MWD (metres) __________ ENDPOINT
Follow-up 6 MONTHS

Major adverse event: Y/N
(tick one or more – with date where relevant)

Unplanned HF admission
Unstable angina
MI
Stroke
TIA
Pulmonary embolism
Cardiac Transplantation
Death

Any unplanned hospital admission? Y/N ________________________

Significant clinical event? Y/N ________________________

6 month CLINICAL EXAMINATION

DATE_________

Height ______ m Weight ______ kg
BP (mmHg) ______/_______
Heart rate: (see 6MW) ______ bpm
ECG: rhythm AF SR Flutter other (______)
QRSd ______ ms

JVP: normal raised markedly raised (>10cm)

Murmur none systolic diastolic ________________________

3rd HS Y/N 4th HS Y/N

Chest normal crepitations wheeze reduced breath sounds dull to percussion

P. oedema: none mild (ankle) moderate (knee) severe (thigh-sacral)

Comments: ____________________
### 6 month INVESTIGATIONS

**Date________**

**Comments (free text)________________________________________________________________________**

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
</table>

**Quality of Life questionnaire. □**  
**Score _____/105 ENDPOINT**

**Blood tests. □**  
**DATE________**

**BNP (pmol/L)_________________ENDPOINT**

**Apelin_________________ENDPOINT**

**ECG □**

**DATE________**

**QRS rate (bpm)_____**

**Rhythm at evaluation: sinus, AF, AT, other _____**

**QRSd (ms)_____**

**Axis (degrees)_____**

**LBBB/RBBB no, LBBB, RBBB, other _____**

**ECHOCARDIOGRAM □**

**DATE________**

**SIX MINUTE WALK TEST. (6MW) □**

**HRpre (bpm)_____**

**HRend (bpm)_____**

**6MWD (metres) ______________ ENDPOINT**

**HOLTER □**
Final visit 12 MONTHS

Major adverse event: Y/N
(tick one or more – with date where relevant)

- Unplanned HF admission
- Unstable angina
- MI
- Stroke
- TIA
- Pulmonary embolism
- Cardiac Transplantation
- Death

Any unplanned hospital admission? Y/N ________________________
Significant clinical event? Y/N ________________________

12 month CLINICAL EXAMINATION

DATE ___________

Height ______ m  Weight ______ kg
BP (mmHg) _______/_______
Heart rate: (see 6MW) ______ bpm
ECG: rhythm AF SR Flutter other (______)
  QRSd ______ ms

JVP: normal raised markedly raised (>10cm)

Murmur none systolic diastolic ________________________

3rd HS Y/N 4th HS Y/N

Chest normal
  crepitations wheeze
  reduced breath sounds dull to percussion

P. oedema: none mild (ankle) moderate (knee) severe (thigh-sacral)

Comments: ____________________
<table>
<thead>
<tr>
<th>Investigation</th>
<th>Value</th>
<th>ENDPOINT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quality of Life questionnaire.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>______/105</td>
<td>ENDPOINT</td>
</tr>
<tr>
<td><strong>Blood tests.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP (pmol/L)</td>
<td></td>
<td>ENDPOINT</td>
</tr>
<tr>
<td>Apelin</td>
<td></td>
<td>ENDPOINT</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS rate (bpm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhythm at evaluation:</td>
<td>sinus, AF, AT, other</td>
<td></td>
</tr>
<tr>
<td>QRSd (ms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axis (degrees)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBBB/RBBB</td>
<td>no, LBBB, RBBB, other</td>
<td></td>
</tr>
<tr>
<td><strong>EXERCISE TREADMILL TEST (MVO2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ECHOCARDIOGRAM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RADIONUCLIDE VENTRICULOGRAPHY.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td></td>
<td>ENDPOINT</td>
</tr>
<tr>
<td><strong>SIX MINUTE WALK TEST. (6MW)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRpre (bpm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRend (bpm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD (metres)</td>
<td></td>
<td>ENDPOINT</td>
</tr>
<tr>
<td><strong>HOLTER</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10.3 Case report form for ARC-HF ablation procedures

