Interventional techniques in the management of persistent atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) is a common cardiac rhythm problem experienced by patients and comprises an increasing demand on healthcare systems. AF is characterised by advanced neurohormonal remodelling in the atria resulting in dilation and variable degree of atrial fibrosis that can be measured by imaging techniques with difficulty in developing methods of identifying and quantifying left atrial (LA) fibrosis. LA fibrosis can be estimated by measuring LA scar using non-invasive imaging methods such as strain imaging in advanced echocardiography and in cardiac magnetic resonance (CMR) imaging. Achieving rhythm control strategy utilising catheter ablation (CA) has shown to be advantageous in improving quality of life (QOL) in patients with paroxysmal AF. The most effective method in management of AF has remained elusive in non-paroxysmal AF. Thoracoscopic surgical ablation (TSA) has been developed over the last decade by experienced surgeons with some promising early results but has not been investigated in long-standing persistent AF (LSPAF).

I have attempted to answer some of the relevant questions that have remained in management of LSPAF by conducting a multicentre randomised control trial comparing efficacy between CA and TSA (CASA-AF RCT) and improvements in quality of life indices. In a sub-study, I measured LA volumes using echocardiography and CMR to determine reverse remodelling and LA function using tissue Doppler imaging and strain imaging to predict AF recurrence. In a CMR sub-study, a novel automatic LA segmentation algorithm was used to quantify LA fibrosis before and after ablation. I was able to quantify the response of the autonomic nervous system to targeted ganglionic plexi (GP) ablation as part of TSA compared to CA by measuring heart rate variability.

I am hopeful that the knowledge gained from this thesis will help with an appropriate selection that will improve the management of patients with LSPAF.

DECLARATION OF ORIGINALITY

I declare that all work included in this thesis is original work as a result of the literature review, data collection, data analysis that I performed with some assistance mentioned below. The CASA AF randomised control trial was designed by Dr. Shouvik Haldar and Dr. Tom Wong, and funding was obtained from the NIHR EME grant.

I designed the database alongside Dr. Ines Kralj-Hans (trial manager) in collaboration with King's College Trials Unit. The patient information sheet was written by me to distribute to potential candidates in 6 sites: Royal Brompton Hospital, Harefield Hospital, Ealing Hospital, St Peters and Ashford NHS Trust, Liverpool Heart and Chest Hospital, and Brighton and Sussex NHS Trust. I obtained honorary research contracts with these institutions to screen cardioversion and ablation waiting lists for potentially eligible patients with long standing persistent atrial fibrillation. All patients from July 2015 to December 2017 we contacted by me to take part in the study apart from Liverpool and Brighton where the respective research nurses and principle investigators contacted the patients to consider enrolling into the study. I attended all the baseline and follow up assessments at the Royal Brompton and Harefield NHS trusts between July 2015 and December 2017.

I managed to recruit 98 patients into the study and 92 had undergone randomisation and received appropriate allocated ablation prior to returning to clinical training as ST7 in electrophysiology in Nottingham. If there were instances of two cases being performed in two different study sites, then Dr. Charles Butcher would assist by travelling to the closest location and obtain the study data from the procedure while ensuring protocol is followed.

The rest of the recruitment of 22 patients was completed by Dr. Vennela Boyalla over the next 6 months from January 2018 to June 2018 when I returned to clinical training in EP as ST7 in cardiac electrophysiology from January 2018.

The imaging standard of protocol was written by me with assistance from Dr. Raj Khattar. The quality control of the imaging studies was performed by me and feedback provided to Cathy West (imaging tech lead) to train the allocated sonographers appropriately. The analysis of all the echocardiogram parameters was performed by me by training on non-vendor platform called TOMTEC.

CMR methodology and development of an automatic segmentation algorithm was published by Dr. Guang Yang and me while being supervised by Dr. Jennifer Keegan, Dr. Raad Mohiaddin, and Dr David Firmin. The automatic segmentation and scar quantification software was located in the MRI department and I converted the raw data to a format suitable for the MATLAB program that was run by Dr. Guang Yang.

ILR data were collected meticulously by ensuring no data were lost when the ILR was full by calling the patients to perform manual downloads. The ILR data were checked three times a week by me to ensure ILR were not overwriting for the first two years until a corelab physiologist was appointed to analyse the arrhythmias recorded on the ILR.

Heart rate variability protocol, methodology, downloads and collection of data, processing of data into readable graphs was performed by me and sent to Prof. Marek Malik for digitization and extraction of the data into excel files.

All the data was statistically analysed by me using SPSS version 25. The statistical analysis of the data from the imaging chapters was reviewed by Dr. Raj Khattar. Further guidance of statistical analysis regarding collinearity of variables such as strain and strain rate and logistic regression was obtained from Dr. Simon Jones.

The manuscripts arising from the thesis were led by me in a joint effort with the team members listed in each abstract and manuscript publication. There was no act of plagiarised performed intentionally in the thesis.

Dr Habib Rehman Khan

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The PhD tenure and thesis has been achieved through dedication and patience. I want to thank Dr. Tom Wong for his guidance in the project, and assistance in establishing the CASA AF trial with its various challenging aspects. I want to thank my second supervisor Professor Martin Cowie for supporting and guiding me throughout the PhD period and for meticulous proof reading of the chapters, all of which has been invaluable.

I would also like to particularly thank Dr. Ines Kralj-Hans, the trial manager for CASA, who was a guiding light throughout my research period and has continued to support my work through words of encouragement and guidance. Her belief in me and perseverance with all the challenges has been an enriching experience. Dr. Vennela Boyalla took on the role of research fellow in my place when I returned to clinical training and she did a marvellous job to complete the recruitment for the CASA AF RCT and has been instrumental in periods lacking motivation. I recruited 98 patients in the CASA AF RCT while Dr. Boyalla completed the study by recruiting the remainder 22 patients.

I would like to thank the support and help from the research teams in Royal Brompton and Harefield Hospitals respectively that made the journey of data entry seem so effortless. Team members from all the sites that made the CASA AF RCT successful are the following individuals: Dr. Toufan Bahrami, Dr. Jonathan Clague, Mrs. Joanne Daradar, Dr. Anthony DeSouza, Dr. David Firmin, Dr. Shouvik Haldar, Ms Safia Hamid, Dr. Wajid Hussain, Dr. Julian Jarman, Dr. David Jones, Dr. Riyaz Kaba, Dr. Jenny Keegan, Dr. Raj Khattar, Dr. Vias Markides, Dr. Neeraj Mediratta, Dr. Raad Mohiaddin, Iulia Munteanu, Dr. Dudley Pennell, Paula Rogers, Dr. Tushar Salukhe, Mr Rick Wage, Ms Cathy West, Dr. Guang Yang.

CASA AF trial was a multicentre study, and without the support of principal investigators for each site representing catheter ablation and thoracoscopic ablation the trial would not have completed, results compiled and analysed for timely presentation to the scientific community. The principal investigators were as follows: Dr. Dhiraj Gupta and Dr. Neeraj Mediratta in Liverpool Heart and Chest Hospital; Dr. Jack McCready and Dr. Jonathan Hyde in Brighton and Sussex NHS trust.

I would also like to thank the London Health Sciences Centre, London – Ontario, Canada to allocate me dedicated time to write my thesis and for their endless support, in particular Dr. Allan Skanes, Dr. George Klein, Dr. Anthony Tang, Dr. Lorne Gula, Dr. Raymond Yee and Dr. Peter Leong-Sit.

I would like to thank my beautiful wife Dr. Aisha Rashid along with my beautiful, intelligent and tolerating children Hesham and Sireen. They unconditionally supported me from Canada for 2 years while I was writing up the thesis and completing my clinical training in cardiac electrophysiology. I will never forget their sacrifices and support to allow me to pursue my passion for research. Hopefully, this research will create a better future for them in decades to come.

I would like to thank my parents who silently prayed in the background for my success as they have always done in the past.

Last and most importantly, I would like to thank the Lord for creating such a diverse and complex universe that allows researchers like me to be completely mesmerised by the beauty and complexity of the working human body.

TABLE OF CONTENTS

ABSTRACT **2**

DECLARATION OF ORIGINALITY **4**

COPYRIGHT DECLARATION **7**

ACKNOWLEDGEMENTS **8**

PUBLICATIONS FROM THE RESEARCH **19**

PRESENTATIONS FROM THE RESEARCH **21**

ABSTRACTS FROM THE RESEARCH **22**

ABBREVIATION LIST: **24**

LIST OF FIGURES **30**

LIST OF TABLES **35**

CHAPTER 1 ..... **39**

INTRODUCTION AND LITERATURE REVIEW OF ABLATION TECHNIQUES IN ATRIAL FIBRILLATION **39**

1.1 ATRIAL FIBRILLATION AS A DIAGNOSIS AND DISEASE **39**

1.1.1. DEFINITION AND CLASSIFICATION OF ATRIAL FIBRILLATION 39

1.1.2 PATHOGENESIS AND RISK FACTORS FOR ATRIAL FIBRILLATION 41

1.1.3 MECHANISMS OF ATRIAL FIBRILLATION 44

1.2 SYMPTOMS OF ATRIAL FIBRILLATION **47**

1.3 TREATMENT OF ATRIAL FIBRILLATION **49**

1.3.1 RATE CONTROL 49

1.3.2 RHYTHM CONTROL- CARDIOVERSION 50

1.3.3 ABLATION TECHNIQUES 52
1.3.3.1 RADIOFREQUENCY ABLATION 53
1.3.3.2 CRYOABLATION 55
1.3.3.3 MINIMALLY INVASIVE THORACOSCOPIC SURGICAL ABLATION 56
1.3.3.4 HYBRID ABLATION 60
1.3.3.5 COX-MAZE SURGICAL PROCEDURE 61
1.4 SIDE EFFECTS OF MEDICATIONS 61
1.5 ATRIAL FIBRILLATION AND ITS IMPACT ON HEALTH SERVICES 62
1.5.1 COST OF MEDICATIONS 63
1.5.2 COST OF ADMISSIONS, VISITS TO HOSPITALS AND PHYSICIANS 65
1.5.3 COSTS OF GENERAL PHYSICIANS VISITS 68
1.5.4 COST OF PROCEDURES 68
1.5.5 HEALTH AND QUALITY OF LIFE MEASUREMENTS 71
1.6 REDUCTION OF RISK OF THROMBOEMBOLIC EVENTS 73
1.6.1 ROLE OF ANTICOAGULANTS IN PREVENTION OF THROMBOEMBOLISM 73
1.6.2 ROLE OF LEFT ATRIAL APPENDAGE CLOSURE AND EXCISION IN THROMBOEMBOLISM PREVENTION 74
1.7 SUBSTRATE ANALYSIS OF LEFT ATRIAL SCAR AND LEFT ATRIAL FUNCTION USING IMAGING MODALITIES 76
1.7.1 LEFT ATRIAL VOLUME ASSESSMENT 76
1.7.2 LEFT ATRIAL SCAR ASSESSMENT 78
1.8 LEFT ATRIAL FUNCTION AS A PREDICTOR OF ATRIAL FIBRILLATION RECURRENCE 81
1.9 ROLE OF GANGLIONIC PLEXI ABLATION IN REGULATION OF AUTONOMIC NERVOUS SYSTEM MODIFICATION AND MANAGEMENT OF ATRIAL FIBRILLATION 84
1.9.1 COMPOSITION OF THE AUTONOMIC NERVOUS SYSTEM 85
1.9.2 ANATOMY OF GANGLIONIC PLEXI AROUND HEART 86

1.9.3 MECHANISM OF ATRIAL FIBRILLATION ACTIVATION VIA GANGLIONIC PLEXI 86

1.9.4 MEASURING AUTONOMIC NERVOUS SYSTEM ACTIVITY IN PATIENTS WITH ATRIAL FIBRILLATION 87

1.10 LIMITATIONS IN CURRENT STANDARD TREATMENTS IN MANAGEMENT OF ATRIAL FIBRILLATION 88

1.11 SUMMARY OF LITERATURE REVIEW, AIMS AND HYPOTHESIS OF THE THESIS..... 89

CHAPTER 2 95

COMPARISON OF CATHETER ABLATION VERSUS THORACOSCOPIC SURGICAL ABLATION (CASA-AF) RANDOMISED CLINICAL TRIAL..... 95

2.1 METHODS 95

2.1.1 PRIMARY OUTCOME 95

2.1.2 SECONDARY OUTCOMES 96

2.1.3 PATIENT SELECTION 97

2.1.4 STATISTICAL ANALYSIS 99

2.2 TRIAL SCHEDULE..... 100

2.3 BASELINE STUDY VISIT..... 102

2.4 RANDOMISATION 105

2.5 ANTICOAGULATION PROTOCOL 105

2.6 ABLATION PROTOCOL 106

2.6.1 CATHETER ABLATION PROTOCOL..... 106

2.6.2 THORACOSCOPIC SURGICAL ABLATION PROTOCOL..... 108

2.7 CARDIAC RHYTHM MONITORING PROGRAMMING AND PROTOCOL..... 120

2.8 POST OPERATIVE MANAGEMENT 122

2.8.1 ANALGESIC 122

2.8.2 ANTIBIOTIC 123

2.8.3 ANTIARRHYTMIC MEDICATION 123

2.8.4 ANTICOAGULATION 123

2.9 FOLLOW UP 124

2.10 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS 124

2.11 EVALUATION OF ATRIAL AND VENTRICULAR FUNCTION 127

CHAPTER 3 129

SUCCESS OF THORACOSCOPIC SURGICAL ABLATION COMPARED TO CATHETER ABLATION – CASA AF RCT 129

3.1 RESULTS 130

3.2 ACUTE PROCEDURAL RESULTS 135

3.3 BLANKING PERIOD 142

3.4 PRIMARY OUTCOMES 142

3.5 SENSITIVITY ANALYSIS OF PRIMARY OUTCOMES 144

3.6 HOLTER SIMULATION - IMPACT ON RATES OF AF RECURRENCE 145

3.7 AF/AT BURDEN REDUCTION OVER 12 MONTHS OF FOLLOW-UP 146

3.8 SAFETY OUTCOMES: SERIOUS ADVERSE EVENTS AND COMPLICATIONS 148

3.9 IDENTIFICATION OF BREAKS IN LESION SETS 151

3.10 QUALITY OF LIFE MEASURES 153

3.10.1 AFEQT 154

3.10.2 EUROPEAN QUALITY FIVE DIMENSIONAL – FIVEL LEVEL (EQ5D-5L) EVALUATION 156

3.10.3 EUROPEAN HEART RHYTHM ASSOCIATION AF SYMPTOM SCORE 158

3.11 DISCUSSION 160

3.12 LIMITATIONS 170

3.13 CONCLUSION 171

CHAPTER 4 172

LEFT ATRIAL STRUCTURE AND FUNCTION ASSESSED BY ADVANCED ECHOCARDIOGRAPHY IN PATIENTS ENROLLED IN THE CASA-AF TRIAL 172

4.1 BACKGROUND 172

4.2 METHODS 177

4.2.1 POPULATION 177

4.2.2 ECHOCARDIOGRAPHY 177

4.2.2.1 LEFT ATRIAL VOLUMES 178

4.2.2.2 LEFT ATRIAL STRAIN AND STRAIN RATE BY 2D SPECKLE TRACKING ECHOCARDIOGRAPHY 181

4.2.2.3 LEFT ATRIAL TISSUE DOPPLER IMAGING 183

4.3 RESULTS 186

4.3.1 LA VOLUMES 186

4.3.1.1 LA VOLUMES AND VOLUME-DERIVED FUNCTION IN CA AND TSA GROUPS 186

4.3.1.2 COMPARISONS OF LA VOLUMES AND FUNCTION IN THE TWO TREATMENT ARMS 188

4.3.1.3 COMPARISON OF LA VOLUMES AND FUNCTION BETWEEN SINUS RHYTHM AND AF RECURRENCE GROUPS 191

4.3.1.4 LA VOLUMES AND FUNCTION AS PREDICTORS OF AF RECURRENCE 195

4.3.2 LA FUNCTION USING 2D SPECKLE TRACKING ECHOCARDIOGRAPHY FOR LA STRAIN AND STRAIN RATE 202

4.3.2.1 COMPARISONS OF LA STRAIN AND STRAIN RATE IN THE TWO TREATMENT ARMS 203

4.3.2.2 COMPARISON OF LA STRAIN AND STRAIN RATE PARAMETERS BETWEEN SINUS RHYTHM AND AF RECURRENCE 206

4.3.2.3 LA STRAIN AND STRAIN RATE AS PREDICTORS OF AF RECURRENCE 210

4.3.3 TISSUE DOPPLER IMAGING DATA 216

4.3.3.1 COMPARISONS OF THE LA TDI PARAMETERS IN THE CA AND TSA GROUPS 217

4.3.3.2 LONGITUDINAL EFFECTS OF CA AND TSA ON REGIONAL LA WALL MOTION AND FUNCTION 220

4.3.3.3 LONGITUDINAL EFFECTS OF REGIONAL LA WALL MOTION AND FUNCTION ON THE RHYTHM 226

4.3.3.4 COMPARISON OF LA TDI PARAMETERS IN THE SINUS RHYTHM AND AF RECURRENCE GROUPS 230

4.3.3.5 LA TDI PARAMETERS AS PREDICTORS OF AF RECURRENCE 233

4.4 DISCUSSION 236

4.5 LIMITATIONS 244

4.6 CONCLUSION 245

CHAPTER 5 246

VOLUMATIC, STRUCTURAL AND FUNCTIONAL CHANGES FOLLOWING ABLATION ASSESSED BY CARDIAC MAGNETIC RESONANCE IMAGING IN THE CASA-AF TRIAL 246

5.1 BACKGROUND 246

5.2 METHODS 247

5.2.1 CMR PROTOCOL 247

5.2.2 MEASURING ATRIAL VOLUMES AND FUNCTION WITH CMR 247

5.3 RESULTS 250

5.3.1 PATIENTS 250

5.3.2 ATRIAL VOLUMES, EF AND REVERSE REMODELLING: COMPARISONS BETWEEN TREATMENT ARMS (CA VS TSA) 252

5.3.3 ATRIAL VOLUMES, EF AND REVERSE REMODELLING: COMPARISONS BETWEEN SINUS RHYTHM AND AF RECURRENCE 254

5.3.4 PREDICTORS OF AF RECURRENCE 257

5.3.5 PULMONARY VEIN MEASUREMENTS 262

5.4 DISCUSSION 264

5.5 LIMITATIONS 270

5.6 CONCLUSIONS 271

CHAPTER 6 272

CARDIAC MAGNETIC RESONANCE EVALUATION OF LEFT ATRIAL SCAR QUANTIFICATION 272

6.1 BACKGROUND 272

6.2 METHODS 274

6.2.1 DATA ACQUISITION 274

6.2.2 SEGMENTATION 275

DEEP LEARNING BASED METHOD 275

STATISTICAL ANALYSIS 278

6.3 RESULTS 278

6.4 LA SCAR AS A PREDICTOR OF AF RECURRENCE 282

6.5 DISCUSSION 283

6.6 CONCLUSIONS 285

CHAPTER 7 286

EFFECT OF GANGLIONIC PLEXI ABLATION IN THORACOSCOPIC SURGICAL ABLATION ON AUTONOMIC NERVOUS SYSTEM. ANALYSIS OF CONTINUOUS HEART RATE VARIABILITY OVER 1 YEAR FOLLOW UP 286

7.1 BACKGROUND 286

7.2 METHODS 290

7.2.1 GP STIMULATION AND ABLATION 290

7.2.2 HEART RATE VARIABILITY 292

7.2.3 STATISTICS 294

7.3 RESULTS 294

7.3.1 BASELINE 294

7.3.2 EFFECT OF GP ABLATION ON HRV DURING 1ST WEEK 296

7.3.3 EFFECT OF GANGLIONIC PLEXI ABLATION OVER 1 YEAR 298

7.3.4 AUTONOMIC FUNCTION AND RELATIONSHIP TO AF RECURRENCE 301

7.4 DISCUSSION 304

7.5 LIMITATIONS 307

7.6 CONCLUSION 308

Chapter 8 309

CONCLUSION OF THE THESIS 309

8.1 CHAPTER 3 – PRIMARY OUTCOMES OF CASA AF RANDOMISED CONTROL TRIAL 309

8.2 CHAPTER 4 – LA SIZE AND FUNCTION USING ADVANCED ECHOCARDIOGRAPHY 310

8.3 CHAPTER 5 – LA VOLUME AND REVERSE REMODELLING SEEN USING CMR 310

8.4 CHAPTER 6 – LA SCAR MEASURED FROM CMR USING AUTOMATED SEGMENTATION. 311

8.5 CHAPTER 7 – Ganglionic Plexi ablation and assessment using heart rate variability 311

CHAPTER 9 313

FUTURE CONSIDERATIONS 313

REFERENCES 319

PUBLICATIONS FROM THE RESEARCH

S Haldar, HR Khan, V Boyalla, I Kralj-Hans, S Jones, J Lord, O Onyimadu, A Satishkumar, T Bahrami, J Clague, A De Souza, J Clague, D Francis, W Hussain, J Jarman, DG Jones, Z Chen, N Mediratta, J Hyde, M Lewis, R Mohiaddin, T Salukhe, C Murphy, J Kelly, R Khattar, W Toff, V Markides, J McCready, D Gupta, T Wong. Catheter Ablation Versus Thoracoscopic Surgical Ablation in Long Standing Persistent Atrial Fibrillation: CASA AF Randomised Control Trial. European Heart Journal (2020) 41, 4471-4480.