Case report form for ARC-HF RF ablation procedures

<table>
<thead>
<tr>
<th>Patient Study ID</th>
<th>RFA number</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2 3</td>
<td></td>
<td>HH / RBH</td>
</tr>
<tr>
<td>Date <em><strong>/</strong></em>/_____</td>
<td>Operator 1</td>
<td>Operator 2</td>
</tr>
<tr>
<td>3D mapping system: NavX / CARTO</td>
<td>Navigation system: No / Stereotaxis / Hansen</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure time (min)</th>
<th>Ablation time (sec)</th>
<th>Saline dose (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin dose (IU)</td>
<td>Fluoroscopy time (min)</td>
<td>Dose Area Product (cGycm2)</td>
</tr>
</tbody>
</table>

Baseline rhythm AF, SR, AT/flutter Baseline V1 cycle length (ms)

Log all time points on Bard – annotate all geometry and CFE maps

<table>
<thead>
<tr>
<th>Start time</th>
<th>Femoral access time</th>
<th>Transeptal x2 access time</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA geo</td>
<td>-</td>
<td>RACF -</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Start--end</th>
<th>tick if done</th>
<th>Block</th>
<th>Cumulative RF time (sec)</th>
<th>AFCL after stage (ms)</th>
<th>CFE map</th>
<th>CFE regions (tick when acquired)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV1</td>
<td>Y/N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roof line</td>
<td>Y/N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVI line</td>
<td>Y/N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo CS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi CS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFAE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVC iso</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTI line</td>
<td>Y/N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

End time (sheaths out) ________________

Termination of AF No / To AT / To SR

DCCV required to restore SR Yes – successful Yes – unsuccessful No

Comments (free text)

______________________________

Procedural complications (up until discharge form hospital) None / Stroke or TIA / Tamponade / Vascular / other (free text)______________________________

Rhythm at discharge SR AF AT other ________________

ITU stay if needed (days) ________________ Hospital stay (days) ________________
Patient information sheet for ARC-HF

A randomised trial to assess Catheter Ablation versus Rate-Control for Management of Persistent Atrial Fibrillation in Patients with Chronic Heart Failure

ARC-HF Patient information sheet
We invite you to consider taking part in a research project.

What is the purpose of the research?

It is still uncertain what the best treatment is for patients who have both atrial fibrillation (AF) and heart failure. The aim of the research study is to help identify the optimal treatment for patients with these two significant medical conditions. This will be done by comparing two different treatments, catheter ablation and rate-control, which are alternative strategies for treating AF. Patients will be randomly assigned (like tossing a coin) to one or the other, and the effect of each strategy assessed by looking for changes in exercise capacity, symptoms, heart pump function, and quality of life.

Why have I been invited to participate?

We are inviting patients with activity-limiting symptoms (such as shortness of breath, tiredness, or palpitations), significantly reduced heart function, and AF to consider participating.

Background to the research study

What is atrial fibrillation?

Normal heart rhythm depends on regular electrical activity of your natural pacemaker cells – the sinus node, which usually ‘fires’ at about 60-100 beats per minute. The impulse spreads to create a coordinated contraction of the heart and the rate responds to the needs of the body, so the heart speeds up with activity and slows down on resting. In AF, however, the normal sinus rhythm is lost: the upper collecting chambers (atria) have a completely chaotic rhythm (fibrillation) and no longer pump effectively. At the connection to the lower pumping chambers, the heart ‘filters out’ many of the impulses so the heart still pumps – but with an irregular, often fast, heart beat which may respond poorly to the needs of the body.

What is heart failure?

The term can be confusing as it does not mean the heart has actually failed. Heart failure occurs when the pump function of the heart is reduced and can lead to symptoms such as tiredness, swollen ankles and breathing difficulty. Heart failure can cause AF, and vice versa. Patients with heart failure are far more likely than patients with normal hearts to develop AF, which affects about 10% of those with milder forms of heart failure but up to 1 in 2 patients with severe heart failure.

How is atrial fibrillation treated in patients with heart failure?

There are two alternative treatment strategies for AF, which doctors may use to try to improve the symptoms related to it, as well as longer-term health:

1. Rate-control. This means patients taking heart-rate slowing tablets to prevent very fast heart rates and allow the heart to pump more efficiently. AF itself is ‘accepted’ as the long-term heart rhythm.
2. **Rhythm-control.** This means trying to restore and maintain normal rhythm, by the means of electric shock treatment (DC cardioversion) together with long-term tablet medication, or by more recently available ‘cauterisation’ therapy (catheter ablation).

All patients with AF and heart failure should ideally be on blood thinning medication, usually warfarin, to reduce the risk of stroke. Also it is important that other conditions, like diabetes, thyroid problems, and blood pressure are all optimally treated.