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ABBREVIATION LIST:

2D – 2 dimensional

3D – 3 dimensional

AADs – antiarrhythmic drug

ACEi – angiotensin converting enzyme inhibitor

ACT – activated clotting time

AF – atrial fibrillation

AFEQT – Atrial Fibrillation Effect on QualiTy of life

ARB – angiotensin receptor blocker

ANS – autonomic nervous system

ASR – contractile function / active LA pumping / booster function

AT – atrial tachycardia

AUC – area under the curve

AV – atrioventricular

BB / ß-blockers – Beta adrenoceptor antagonists

BMI – Body mass index

BSA – body surface area

CA – catheter ablation

CABG – coronary artery bypass grafting

CASA – Catheter Ablation versus Surgical Ablation

CCB – calcium channel blockers

CCG – care commissioning group

CF – contact force

CFAE – complex fractionated atrial electrograms

$CHADS_2$ – congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke/transient ischemia attack/thromboembolism (double score)

CHA_2DS_2-VASc - congestive heart failure, hypertension, age _75 years (doubled), diabetes Mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category

CHF – congestive heart failure

CI – confidence interval

CLAWS - continuously adaptive windowing strategy

CMR – cardiac magnetic resonance

COPD – chronic obstructive pulmonary disease

CRT – cardiac resynchronisation therapy

CT – computerised tomography

CTI – cavotricuspid isthmus

CVA – cerebrovascular accident

DCCV – direct current cardioversion

DE-MRI - delayed enhancement magnetic resonance imaging

DHP - dihydropyridine

EAM – electroanatomical mapping

ECG - electrocardiogram

EDV - end-diastolic volume

EF - emptying fraction / ejection fraction

EHRA – European Heart Rhythm Association

EP - electrophysiology

EQ5D-5L – European Qol group 5 dimension – 5 level questionnaires

ESR – conduit function / passive emptying

ESV - end-systolic volume

FAM – fast anatomical mapping

GA – general anaesthesia

GRAPPA - generalized auto-calibrating partially parallel acquisition

GP – ganglionic plexi

GT – ground truth

HDL – high density lipoprotein

HEQ – health economic questionnaire

HF – high frequency

HFS – high frequency stimulation

HR – hazard ratio

HRV – heart rate variability

Hz - hertz

IBM – international business machines

ILR – implantable loop recorder

INR – international normalised ratio

IQR – interquartile range

IVC – inferior vena cava

Kg - kilogram

LA – left atrial / left atrium

LAA – left atrial appendage

LAEF – left atrial emptying fraction

LASQ – left atrial scar quantification

LDL – low density lipoprotein

LF – low frequency

LGE – late gadolinium enhancement

LIPV – left inferior pulmonary vein

LSPAF – long-standing persistent atrial fibrillation

LSPV – left superior pulmonary vein

LTCT – long-term cardiac trend

LV – left ventricle

LVEDV - left ventricular end-diastolic volume

LVESV - left ventricular end-systolic volume

LVEF – left ventricular ejection fraction

max - maximum volume

MI – myocardial infarction

MIL – mitral isthmus line

min - minimum volume

ml/m^2 – millilitres per meter squared

MRI – magnetic resonance imaging

ms - milliseconds

MSM – multi-slice trace method

mV – millivolts

MV – mitral valve

MVTT – multi-view two-task segmentation

n – number of patients

NDHP – non dihydropyridine

NHS – National Health Service

NOAC – New Oral Anti-Coagulatnt

OR – odds ratio

PAF -paroxysmal atrial fibrillation

PIS – patient information sheet

PPM – permanent pacemaker

PV – pulmonary vein

PVI – pulmonary venous isolation

PWI – posterior wall isolation

QALY – quality-adjusted life-year

QOL – quality of life

RA – right atrium

RAEF – right atrial emptying fraction

RCT – Randomised clinical trial

RFA – radiofrequency ablation

RIPV – right inferior pulmonary vein

ROC – receiver operating characteristic

RRM – reverse remodelling

RSPV – right superior pulmonary vein

RVEDV – right ventricular end-diastolic volume

RVEF – right ventricular ejection fraction

RVESV – right ventricular end-systolic volume

SAE – serious adverse event

SD – standard deviation

SDNN – standard deviation of the normal – normal RR intervals

SF – short form

SR – sinus rhythm

SSR – reservoir function

SVC – superior vena cava

TDI – tissue Doppler imaging

TE/TR – echo time/ repetition time

TIA – transient ischemic attack

TOE – transoesophageal echocardiogram

TPI – tissue proximity indicator

TSA – thoracoscopic surgical ablation

TTE – transthoracic echocardiography

TV – tricuspid valve

UK – United Kingdom

USA – United States of America

VLF – very low frequency

WACA – wide area circumferential ablation

Δ - delta changes between parameters

LIST OF FIGURES

Figure 1: Schematic diagram of the right and left atrium illustrating mechanisms of initiation and maintenance of AF in the left atrium and associated pulmonary veins..... 45

Figure 2: Schematic representation of CASA-AF study design 102

Figure 3: Schedule of Enrolment, Tests and Assessments in CASA-AF Study (SPIRIT figure) 104

Figure 4: Lesion set for catheter ablation used in CASA AF RCT Trial. CTI – cavotricuspid isthmus line, LIPV – left inferior pulmonary vein, LSPV – left superior pulmonary vein, RIPV – right inferior pulmonary vein, RSPV – right superior pulmonary vein, WACA – wide area circumferential ablation. 107

Figure 5: Phrenic nerve and exposure of right atrium anterior to it on the right-side approach. 109

Figure 6: Oblique sinus and dissection of Sondergaard's groove 109

Figure 7: Preablation mapping of the right inferior PV 110

Figure 8: Preablation mapping of right superior PV 110

Figure 9: Dissector encircling the right superior and inferior PVs 111

Figure 10: Delivery of right-sided clamp 112

Figure 11: Ablation of right-sided atrial antrum using a clamp 112

Figure 12: Superior line ablation 113

Figure 13: Inferior line ablation 113

Figure 14: Superior line lesions adjoining right-sided PV lesions. 114

Figure 15: Post ablation sensing to ensure entrance block into PVs proximal to the ablation line 114

Figure 16: Positive high-frequency stimulation of ganglionic plexus resulting in asystole. . 115

Figure 17: Ablation of Ganglionic plexi at the site of positive testing 115

Figure 18: Left-sided PV antrum ablation 116

Figure 19: Inferior line and superior line join to the left-sided PV lesions 117

Figure 20: TSA with PV lesions and testing of isolation with multipole EP catheter and multipurpose surgical pen 119

Figure 21: Consort diagram of the CASA AF Trial 131

Figure 22: Surgical pen testing and multipole electrophysiology catheter testing of the lesion set delivered in TSA. 138

Figure 23: Patients treatment and flow in the hospital prior to discharge 141

Figure 24: Kaplan-Meier plot of survival free from atrial arrhythmias from the end of the blanking period to the 12 months follow up between TSA and CA. 143

Figure 25: Kaplan-Meier survival analysis between CA and TSA based on per protocol analysis without AADs. 145

Figure 26: Kaplan-Meier survival analysis of simulated monitoring of 1 week every three months using ILR data for freedom of atrial arrhythmias in patients randomised to CA vs. TSA. 146

Figure 27: Kaplan-Meier survival analysis for AF/AT burden reduction ≥75%, CA vs. TSA over 12 months in CASA-AF trial. 147

Figure 28: Details of gaps in PV and linear lesion sets resulting in AF recurrence 152

Figure 29: AFEQT scores between CA and TSA using repeated measures over the one-year follow-up 155

Figure 30: AFEQT scores between SR and AF using repeated measures over one year 156

Figure 31: EQ5D-5L scores between CA and TSA using repeated measures for one-year follow-up. 157

Figure 32: EQ5D-5L scores between SR and AF recurrence using repeated measures analysis for one year follow-up 157
Figure 33: EHRA AF symptom scores between CA and TSA using repeated measures analysis for one year follow-up 159
Figure 34: EHRA AF symptom scores between SR and AF recurrence using repeated measures analysis for one year follow-up 159
Figure 35: LA volume calculation using biplane area length method in 4 chamber view (left panel) and 2 chamber view (right panel) 179
Figure 36: Three components of the LA function using volume indices during sinus rhythm through one cardiac cycle. 180
Figure 37: Left atrial strain (panel A) and strain rate (panel B) showing reservoir, conduit and contractile functions in a patient in SR. 182
Figure 38: TDI sampling obtained at four locations: anterior LA wall, lateral LA wall, inferior LA wall, and septal LA wall. 183
Figure 39: Pulsed wave tissue doppler of the inferior atrial wall below the mitral valve annulus. Mitral annular velocity during onset of ventricular systole (S'), LA reservoir (LA SSR), LA conduit (LA ESR) and LA contractile function (LA ASR). 184
Figure 40: Receiver-operating characteristic curve using baseline LAmax data for the prediction of AF recurrence (A). Kaplan-Meier survival analysis using a baseline LAmax cut-off of 42 ml/m2 (B). 198
Figure 41: Receiver-operating curve analysis evaluating LA p-wave volume at 3 months and its association with AF recurrence (A). Kaplan-Meier survival analysis showing freedom from AF recurrence using a LA p-wave volume at 3 months cut-off value of 35 ml/m2 (B). 201

Figure 42: Baseline LA SSR ROC curve analysis showed strain (AUC = 0.672, p = 0.03) was a strong predictor of AF recurrence in follow-up with optimal cut-off being 10.3% **(A)**. Kaplan Maier survival curves showing that reservoir strain <10.3% is strongly associated (P=0.026) with SR maintenance (72%) **(B)**..... 213

Figure 43: ROC curve of LA contraction using 2D speckle tracking strain at 3 months following ablation as a predictor for AF recurrence over 12 months follow up **(A)**. Kaplan Meier curve analysis of freedom from AF recurrence LA reservoir strain at 3 months categorised as < or > 7.5% **(B)**..... 215

Figure 44: ROC curve analysis of ASR at 3 months with sensitivity and specificity related to detecting AF recurrence (A). In Kaplan-Meier survival analysis, ASR at 3 months < 6 cm/s was associated with 88.5% AF recurrence while >6cm/s was associated with 45.8% AF recurrence over 12 months follow up (B)..... 235

Figure 45: Figure A: Biplane area-length method for LA volume measurements. Areas were measured in two chamber (Left panel) and four chamber (right panel) views at the ventricular end-systole (LA max) and end-diastole (LA min) with the exclusion of LAA and the ostia of the PVs. Figure B: Example of transaxial RA stack cines used to calculate RA volumes. RA endocardial borders were delineated in all slices in both ventricular end-systole (RA max) and end-diastole (RA min) with the inclusion of the atrial appendage and exclusion of the cava veins and the coronary sinus orifice 248

Figure 46: ROC analyses of RA max values (ml/m^2) at baseline and 6 months associated with AF recurrence..... 260

Figure 47: Kaplan-Meier survival curves predicting AF recurrence using RA max values measured at baseline (A) and at 6 months follow up (B)..... 261

Figure 48: Scar distribution (green rendering) based on 3D DE MRI scan, pre- and post-ablation. 281
Figure 49: High-frequency stimulation (60ms burst, 25mA current, and pulse width 2ms) of ganglionic plexus resulting in a response of asystole. 291
Figure 50: Ablation of Ganglionic plexi at the site of positive testing..... 291
Figure 51: Cardiac Compass showing patient activity and heart rate variability over 90 days 293
Figure 52: Digitization method of the graph with a minimum 600 dpi of the BMP images. 293
Figure 53: Comparison between CA and TSA with GP ablation for first-week post ablation296
Figure 54: Level of physical activity between CA and TSA for the first week..... 297
Figure 55: Scatter plot of heart rate variability and physical activity following ablation over the first week 297
Figure 56: Physical activity (PAC) between thoracoscopic surgical ablation (TSA) and catheter ablation (CA) over one year. 298
Figure 57: Heart rate variability (HRV) between groups over one year 299
Figure 58: Linear regression/correlation curve of Heart rate variability and physical activity between CA and the TSA. P = 4.6e-50..... 299
Figure 59: Heart rate weekly averages of day and night between CA and TSA 301
Figure 60: HRV assessment between patients who had targeted GP ablation as part of TSA compared to CA group and HRV differences between patients who had AF recurrence compared to patients who maintained SR..... 302
Figure 61: Bar chart showing the number of episodes of AF and the durations that those episodes lasted for patients who had an AF recurrence. CA - no GP ablation, TSA - with GP ablation. 303

LIST OF TABLES

Table 1: List of common significant side effects experienced by patients taking medications for AF..... 62

Table 2: Modified European Heart Rhythm Association (EHRA) score. 71

Table 3: Eligibility Criteria in the CASA-AF Trial..... 97

Table 4: Programming parameters for Reveal LINQ™ ILR..... 121

Table 5: Known Complications Associated with Ablative Procedures in CASA-AF Study..... 126

Table 6: Baseline characteristics of patients randomised to receive CA or TSA as part of the CASA AF RCT..... 132

Table 7: Procedure details for the index procedure for both TSA and CA groups 136

Table 8: Details of GP lesions in patients undergoing surgical ablation (median, IQR)..... 139

Table 9: Post-operative period prior to discharge following index procedure 140

Table 10: Serious adverse events and significant complications following CA and TSA during the follow-up period 150

Table 11: Quality of life analysis using AFEQT and EQ5D-5L to evaluate the effect of CA and TSA and the effect of rhythm..... 153

Table 12: EHRA score comparison between CA and TSA and the effect of rhythm during the baseline and followup of 12 months..... 154

Table 13: Comparison of baseline demographic characteristics and clinical data in the catheter ablation versus surgical ablation group. 186

Table 14: Changes in LA volumes and volume derived LA function in CA and TSA groups.. 188

Table 15: Comparison of LA volumes and function between the CA and TSA groups..... 190

Table 16: Comparison of LA volumes and volume-derived function in groups based on heart rhythm in follow up..... 192

Table 17: Comparison of LA volumes and volume-derived function between the SR and AF groups 194

Table 18: Univariable and multivariable logistic regression analysis of baseline parameters for the prediction of AF recurrence during follow up. 196

Table 19: Results of univariable and multivariable logistic regression analysis of the 3 months data for the prediction of AF recurrence during follow up. 199

Table 20: Baseline characteristics of patients in strain and strain rate analyses in groups based catheter ablation versus thoracoscopic surgical ablation 202

Table 21: Strain and strain rate measurements in CA and TSA treatment arm. The values are means ±SD..... 204

Table 22: Comparison of LA strain and strain rate parameters between the CA and TSA groups. The values are means ± SD..... 205

Table 23: Within group analyses of strain and strain rate measurements al all three study time points, based on heart rhythm in follow up. 207

Table 24: Comparison of LA strain and strain rate between the SR and AF groups at baseline, 3 months and 12 months following ablation. 209

Table 25: Univariable and multivariable analyses of AF recurrence and association with LA function measured by strain and strain rate..... 210

Table 26: Baseline characteristics of study participants in TDI analysis..... 216

Table 27**:** Within group analyses of LA TDI parameters 218

Table 28: Global LA function comparisons between CA and TSA 219

Table 29: Regional wall TDI measurements: comparison of CA and TSA treatment groups 222

Table 30: TDI regional measurements at different time points in CA treatment arm. 224

Table 31: TDI regional measurements at different time points in TSA treatment arm. 225

Table 32: Regional TDI measurements contrasting groups in SR and AF 226

Table 33: Regional TDI measurements in AF group (n = 35). 228

Table 34: Regional TDI measurements in SR group (n = 17) 229

Table 35: Within group comparisons of TDI measured parameters in patients remaining in SR and those with AF recurrence 231

Table 36: LA function analysed by TDI and its relation to clinical outcomes 232

Table 37: Univariable and multivariable analyses of LA TDI parameters and association with AF recurrence 233

Table 38: Baseline characteristics for patients randomised to CA or TSA with analysis of MRI data 251

Table 39: Within and between group measurements of atrial volumes, EF and reverse remodelling (mean ± SD) in CA and SA group 253

Table 40: Evaluation of atrial volumes, ejection fractions and reverse remodelling based on recurrence of AF. The values in the table are means ± SD. 255

Table 41: Univariable and multivariable regression analysis of cardiac structures associated with AF recurrence 257

Table 42: PV measurements (mm ± SD) showing within and between group comparisons 262

Table 43: PV sizes (mm ± SD) pre- and post-ablation grouped according to AF recurrence 263

Table 44: Proportion of scar tissue in LA at baseline and 6 months after ablation based on multi-view two task segmentation method 280

Table 45: Univariable analyses of data from patients in MRI scar assessment study and AF recurrence. LA scar measurements using both multi-view two task segmentation method (MVTT) and manual measurements (GT) are included for comparison..... 282
Table 46: Baseline characteristics of patients randomised to CA or TSA..... 295
Table 47: Heart rate variability of the patients who had GP ablation (TSA) compared to patients without GP ablation (CA) over the year and 1 week prior to AF recurrence. 302

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW OF ABLATION TECHNIQUES IN ATRIAL FIBRILLATION

1.1 ATRIAL FIBRILLATION AS A DIAGNOSIS AND DISEASE

1.1.1. DEFINITION AND CLASSIFICATION OF ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most frequent heart rhythm disturbance, affecting 1-3% of the population[1]. The prevalence of AF increases with age, from 0.5% at 40-50 years to 5-15% at 80 years[2-5]. With an ageing population, AF will affect an increasing proportion of the population, particularly in the developed countries [5-8]. In the United Kingdom(UK) alone, National Health Service (NHS) admissions have risen 60% over 20 years, with the total cost to the NHS of £2.2bn a year and projected to double by 2050[3,5,9,10]. Recent trends from North America also show increasing yearly admission rates for AF management including acute cardioversions which raise the costs and consume significant proportions of the allocated budget[5,11,12].

AF is characterised on examination by an irregularly irregular pulse due to irregular ventricular complexes and electrically on electrocardiogram (ECG) by loss of p wave signifying absent atrial contraction, resulting in loss of the late diastolic ventricular filling[13,14]. Thrombus can form in the atria in sinus rhythm in patients with advanced comorbidities resulting in lack of atrial contractility [15,16]. However, AF increases the risk substantially of thromboembolism resulting in stroke through the stasis of blood in the left atrium[15,17]. AF is currently defined as documented evidence either on ECG or recording devices of an episode greater than 30

seconds of continuous fibrillation of the atria [18-23]. The length of AF defines the subsequent categorisation, which is universally used as follows[18-21,24]:

1. Paroxysmal AF (PAF): AF terminating spontaneously or with intervention within seven days of onset.
2. Persistent AF: AF continuing for more than seven days.
3. Longstanding persistent AF (LSPAF): AF continuing for more than 12 months.

There are other definitions of AF depending on clinical presentations, aetiology and symptoms as described in the following definitions [18-21,25,26]:

- Lone AF: Used to describe AF without aetiology particularly in those who are less than 60 years of age. Lone AF is now not frequently used as the causes of AF are more readily detected with improving diagnostics including laboratory, imaging modalities such as echocardiography, high resolution computed tomography (CT), and cardiac magnetic resonance imaging (CMR).