**How might this study help identify the optimal treatment?**

Doctors still do not know how best to treat AF that occurs in patients with heart failure. Some studies have shown that patients do better if they get back to normal rhythm, whilst others showed no overall long-term benefit from giving tablet-based rhythm control compared with leaving patients in AF and just giving rate-control. **DC cardioversion** can restore normal rhythm but does not prevent recurrence of AF, whilst **rhythm-controlling drugs** carry a risk of side effects and do not prevent over half of patients experiencing further AF.

The more recent therapy of **catheter ablation** can treat the abnormalities that cause AF to persist and, although like any procedure carries some risk (see page 5), it can offer long-term remission from AF and may be a better rhythm-control strategy. Small studies have shown that catheter ablation for AF is beneficial in patients with heart failure, but it has not yet been directly compared with medical rate control. Without **head-to-head** direct comparison of ablation (to restore normal sinus rhythm) versus medical rate-control, doctors will not know which is the better treatment of AF in patients with heart failure. With the aim of answering this important question, we are conducting a **randomised clinical trial.** This involves assigning patients at random to one of the two treatments, to see if either shows benefit. By randomising patients, there is less chance of unfair bias towards either treatment.

**The research study – participant information**

**What will happen to me if I agree to take part in this study?**

We will first check that you are on optimal medication for your heart failure. You might also be on additional tablets to treat your AF. If you meet the entry criteria and are willing to participate we will arrange for you to have a ‘baseline’ assessment including some standard tests of heart function. The aim is see how you are before and after the treatments, using several different methods - as no single test can definitely tell us whether you or your heart have improved. We will arrange with you a day for you to attend for the following tests (some of which you might already have had during your recent clinic visits and therefore may not need to be repeated). You should wear comfortable shoes and clothing that will allow you to perform the walking/exercise tests.

- **History & clinical examination** – like at a normal out-patient clinic visit.
- **Quality of Life questionnaire.** This is a single-page questionnaire consisting of 21 questions about your symptoms: you circle a score for each on scale of 0-5. It takes about 5 minutes to complete.
- **Blood tests.** About 30ml of blood will be taken for routine tests (blood counts, kidney/liver/thyroid). Some samples will be stored for tests looking at specific proteins relevant to heart function.
- **ECG (Electrocardiogram) and Exercise treadmill test (MVO2)** to assess maximum exercise capacity and your body’s ability to use oxygen. You will breathe normal air through a mask while walking on a treadmill, which gradually increases in speed and steepness (in a way designed for patients with weakened hearts). You will be supervised and monitored throughout by medical staff, and can stop once you are too tired or if you feel unwell. Typically this test takes 10-15 minutes.
- **Echocardiogram** (heart ultrasound scan). You are likely to have already had this scan, which looks at the heart muscle and valve function by ultrasound. It takes 15-20 minutes.

- **Radionuclide ventriculography (RNV scan)**. This scan involves an injection of a small amount of radioactive substance into the bloodstream, which highlights the heart chamber on a scanner allowing very accurate measurement of your heart’s pumping function. It takes about 30 minutes, during which time you will be lying on the scanning bed.

- **Six minute walk test**. You will be asked to walk as far as you can in six minutes along a flat corridor circuit, resting if necessary at the seats provided. Your heart rate will be checked.

- **Holter recorder** (24-48 hour wearable heart monitor). You will wear the monitor home so we can check your heart rate during routine activities. The recorder should be removed if you have a bath or shower; you will be shown how to put it back on. We will arrange its return with you.

After these tests you will be randomly assigned by computer to one of two groups: **medical therapy (rate-control)** or **catheter ablation (rhythm control)**. You have an equal chance of being in either group.

### What will happen if I am assigned to medical therapy (rate control)?

**What is rate-control?**

Rate control is a strategy of preventing excessively fast heart beats during AF, by giving treatment to slow down the pumping chambers of the heart. You will probably already be on such rate control medication. Some patients also have a pacemaker to prevent slow heart beats. Research has shown that fast and erratic heart beats caused by AF worsen symptoms, reduce exercise capacity, and trigger or worsen heart failure in some cases. Previous large research studies have therefore used heart-rate ‘targets’ or ‘goals’ for AF patients, with maximum levels for rest and exercise.

The dose of medicine required to achieve rate control varies widely between patients and needs adjusting on an individual basis. This usually involves a number of repeat medical assessments before the medication can be judged ‘optimal’.