- Early persistent AF: Duration of continuous AF of more than seven days but less than three months. Persistent is also referred to patients who require anti-arrhythmic drugs (AADs) or direct current cardioversion (DCCV) to remain in sinus rhythm (SR).

- Permanent AF: Continuous AF when the physician and the patient both feel that restoring sinus rhythm is not a reasonable approach, and AF is accepted. This terminology is not used when the patients are receiving AADs or ablation therapies to maintain sinus rhythm but are instead called persistent AF.

- Silent AF: This term refers to an opportunistic diagnosis of AF on ECG during routine assessments in non-symptomatic patients.

- Valvular AF: This term refers to AF related to valve replacements or more than mild mitral valve disease.

1.1.2 PATHOGENESIS AND RISK FACTORS FOR ATRIAL FIBRILLATION

Risk factors for AF are considered to be either non-modifiable or modifiable[27-32]. Over the last few decades addressing modifiable risk factors has an essential role in the management and prevention of AF recurrence before and after ablation[28-31].

Risk factors for AF onset and prevalence that are *not* modifiable include increasing age, a first-degree family relative with AF, gender, ethnicity, end-stage heart disease and non-operable valvular heart disease [18,27,30,33-39].

Modifiable risk factors for AF include increased body mass index (BMI), diabetes mellitus or impaired glucose tolerance, smoking, hypertension, lipid disorders, alcohol consumption, endurance training, congestive heart failure (CHF), thyroid abnormalities, sleep deprivation, and obstructive sleep apnoea [18,27,28,35,40-45]. Higher BMI correlated with increased risk of AF occurrence ranging between 4-17% in the Framingham Heart Study, Danish registry data and Women's health study[46-48].

Patients with impaired glucose tolerance or diabetes mellitus are found to have a greater prevalence of AF and reduced efficacy of ablation in patients who have poor glycaemic control from medications [49,50]. The AF incidence is not only due to direct effects of hyperglycaemia effecting the neurohormonal systems but also from structural remodelling in the atria[49,51,52].

Smoking has been linked to AF and multiple other risk factors such as hypertension, premature atherosclerotic disease although the precise mechanism is not entirely understood. Active smoking or being an ex-smoker has been linked to AF incidence and prevalence in the community as described in the Rotterdam study [53-55]. Smoking is also an independent risk factor irrespectively of other coexisting risk factors for adverse events such as bleeding in patients with nonvalvular AF [56]. Second hand smoking has also been shown to be associated with an increased risk of AF as shown in a population-based case-control study [57]. Reduction of smoking and cessation leads to reduction in AF and reduction of adverse events including stroke, and other cardiovascular events [58].

Hypertension leads to long-term changes in the cardiovascular system including changes in the heart such as left ventricle (LV) hypertrophy resulting in diastolic impairment, enlargement of atria propagating AF [59] and is implied as one of the major risk factors for stroke in elderly patients with AF [60]. Hypertension usually coexists with other risk factors such as diabetes mellitus, lipid disorders and endocrine disorders, resulting in end organ damage from combination of microvascular and macrovascular complications.

The combination of some of the frequently recurring risk factors are well known to be a cause of adverse events in AF such as stroke and are used in risk stratification for thromboembolism such as the $CHADS_2$ and the CHA_2DS_2VASc score [61-65].

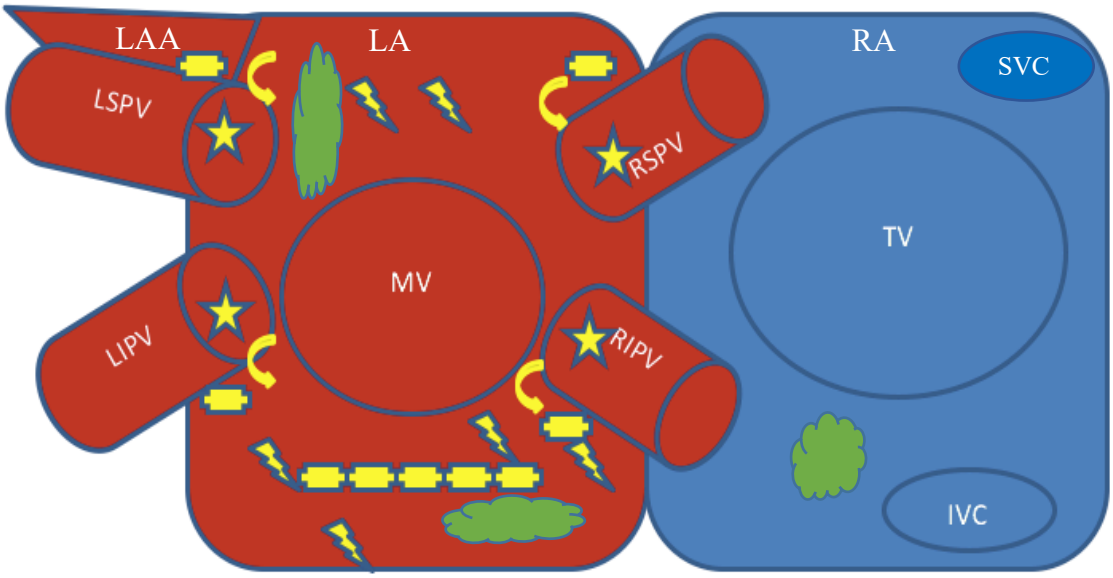
Alcohol consumption beyond recommended quantities leads to higher incidence and maintenance of AF as seen in the Copenhagen City Heart Study[27,66]. The exact mechanism of how alcohol causes increased frequency of AF is not clearly understood, although long-term high levels of alcohol consumption can cause dilated cardiomyopathy resulting in atrial dilation which can cause arrhythmias. Proposed mechanisms revolve around electrophysiological changes in atria and autonomic nervous system with increased activity and oxidative stress from coexisting conditions such as diabetes mellitus as summarised by Suzuki [67]. Alcohol intake combined with other risk factors, such as smoking and hypertension, has a dose dependent relationship once consumed at greater than 1.5 units per day as described in a meta-analysis by Kodama et al. in 2011[68]. Increased risk of bleeding is also seen in patients who have moderate or higher consumption of alcohol and receiving anticoagulation for prevention of thromboembolism [69-71]. Reduction or abstinence from alcohol in patients with confirmed PAF or persistent AF leads to reduction in arrhythmias recurrences as shown in a randomised study by Voskoboinik et al. [72].

Optimisation of heart failure by medications and cardiac devices such as cardiac resynchronisation therapies has been shown to help manage AF and, in some cases, prevent onset of AF [73].

Maintaining a healthy lifestyle is shown to be protective from new onset AF as described by Larsson et al. in a cohort study of 72390 patients. Healthy lifestyle was defined as BMI <25kg/m^2, regular exercise >20min/day, alcohol consumption <2 drinks/day for men and <1 drink/day for women and being a non-smoker[74].

1.1.3 MECHANISMS OF ATRIAL FIBRILLATION

The first mechanism of AF initiation by pulmonary vein(PV) ectopy was described by Haissaguerre et al. in 1998[75]. Since then many hypotheses have been proposed as more research shows increasing complexities perpetuating for AF initiation, progression and maintenance of AF via triggers, rotors with fibrillatory propagation, macro and micro re-entrant circuits within the atria or endo-epicardial connection and autonomic regulation through ganglionic plexi (GP) shown in Figure 1[18,21,76-78].



	Ganglionic Plexi
	Re-entry circuits into pulmonary veins
	Ectopy in the atrium
	Pulmonary vein ectopy
	Macro and micro entry circuits associated with scars

Figure 1: Schematic diagram of the right and left atrium illustrating mechanisms of initiation and maintenance of AF in the left atrium and associated pulmonary veins

Footnote 1: IVC – inferior vena cava, LA -left atrium, LAA – left atrial appendage, LIPV – left inferior pulmonary vein, LSPV – left superior pulmonary vein, MV – mitral valve, RA – right atrium, RIPV – right inferior pulmonary vein, RSPV – right superior pulmonary vein, SVC – superior vena cava, TV – tricuspid valve

The mechanisms of AF maintenance are multiple and described in several different models: tachy-paced AF model, the CHF model of AF, atrioventricular (AV) node block AF model and autonomic driven AF [79-84]. These models showed an easy induction and maintenance of AF in animals, with longer durations of AF associated with atrial scar. Histology of the atria and ventricular myocardium showed diffuse interstitial changes, including myofilament fragments and mitochondrial disruption which was not seen in the healthy control [85].

Tachycardia paced AF model was created by pacing atria of dogs which resulted in atrial electrical remodelling with reduced atrial effective refractory periods, reduced conduction in the atria, and sinus node dysfunction resulting in initiation and maintenance of AF [82]. Heart failure AF model did not show a change in the atrial effective refractory period suggesting that the AF was likely due to the cause of the underlying mechanical dysfunction associated with CHF[86]. The pacing models have allowed for targeted therapies to be considered such as the Connexin 43 gene transfer therapy that prevents AF in pigs treated with Adenovirus encoding for Connexin 43[87]. The AV node block model used in goat, along with persistent AF model with rapid atrial pacing was compared to controls. Comparison between these models showed an increase in the LA size and reduced LA contractility due to reduction in action potential duration secondary to reduced inward calcium current and reduction in sarcoplasmic reticulum calcium load resulting in atrial myofibrillar remodelling [84].

Prior to initiation of AF and soon after, the atria undergo structural and electrical changes resulting in LA dilation, increased action potential duration, and reduced atrial contraction

called atrial remodelling [88]. Structural changes with dilation of the atria occurs not only by volume overload but also by increased left atrial (LA) pressure due to obstruction from mitral valve disease or obstructive pathologies in the LV such as hypertrophic cardiomyopathy, hypertensive heart disease, infiltrative cardiomyopathies[89,90]. Biochemical and hormonal changes also take place at the cellular level with an increase in atrial natriuretic peptide, angiotensin II, transforming growth factor-beta, platelet-derived growth factor, and release of inflammatory mediators. Inflammatory mediators include interleukins, cytokines, and C-reactive protein. These processes at the cellular level also promote atrial fibrosis[91-93]. Structural and electrical changes include atrial stretch and accompanying fibrosis from the biochemical changes resulting in a very complex substrate that allows for initiation and continuation of AF [94,95]. Atrial remodelling can occur well before the onset of AF and persist following the restoration of SR [96]. The rate of atrial remodelling can progressively worsen depending upon the underlying cause of AF such as diastolic dysfunction, ischemic heart disease, and valvular heart disease if left untreated. Electrical remodelling occurs quickly within days while the structural remodelling can take a few months. The chronicity of AF invariably leads to significant electrical and structural remodelling of the atria through progressive dilatation with or without accompanying fibrosis [97,98].