**Rate-control treatment**

The aim of treatment will be to control your heart rate (pulse) by optimizing the rate-control medication. We will assess you at several points during the study period to see how this affects your symptoms, exercise capacity, and other heart function results.

- Your baseline assessment will help us establish whether you have satisfactory rate control.
- Targets for rate control will be a heart rate <80 (beats per minute) at rest and <110 during walking
- If necessary we will see you again after 4-8 weeks to check that rate control has been achieved and to fine-tune your medication as necessary.

You will then be seen for follow up as below, undergoing the same assessments and investigations as the catheter ablation patients. Your medication will again be carefully reviewed and adjusted as necessary at each of these visits, using the information from the walking and monitoring tests, so that we can ensure you are on optimal treatment.

### What will happen if I am assigned to catheter ablation (rhythm control)?
What is catheter ablation?

Catheter ablation was introduced in the late 1980s and can be used to treat many heart rhythm problems. This minimally invasive procedure has been adapted and developed in the last 10 years to treating more complex rhythms such as AF. It is performed by passing a long wire (catheter) to the heart, through a small puncture in a vein in the leg, and using radiofrequency energy to heat up small discrete areas of the heart tissue to eliminate abnormal electrical impulses (ablation). Each treated area is very small (3-4 mm) so the technique can be applied in an accurate point-by-point fashion. During catheter ablation of AF, only a selected part of the upper heart chambers is treated, so the main pumping chambers are unaffected.

The catheter ablation procedure

We will arrange an admission date with you for the procedure. You will be in hospital for 2 days in most cases. Our institutional protocol for catheter ablation is well established, so none of the below is ‘experimental’, being used routinely for the patients undergoing these procedures.

You should continue taking warfarin as normal, aiming for a target of INR 2-3 in the 4 weeks prior to the procedure. We will tell you if any medication needs to be stopped before the procedure, otherwise continue all tablets as normal.

You will be admitted to a hospital ward the afternoon before or morning of your procedure, where you will be assessed by medical staff including an anaesthetic doctor. A drip-tube (cannula) will be inserted in your arm for routine blood tests and for administering medications. You should not eat or drink (except sips of water to take tablets) for 6 hours before your procedure.

The whole procedure lasts about 3-5 hours and is carried out under general anaesthetic (sometimes local anaesthetic and sedative medication), in the cardiac catheter laboratory (a room similar to an operating theatre with specialist equipment such as X-ray cameras and other equipment needed for the procedure). Once you are under anaesthetic, we will check there is no blood clot in your heart by doing an ultrasound test via your food-pipe. Then the skin in your groin area will be cleaned and small plastic tubes placed in the veins and artery. Thin plastic-coated wires called catheters will be inserted through the tubes and steered to the heart. The left atrium, the main area for treatment, will be accessed with a long needle and plastic tube via the groin. You will then receive blood-thinning medication (heparin) to prevent blood clot formation during the procedure. The ablation will then be performed to eliminate the abnormal areas of electrical activity. If you remain in AF afterwards, you will undergo a DC cardioversion at the end of the procedure.

At the end of the procedure, blood thinning will be stopped and the tubes removed from your groin. Local anaesthetic will be given to numb the area, and then the anaesthetist will wake you up. Some patients may be looked after in intensive care or ‘recovery’ before returning to the ward. You will need to lie flat for 1-2 hours after the procedure to reduce the chance of groin bleeding.

You will typically be discharged the day after the procedure unless you require other medical care.

If you experience a recurrence of abnormal heart rhythm in the first 2 months after ablation, we would try to restore your normal rhythm by performing DC cardioversion, as a day-case under brief general anaesthetic. Recurrence after 2 months suggests the procedure was not completely effective – we would then offer a second ablation procedure, as per standard practice. Some patients require several

* If a clot is present it would be unsafe to proceed and you would be woken up; we would increase the dose of your warfarin, and bring you back after 2 months for a repeat procedure.

** You should not drive for 2 days after the procedure, because of DVLA regulations.
ablation procedures to achieve long-term remission from AF (the maximum number you can undergo during this study is three). After ablation, you will be followed up as below.

**What follow up will I receive?**

We would like to find out about the effect of each type of treatment on your day-to-day living, exercise capacity, and heart function. Hence we will arrange a follow-up timetable with you (as below) for repeat tests, which can again be performed during a daytime visit to the hospital. At each visit you will be carefully assessed and your medical treatments reviewed and adjusted as necessary.