1.2 SYMPTOMS OF ATRIAL FIBRILLATION

Patients with AF present with a broad spectrum of symptoms due to the frequency of AF episodes and fast ventricular rate in response to AF[6,99,100]. The rapid ventricular rate during periods of AF is the predominant reason for patients to have symptoms [101,102]. Dyspnoea at

rest or exertion, leg swelling, and signs of CHF usually accompany AF with a fast ventricular response. Mild to severe CHF symptoms can accompany AF particular in settings with concomitant heart disease such as angina or valvular heart diseases particular mitral and aortic valve diseases[103-105]. CHF due to the above can affect the cardiac output and its secondary effect on other organs such as kidneys resulting in acute or chronic kidney disease, hepatic congestion, thromboembolism resulting in a stroke, intestinal ischemia, limb ischemia and ischemia to other vital organs[6,7,21,106,107].

Most patients with PAF do not tolerate the acute onset of symptoms and seek the attention of the closest physician such as the family doctor or accident and emergency departments. Patients can also be asymptomatic or have mild forms of symptoms, mainly in the elderly due to reduced exertion in daily routine[108]. AF incidence rises with age, and in the elderly, most of the patients unknowingly perceive their symptoms to be part of ageing and not AF[100]. Asymptomatic patients can be picked up incidentally during routine health checks, health checks in preassessment clinics for another procedure and recently more readily with advanced self-monitoring smart devices such as watches[109-113]. Some patients first get diagnosed with AF during a significant life-threatening event such as a stroke, myocardial infarction (MI) or an admission for acute CHF[114-118].

Endocrine disorders such as hyperthyroidism, adrenal glands/kidneys (pheochromocytoma, primary aldosteronism, hypercalcemia), metabolic syndrome can be associated with AF and cause symptoms such as alternating body weight, tremors, sweating, seizures, and blood pressure (low or high) abnormalities [119-121]. Generalised fatigue, mild leg swelling, reduced exercise tolerance and psychogenic symptoms can be present with patients who have

longer forms of AF such as LSPAF[122,123]. Most of the patients also exhibit symptoms from side effects of medications such as fatigue and breathlessness[124-126]. For the reasons mentioned above, more definitive therapeutics of AF are continuously evolving and being developed to understand mechanisms of AF, test current therapies available and invent new strategies for maintaining sinus rhythm [127-130] .

1.3 TREATMENT OF ATRIAL FIBRILLATION

There are two principal therapeutic strategies for AF: rhythm control and rate control. Rhythm control is preferred in symptomatic patients, especially younger, more active patients with symptoms *despite* adequate rate control. Traditionally, rhythm control is attempted with AADs and DCCV. Long-term efficacy of AADs is reduced, and they are associated with side-effects and the risk of pro-arrhythmia [7,20,131-136]. Subsequently, there has been an increasing incentive to have more invasive strategies than just pharmacological options for AF management.

1.3.1 RATE CONTROL

Symptoms driven by AF are mostly palpitations, breathlessness, light-headedness, syncope, and angina reflective of a fast-ventricular rate response [137,138]. Rapid control of the ventricular rate response to AF can be achieved by using certain drugs in the Vaughan-Williams classification particularly good at quick atrioventricular node blockade such as ß-blockers (BB), digoxin and calcium channel blockers (CCB) [137-140]. Both these agents are the

most common agents aimed to reduce ventricular response to high atrial rates and used long-term for rate control in persistent AF and LSPAF [139,141-143].

In the elderly population, sometimes rate control strategy is limited by advancing conduction tissue disease resulting in patients having periods of bradycardia due to poor AV node conduction and at other times result in tachycardia due to AV node recovery leading to heart failure if left unchecked[144-147]. This can lead to significant increase in presentations to emergency departments with presyncope and falls from bradycardia or alternatively with congestive heart failure (CHF) from poorly controlled ventricular rate response to increased AV conduction[148-151]. In these instances, implanting a pacemaker to prevent bradycardia and allowing for more aggressive pharmacological suppression of the AV node has been shown to have favourable long-term outcomes particularly in the >60years old population [149-153].

The improvements in pacing techniques resorting away from RV apical pacing to HIS bundle pacing, left bundle branch area pacing (LBBAP) and cardiac resynchronisation therapy (CRT) has shown to maintain LV function and prevent heart failure during medium to long-term follow up[151]. In patients with heart failure and persistent or permanent AF, CRT and AV node ablation were superior to optimal medical therapy as demonstrated in the APAF-CRT trial reported by Brignole et al. in 2018[154].

1.3.2 RHYTHM CONTROL- CARDIOVERSION

Rhythm control can be achieved by using either chemical cardioversion with medications such as flecainide, propafenone, amiodarone, dronedarone and vernakalant [155,156]; *or* by

using DCCV in patients who are acutely symptomatic[155]. Landiolol has recently been tried to prevent AF post operatively and is shown to be cost effective compared to conventional betablockers / Beta adrenoceptor antagonists (BB/ß-blockers)[157,158]. Although rhythm control strategy is preferable, it appears to be difficult to maintain using pharmacological therapies or with electrical cardioversion during long-term follow up and with significant life-threatening side effects of the medications.

1.3.2.1 ELECTRICAL CARDIOVERSION

Electrical cardioversion is achieved by delivering electricity in the form of direct current (DCCV) to the myocardium [159,160]. Two pads that are good conductors of electricity are applied to the skin opposite to each other to allow for current to travel in one direction (uniphasic cardioversion) or two directions (biphasic cardioversion) [161]. Factors that affect the success of cardioversion include chest wall impedance (lung volumes, pulmonary congestion, fat, hair) and myocardial thresholds [161-163]. Myocardial thresholds can be altered due to electrolyte imbalances, myocardial injury from coronary ischemia and medications that affect the action potential [162,164]. In a recent study, if patients can tolerate being in AF acutely, then most of them do not need to be cardioverted electrically or chemically as PAF will terminate in at least 90% of the cases[155,165].

1.3.2.2 CHEMICAL CARDIOVERSION

Chemical cardioversion is the restoration of sinus rhythm by giving medications via the oral or intravenous route to allow for a chemical to affect the action potential of myocardial

activity and suppress mechanisms of atrial or ventricular arrhythmias [18,166-168]. Medications that are frequently used to achieve chemical cardioversion include class 1 and class 3 anti-arrhythmic medication of the Vaughan classification [18,169-171].

Atrial arrhythmias are usually cardioverted using Flecainide if the ventricular function is normal, or Amiodarone if there are doubts about ventricular function[170,172,173]. Flecainide is short-acting and has a faster onset and therefore, can be used effectively in emergency departments [166,167,171].

Amiodarone has a more prolonged onset and longer-lasting effects and is dose-dependent. It is the preferred choice in achieving and maintaining SR over more extended periods or in difficult to control arrhythmias post ablation [174-178].

Vernakalant has been described as an atrial selective antiarrhythmic drug used in symptomatic patients with AF duration of fewer than seven days[156,179,180]. A small study showed Vernakalant to be quicker and safer than Flecainide in reverting patients to sinus rhythm[171,181].

1.3.3 ABLATION TECHNIQUES

Interventional treatments (surgical or catheter) have evolved over the years and nowadays allow reliable clinical success in treating PAF, albeit with repeat procedures necessary in a proportion of patients [18,182,183]. However, the best strategy for achieving long-term SR in

symptomatic patients with LSPAF is not achievable despite different ablation strategies targeting currently known mechanisms of AF initiation and maintenance[184-191].

1.3.3.1 RADIOFREQUENCY ABLATION

Pharmacological rhythm control strategy in AF management aims to restore and maintain SR [18,19,177]. However, AF recurrence, side effects of antiarrhythmic drugs, and risks of pro-arrhythmia may offset the benefits of this treatment [132-135,192]. Consequently, there have been increasing efforts to develop non-pharmacological methods to treat AF patients, such as percutaneous catheter ablation (CA) and thoracoscopic surgical ablation (TSA). Since the discovery of PV triggers for the initiation of AF, isolation of the PVs is a cornerstone for all ablation procedures described more than two decades ago [193-201 202]. However, despite efforts to improve the targeting and delivery of CA, the success rate for a single procedure is just 30-50% at five years follow-up [193,203-206].

Radiofrequency ablation (RFA) technology results in heat production at the tip of the conductive catheter resulting in tissue damage at the level of contact [207]. Catheters are delivered to the target tissue by the venous system return to the heart, most commonly through femoral veins. In rare cases, other venous accesses are required to get specific catheters into awkward positions such as the coronary sinus[208].

The LA is approachable by creating a small puncture in the intra-atrial septum using a transseptal needle, SafeSept® transseptal puncture wire, or radiofrequency based transseptal puncture set [209-215]. Catheters typically used in the left atrium create a 3D

geometry of the LA and simultaneously collect other information like LA volume and local voltage of the atrial myocardium[18,216-220]. To create 3D geometry, other imaging modalities like CT or CMR can be performed prior to the procedure upon which a fast anatomical mapping (FAM) can be created to reduce procedure time[221].

In AF ablation, irrigation catheters are commonly used with and without contact force technology such as Thermacool Smartouch® ablation catheters (Biosense Webster, Irvine, CA, USA)[222-225]. The contact sensing technology allows the operator to ensure enough contact is applied to the atrial tissue in order to deliver adequate energy creating a transmural lesion [18,221,226-230]. Higher contact force applied to tissue during electroanatomical mapping and ablation results in poor correlation of mapping surface with other imaging modalities like CT or cardiac ultrasound to delineate anatomy as the sampling surface is pushed away when >5grams of contact force is applied during mapping [221]. Therefore, understanding of limitations to the 3D electroanatomical maps and use of 3D radiological reconstructions from CT or CMR is important in planning of procedure and during the time of the ablation due to shift in anatomy [221].

Although pulmonary venous isolation (PVI) was initially described to be successful in treating PAF, more procedures are also being performed for symptomatic persistent and LSPAF patients. In persistent and LSPAF cases, the frequency of AF recurrence following ablation remain high despite PVs being isolated during redo CA electroanatomical mapping (EAM) suggesting another trigger of AF[231-237]. Subsequently, linear lesions along the roof, isolation of posterior wall, mitral isthmus line, exclusion of left atrial appendage (LAA) and

complex fractionated atrial electrograms (CFAE) have been identified as suitable targets to terminate AF [238-245].

1.3.3.2 CRYOABLATION

Cryoablation first evolved from animal studies, where it shows that surrounding tissue damage and distortion is minimal [246,247]. In humans, cryoablation was first used to ablate the AV node [248,249]. This technique depends on the delivery of the cooling agent, nitrous oxide, to the tip of a closed catheter resulting in ice formation opposed to the atrial tissue. The cooled tip causes local cellular damage resulting in cell death and scar formation [248].

Cryoablation for AF was tested first in patients having surgical procedures for valvular repair, coronary artery bypass grafting (CABG), with concomitant AF [250-252]. Improved efficacy and safety from cryoablation led to the development of the Arctic Front™ generation series of cryoablation balloon (Medtronic, Minneapolis, USA)[253-258]. The delivery of cooling is along the surface of the balloon in contact with the atrial tissue for range of 150 to 230 seconds as shown in the Cryo Dosing study resulting in circular lesions around PVs ostia [253,256,259,260].

Improving safety and success with cryoablation has led to consideration of offering cryoablation as first line against AADs [261]. AF recurrence following ablation and limitations of cryoablation are numerous gaps seen during redo ablation procedures and inability to easily create linear lesions sets due to lack of contact force feedback in cryoablation catheters at the moment[262,263].

The efficacy of cryoballoon ablation has been tested in PAF, but small studies have reported this technology to be successful in patients with persistent AF [256,259,264,265]. Tondo et al. (2018) enrolled 486 patients(persistent AF = 434, LSPAF = 52) in a prospective study and Sawhney et al. (2020) enrolled 609 patients (persistent = 487, LSPAF = 122) from a multicentre European study showing optimistic results with cryoablation in persistent AF and LSPAF reported to be successful in 63.9% and 57.1% respectively using office based ECG during 3-monthly follow-up [266,267].

1.3.3.3 MINIMALLY INVASIVE THORACOSCOPIC SURGICAL ABLATION

Open heart surgery advancements and in-depth understanding of the anatomy led to cardiothoracic surgeons developing a minimally invasive thoracoscopic cardiac surgical procedure for single by-pass grafts and single valve interventions performed in animal models [268]. In humans, minimally invasive and video assisted surgical ablation started with excision of lung cancerous lesions, and subsequently to operate on by-pass grafts, valvular surgery and epicardial ablation for concomitant AF patients [269-274].

TSA is now performed in specialised tertiary centres with high volume of thoracoscopic cases and early learning curves for all thoracoscopic cases seen usually in the first 20 cases[275]. TSA has shown higher long-term success rates for a single procedure but this comes with a procedural significant adverse event rate of 15-25% particularly phrenic nerve palsy in 4-6%, pneumonia 5-10%, pacemaker insertion1-4%, and rarely bleeding or cardiac perforation requiring sternotomy in 0.5-2.5% [191,276-281].

TSA lesion sets evolved from open surgical procedures performing a "cut and sew" strategy adapted from the Cox-Maze series of procedures to deliver lesions by scar formation creating a line of isolation between the LA and PVs [282,283]. Video-assisted TSA offers an option for ablation in patients where open-heart surgery is not required [272,284,285]. The video-assisted TSA allows for bipolar RFA technology advancements into surgical cases to deliver epicardial lesion sets along with epicardial GP ablation and LAA ligation in PAF, persistent AF and LSPAF [281].

The results from TSA studies conferred its efficacy in treating all classes of AF but with a higher degree of complications and reduced quality of life indices compared to catheter RF ablation with no differences in mortality[286-289]. Despite the higher degree of comorbidities related to recovery, there have been promising results with TSA showing significantly better short-term and long-term results compared to catheter ablation in all forms of AF[191,286,290,291]. During recovery from TSA, the pericardium and regions of ablation heal with adhesions and therefore, a repeat procedure for AF recurrences can only be catheter ablation at this stage which has paved the way for hybrid ablation strategies currently in development.

ADVANTAGES OF MINIMALLY INVASIVE THORACOSCOPIC SURGICAL ABLATION

The following are some of the advantages of TSA according to the literature [191,284-286,288,292-294]:

1. Improved visualisation of regions of interest:

TSA has the main advantage to visualize areas where RF ablation will be performed directly using video assisted equipment. The lungs are decompressed and pushed out of the field of view by positive pressure from carbon dioxide pumped through ports into the chest cavity. 3D mapping systems are not required, and linear lesions can be created more easily with contiguous lines.

2. Transmural and complete lesion sets:

   The bipolar radiofrequency clamps are capable of delivering high energy between the two poles of the clamps and create transmural lesions. Bipolar ablation pens are capable of creating extensive transmural lesions and also sensing electrical tissue activity. The sensing and pacing feature of the bipolar ablation pens is used to test for entrance and exit blocks at the veins and around linear lesion lines by pacing inside regions of block and checking for atrial capture.

3. Isolation of left atrial appendage (LAA)

   LAA can be electrically and mechanically isolated using a specialised clip delivered, by an extension of incision in one of the ports on the left side to allow for the larger size, over the stump of the LAA to its base. It is guided by simultaneous transoesophageal echocardiogram (TOE) to ensure the entire base of the LAA is excluded.

LIMITATIONS OF MINIMALLY INVASIVE THORACOSCOPIC SURGICAL ABLATION

Several limitations of TSA were reported in the literature [191,284-288,294,295].

1. Invasive nature of the procedure:

   TSA is less invasive than open-heart surgery but is more invasive than CA. It requires three ports on each side of the chest along with mini-thoracotomy for delivery of LA clip. The result of 6 incisions is a higher risk of infection and longer recovery time in hospital (5 -7 days) and post-op recovery can last up to 30 days.

2. Higher complication rates:

   Due to its invasive nature, there are increased risks of complications such as phrenic nerve damage, surgical emphysema, pneumothorax, pleural effusions requiring intervention, infection, myocardial damage requiring sternotomy in life-threatening situations.

3. Inability to locate lesion gaps:

   Despite contiguous line appearance, there are situations when gaps are present and identifying those is not possible. The isolater pen head, 20mm x 10mm in dimension, has two pace and sense electrodes that might not be in approximation to the area of interest and sense or pace inappropriately. However, gaps in lesion sets can be checked by performing an epicardial electrophysiology (EP) study using a decapolar EP catheter and EP mapping system.

4. Pericardial adhesions

   Freedom from pericardial adhesions is essential for the procedure to complete without complications. Hence, any pericardial inflammation in the past results in adhesions that do not allow for the procedure to complete. Similarly, surgical ablation

can only be performed once due to the development of pericardial effusions leading to adhesions after closure of pericardiotomy.

1.3.3.4 HYBRID ABLATION

Hybrid ablation is a combination of TSA and CA. The two procedures are performed either simultaneously or within few weeks apart called staged hybrid procedure[184,185,296-298]. Current guidelines include hybrid ablation procedures for the management of AF as class IIb level of evidence as being moderate [299-301]. The delivery of hybrid procedures is dependent upon excellent communication and teamwork between cardiologists and cardiac surgeons. The TSA procedure delivers lesions first, and the cardiologists then apply lesions to any gaps found after EP testing. This combined approach ensures that the surgical lesions have been tested over time and integrity ensued[302].

ADVANTAGES OF SIMULTANEOUS AND STAGED HYBRID PROCEDURE

The following are the advantages of a hybrid procedure for AF ablation [184,185,297-299,302-306]:

- PV reconnection is present in reported rates of 77-87%, 70% on the roofline, 40% on the floor after three months following surgical ablation. Identification of the gaps in lesions and closing those with CA will ensure completeness and longevity of the isolated lesion line.

LIMITATIONS OF SIMULTANEOUS AND STAGED HYBRID PROCEDURE

- There is significant oedema following surgical ablation, and catheter testing can yield a false sense of PV isolation.
- Staged hybrid programmes require patients to be admitted twice for the procedure.
- The other limitations are similar to the TSA and CA limitations mentioned above.

1.3.3.5 COX-MAZE SURGICAL PROCEDURE

Cox surgical procedure was developed in 1991 by Cox JL et al. as a definitive surgical method to treat AF [282]. Initially, Cox I and II procedures resulted in significant LA dysfunction, longer procedure times, and other unexpected arrhythmias. Cox III procedure shortened the procedure time, had fewer complications and higher maintenance of SR in more than 90% of patients over five years follow up [282,307-310]. Over the years, Cox procedure has evolved to Cox-Maze with use of lines to complete lesions sets to isolate PVs and modify LA substrates responsible for AF. It is also associated with fewer complications [308]. Currently, the Cox-Maze IV procedure is the full set of surgical lesions for the treatment of AF. The cox-maze procedure has been adapted for delivery through thoracoports to reduce the burden of complications but deliver the full set of lesions [275,311].

1.4 SIDE EFFECTS OF MEDICATIONS

Side effects of medications are due to multiple factors including long term usage, allergies to compounds, excessive mechanism of actions in individuals, and side effects noted by

manufacturers during phase 1 and phase 2 trials of safety. The long term side effects of medications depend on the class and mechanism of action. Common side effects are listed below in Table 1[312-318].

Table 1: List of common significant side effects experienced by patients taking medications for AF.

Beta-blockers	Fatigue; Negative chronotropic effects – sinus bradycardia, AV node block; Increased airway resistance; Exacerbation of peripheral vascular disease; increased hypoglycaemia episodes; depression, sexual dysfunction, hypotension
Calcium channel blockers	Leg swelling, hypotension, constipation, rash, nausea, flushing, drowsiness
Amiodarone	Nausea, vomiting, constipation, weight loss, fatigue, pulmonary fibrosis, heart block, liver injury, thyroid function abnormalities
Digoxin	Nausea, vomiting, renal impairment, digoxin toxicity
Flecainide	PR and QRS duration prolongation, dizziness, headache
Propafenone	Constipation, diarrhoea, dizziness, anxiety, palpitations, metallic taste, dyspnoea, depression, dry mouth, fatigue, nausea

Footnote 2: Some of the effects are from alterations in the electrophysiological properties of the agents on the sinus node, AV – atrioventricular node, and HIS Purkinje system resulting in slow conduction over the effected conduction system

1.5 ATRIAL FIBRILLATION AND ITS IMPACT ON HEALTH SERVICES

1.5.1 COST OF MEDICATIONS

Cost of medications reduces over time once trade licences convert to a generic production of medications, thus improving overall costs of managing AF [319-321]. ß-blockers, CCB, sotalol, amiodarone, propafenone, flecainide amongst other commonly used medications for rate and rhythm control have been available for many decades. For the management of AF, these medications are cheap and readily accessible [192,322-326].