<table>
<thead>
<tr>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life Questionnaire</td>
<td>Quality of Life Questionnaire</td>
<td>Quality of Life Questionnaire</td>
</tr>
<tr>
<td>ECG, Blood tests, MVO2</td>
<td>ECG, Blood tests, 6 minute walk,</td>
<td>ECG, Blood tests, MVO2, RNV scan, Echocardiogram,</td>
</tr>
<tr>
<td>6 minute walk</td>
<td>Echocardiogram, 24-48h Holter</td>
<td>24-48h Holter, 6 minute walk</td>
</tr>
</tbody>
</table>

After this time, the study will be completed, and you will be referred back to your original specialist doctor. We will then analyse all the results from the patients who have participated in the study. Once the data analysis is complete, we aim to publish the results in scientific journals and would notify all participants of the outcomes, via your GP or in person. If you continue to require specialist heart-rhythm care, you will be offered further follow up in an appropriate cardiology clinic at Royal Brompton or Harefield Hospital.

**Are these treatments safe? Are there any risks?**

Your safety is of utmost importance to us. We appreciate that all medical treatments involve some degree of risk, and this is offset against potential benefit. Neither arm of the study involves experimental treatments in that both rate-control and catheter ablation therapies are recognised treatments for patients with AF. Royal Brompton and Harefield NHS Foundation Trust carry out around 500 AF ablation procedures annually and is one of the largest UK centres. We also have a specialist heart failure team, run by internationally recognised experts in the field; hence your care will be overseen by highly experienced health care professionals.

All procedures involving the heart carry a risk of a significant complication. This may be balanced against both the long-term risk of stroke/major bleeding if remaining in AF (on warfarin) – approximately 1% per year, the benefits of being back in normal rhythm, and the possibility of side-effects and adverse reactions on rhythm-control medication. The catheter ablation procedure is associated with the following possible complications, of which you should be aware:

- Stroke or other major blood clot can occur in 1 in 200 cases (0.5%). To minimise this risk, the presence of a blood clot in the heart will be ruled out by ultrasound assessment before the procedure, and also your blood will be carefully thinned during ablation.
- In 1-2% of cases, blood can leak around the heart during or after the procedure. This may require a small plastic tube to be inserted just under the ribcage at the upper part of the tummy. Rarely, in about 1 in 500 cases (0.2%), the leakage has to be operated on by open chest surgery.
- Narrowing of a blood vessel (pulmonary vein) that carries blood from the lungs back to the heart is rare with modern ablation techniques, but may require treatment in about 0.5% (1 in 200 cases).
• Bruising and other problems relating to blood vessel damage may occur in up to 5% of cases. Most of these are small haematomas (blood collection larger than a bruise), which usually get better in a few days. Less common is a blood collection communicating directly with the artery below (pseudoaneurysm), or formation of an abnormal vein–artery connection (fistula). These usually get better by themselves with time; operations are only required in less than 1 in 100 cases (<1%).

• The nerve responsible for the movement of one side of the breathing muscle (diaphragm) can rarely be damaged by the ablation, in 0.3% of cases, which is only permanent in less than 1 in 1000.

• Inadvertent ablation of the specialised conducting tissues of the heart can require insertion of a permanent pacemaker. The risk of this is very low at approximately 0.25% or 1 in 400.

• Life-threatening complications are rare: according to a worldwide survey, the risk of death associated with catheter ablation of AF is 0.1% (1 in 1000).

You will be exposed to some radiation during the RNV scans and ablation procedures. We are all exposed to natural background radiation every day of our lives, and each X-ray or nuclear medicine examination adds a small additional dose on top of this. Such additional exposure may slightly increase the risk of developing cancer many years or decades later. To quantify this, we have worked out the maximum exposure you could receive as allowed by this study protocol – that being if a patient underwent the RNV scans plus three ablation procedures, each with the maximal permitted X-ray dose (i.e. the majority of patients will receive a much lower dose, thus the following risk is an overestimate). At this level of exposure, about 1 in 500 people may acquire a cancer during their whole lifetime. We all have about a 1in3 to 1in4 chance of getting cancer during our lives, so the actual increase in risk is small (e.g. 33.3% increased to 33.5%). Skin injury such as redness similar to sunburn may rarely occur, but should not occur using modern X-ray equipment. Total radiation dose at ablation will be minimised by use of pulsed X-ray and the special mapping system.

Are there any benefits?

At present we do not know which treatment group will benefit more, because the reason to perform the study is to establish which form of treatment for AF is better for patients in heart failure. It is possible that participants may benefit from being in the clinical trial simply because of undergoing more detailed tests and slightly more frequent visits to see doctors than usual (depending on your previous circumstances). This might provide the opportunity for us or your doctor to look after any heart problems more closely and to pick-up any other health related problems sooner than in routine clinical care.

Do I have a choice?

Yes. Your participation in this study is entirely voluntary, and there is no obligation to participate. If you choose not to join the study your medical care will not be affected. You may withdraw from the study at any time without compromising your future medical treatment.

Are there any financial incentives for participation?

There are no financial incentives for participation.

I'm considering taking part in the research study, but I would like time to consider this information further before deciding. By when do I need to inform you?

We are keen for all patients to have a clear understanding of the reasons for the research trial and what it will involve, and have the opportunity to ask questions prior to enrolment. Most will need a few days to consider the information in this sheet, discuss it with family members, or perhaps do their own
research into the subject via the internet. We would ask participants to answer if possible within 1-2 weeks, depending on their circumstances. See contact details below.

Confidentiality

All aspects of this study, including results, will be strictly confidential and only the researchers will have access to your personal information. Person-identifiable data will be stored on secure non-portable NHS computer systems. Investigation data used for analysis spreadsheets will be de-identified by the use of numerical codes. Publication of the results from this study will only use de-identified information. The samples that are frozen on-site for later analysis will only display your confidential study code number.

Will my general practitioner be informed of my participation?

Yes, if you give your permission on the consent form. Informing your GP is professionally courteous on our part, and can help continuity in your medical management.

What if something goes wrong?

In the event that something goes wrong and you are harmed during the research and this is due to someone’s negligence then you may have grounds for a legal action for compensation against the Royal Brompton and Harefield NHS Trust, although you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you. NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm.

I am told I am not eligible to participate in the trial – could you explain why?

Patients have to fit the ‘inclusion criteria’: symptoms of heart failure above 18 and under 80 years old, confirmation of significant heart impairment on heart scan, and at least 7 days of AF. It may not be appropriate for patients with certain medical conditions to undergo the investigations and/or treatments set out within this trial, thus there are also certain ‘exclusion criteria’: these include advanced kidney, liver, brain or muscular disease, previous AF ablation treatment, recent surgery (including a pacemaker if the leads were implanted less than 6 months ago), or an inability to take certain medications like warfarin. You may ask the research doctor to discuss these further.
Contact details

If you require further information before deciding, wish to enrol, or have any questions about your treatment during the study, please contact:

**Dr David Gareth Jones, Fellow in Cardiac Electrophysiology**

*email* davidgarethjones@nhs.net  
*mobile (text/voicemail)* 07847 095863  
*telephone via* Brompton switchboard (020 7352 8121)  
*fax* 0871 2668748

**Alexandra Wise, BHF Arrhythmia Nurse Specialist**

Ask for bleep 1146 via Brompton switchboard  
*email* a.wise@rbht.nhs.uk

For urgent matters outside of normal working hours, you may contact:  
**On-call cardiology registrar**, via Brompton or Harefield switchboard

To *confidentially* discuss any concerns and queries about your experience at the hospital while participating in this research, and for advice or support, you may contact:

**Royal Brompton and Harefield Patient Advice and Liaison Service (PALS)**

Royal Brompton Hospital, Sydney Street, London SW3 6NP  
Tel: 020 7352 8121  
Fax: 020 7351 8108

Harefield Hospital, Hill End Road, Harefield, Middlesex UB9 6JH  
Tel: 01895 826 572

Email: patientadviceandliaisonservice@rbht.nhs.uk

*Thank you very much for reading this information sheet.*

**The ARC-HF Study Investigators**

**Principal Investigator**  
Dr Tom Wong, RBH & HH

**Study coordinator/co-investigator**  
Dr David Gareth Jones, RBH & HH

**Co-investigators**  
Dr Shouvik Haldar, RBH & HH  
Dr Vias Markides, RBH & HH  
Dr Rakesh Sharma, RBH  
Dr Theresa McDonagh, RBH  
Dr Shelley Rahm-Haley, HH  
Professor Richard Underwood, RBH