The development of new strategies of managing AF with new oral anticoagulants (NOAC) such as direct thrombin inhibitors or factor Xa inhibitors has been a game-changer over the last decade [327]. Despite being costly under patented licences, they have markedly reduced venous thromboembolism resulting in reduced costs of managing AF overall [328,329].

The costs of long term medications add to their non-desirable side effects and further increase the costs of AF management through hospitalisations, the need for pacemakers, lymphedema, the advancement of renal disease, and significant lethargy [330-332].

1.5.1.1 ß-BLOCKERS

ß-blockers are widely used in the management of AF. The role of ß-blockers is predominantly to reduce AV node conduction, thereby reducing the ventricular rate and improving symptoms of palpitations and CHF. Sometimes ß-blockers can convert AF to SR. This only appears to work in patients with AF driven by high levels of adrenergic stimulation which increases intracellular Ca^{++} that results in action potential after-depolarisation [333].

1.5.1.2 CALCIUM CHANNEL BLOCKERS

CCB has into two classes: the dihydropyridine (DHP) group and non-dihydropyridine (NDHP) group [334]. DHP class is used predominantly for hypertension. NDHP class has two agents, verapamil and diltiazem. The two classes have a similar action on blood pressure but different effects on heart rates. NDHP class is useful in treating angina and arrhythmias in the setting of normal LV function [335]. The safety in reduced LV function is not well established due to negative inotropic properties of NDHP resulting in worsening CHF particularly in the setting of arrhythmias with fast ventricular rate responses such as new-onset atrial flutter and AF [139,142,335]. In the rate control strategies, ß-blockers and CCB have shown similar rate control properties at 30 days with similar readmission rates to hospitals[138,334]. CCB are not costly and are preferable for rate control strategies in patients who are intolerant of BB therapies.

1.5.1.3 AMIODARONE

Amiodarone is a potent class III antiarrhythmic used in the management of AF for many decades. Although it is mostly used for a limited time due to side effects from prolonged use such as liver, thyroid and skin reactions, it has been a mainstay for rhythm control strategy before the era of ablation and in persistent AF management.

1.5.1.4 ANTICOAGULATION

Anticoagulation is one of the most important aspects of AF management to reduce number of strokes, disabilities and overall costs to the healthcare as a result of complications of AF[336-344]. Anticoagulation has regularly been done with warfarin for many decades, and despite its low cost as a medication, there are associated costs from adverse events and necessitating the need for an anticoagulation clinic. The anticoagulation clinic is responsible for accurate dosing of the warfarin according to the most recent international normalised ratio (INR) reading. INR is a laboratory measurement of the time it takes for the blood to clot and requires laboratory testing of millions of patients worldwide on a regular basis. Despite the regular laboratory analysis, patients can run in subtherapeutic ranges resulting in thromboembolic events leading to increased comorbidity and higher healthcare utilisation[345-347]. Anticoagulation advancements recently with introduction of new oral anticoagulants (NOACs) have made them more expensive than warfarin to purchase, but allowed for markedly reduce monitoring and reduction in overall healthcare costs by reducing anticoagulation clinics, reducing comorbidities from thromboembolism related to its steady-state in blood [331,348-357]. Warfarin still is a useful medication to use in cases where NOACs are currently not licensed for use such as prosthetic valves, or with patients with reduced renal clearance [358].

1.5.2 COST OF ADMISSIONS, VISITS TO HOSPITALS AND PHYSICIANS

Cost of recurrent admissions to hospital is exponentially rising around the world due to increasing disease incidence and burden secondary to comorbidities [11,359]. The push towards

the early restoration of SR has caused physicians to be more aggressive in managing AF with cardioversion, either chemically or electrically [360]. In patients known to have PAF, there is evidence that the majority will self-revert back to SR with no intervention apart from rate control strategy [155]. The rate of AF recurrence is also similar to early cardioversion versus delayed cardioversion unless patients are very symptomatic [155]. The incremental costs of recurrent hospitalisations due to poorly controlled heart rate or for early rhythm control strategies is taking its toll with large proportions of allocated budgets going towards this disease alone [11]. Impact of poorly controlled AF results in CHF with further consequences not only on costs of management but on levels of comorbidity and mortality [361]. Recent changes with improved anticoagulation strategies such as direct oral anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban) resulted in the reduction of the overall costs of AF due to fewer hospitalisations for bleeding, acute strokes, and costs of anticoagulation services [107,327,330,332,362-371].

Strokes can be devastating for individuals and their families if they are left with significant neurological deficits or if they die from stroke [2,107]. Hospitalisations due to stroke rise in patients with increasing $CHADS_2$ (congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke/transient ischemia attack/thromboembolism – double score) and CHA_2DS_2VASc (congestive heart failure, hypertension, age _75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category) score as a result of procoagulant state in LA due to AF. Increasing the duration of AF raises the risks of a procoagulant state. The use of anticoagulants can decrease stroke risk and result in reduced hospitalisations. Major trials such as ARISTOTLE, RE-LY, ROCKET-AF amongst others, compared the use of apixaban,

dabigatran and rivaroxaban respectively to warfarin in a randomised fashion and found them to be cost-effective and non-inferior to warfarin [327,364,365,372-376].. Incidence of thrombogenic stroke is 380 per 100000 and rising due to changes in patients' characteristics such as LA size, LAA dimensions, length of AF, and age [377]. The resultant in-hospital mortality in strokes can be as high as 8% due to factors such as inappropriate levels of anticoagulation or no anticoagulation [378]. Costs related to anticoagulation can be reduced by allowing more informed care decision and considering rivaroxaban, as compared to warfarin, early in the treatment of non-valvular AF can save up to $8746 over 100 days following implementation of nurse practitioner services[353,354].

Hospitalisation rates can be due to either known AF or new-onset AF following proarrhythmic states such as septicaemia, kidney disease, alcohol, cardiac surgery or endocrine disorders such as thyrotoxicosis [379-382]. Hospital costs from initial admission and readmissions can be very costly due to treatment in the cardiac care unit, intensive care units and can run in thousands of dollars per patient per day [332,383-387]. The implications of AF and its associated complications such as thromboembolism and heart failure are not limited to hospitals only, but also the nursing homes, rehabilitation centres and other medical facilities resulting in multifaceted utilisation of healthcare resources [332,388].

If rhythm control strategy is considered by an ablation strategy, then procedure related complications such as vascular injury, pericardial effusion or tamponade, acute thromboembolism, bradycardia, AV node block, and complications of anaesthesia can also lead to prolonged hospitalisations [371,389,390].

1.5.3 COSTS OF GENERAL PHYSICIANS VISITS

In 2008, there were 851,095 visits to the general physician office in the USA according to the Office of Health Economics, and the frequency of visits is similar for the population in other health authorities [388,391,392]. Patients with a primary and secondary diagnosis of AF accounted for 5.7 million bed days. A large percentage of patients diagnosed with AF visit their local medical facilities on average of once a year and account for greater than 850,000 visits to general physicians and 5.7 million bed days [332,368,388]. These costs do not account for anticoagulation options with warfarin or NOAC. Cost analysis of NOACs against warfarin are favourable due to cost reduction of visits, no maintenance blood sampling requirements and reduction of patent costs over time [327,364,391]. Costs can be more efficient with changes in practices such as performing procedures under general anaesthesia (GA) as opposed to sedation [393].

1.5.4 COST OF PROCEDURES

1.5.4.1 RADIOFREQUENCY ABLATION

The costs of procedures are variable across the globe due to various health systems and funding from either public allocations or private insurance companies [394-397]. In the UK NHS, the cost of the procedure is a tariff set out by the Care Commissioning Group (CCG). These tariffs change regularly and are reviewed based on what the providers are offering to individual trusts.

The cost of a single RFA in USA, Germany and the UK are around $14 291, € 9505, £ 5622 respectively [398]. It Is important to recognise the cost effectiveness models are not only important for short-term symptomatic relief from AF but also aimed for long-term effectiveness and improvement in quality-adjusted life-year (QALY) over a lifetime.

In an Australian model of healthcare mirrored to the healthcare in the UK, effectiveness of medical therapy was inferior compared to CA to alleviate AF-related symptoms but with higher costs for each QALY gained[397]. Evaluation of CA over 5 year time horizon suggests that the procedural success should be greater than 70% for it to be considered cost-effective[399]. Over the last 10 years, catheter ablation has become more safer with advances in mapping and ablation technologies leading to quicker discharges, and in some centres, same day discharges[400].

1.5.4.2 CRYOABLATION

The cost of cryoablation is higher as the technology is new and patented by Medtronic [253,401]. The new technologies of cryoablation such as Arctic Front ™ balloon (Medtronic, Minneapolis, USA) are becoming more effective in the management of AF and less expensive [398,402,403]. Cryo-balloon ablation is used primarily for PAF and not for persistent and LSPAF [404]. The cost-effectiveness of cryo-balloon ablation is similar to RF CA, but cryoablation is a shorter procedure with similar success rates at two years follow up [402]. The costs of cryo-balloon ablation cannot be replicated in all systems, and the procedure can sometimes be more expensive due to the need for redo catheter ablation soon due to gaps in the lesion sets [405].

Review of different healthcare models such as Germany, UK and USA currently favours cryoablation to be more cost-effective, €640, £364, and $925 less respectively, compared to catheter ablation in the follow up period of 1.5 years[398]. Cost effectiveness analysis over 10 year horizon has suggested that cryoablation is more costly compared to RF CA at the time of procedure and also during follow up as reported by Sun et al. in 2019[406]. Long-term data are still required to identify the true potential of cryoablation as a cost-effective procedure when it comes treating AF.

1.5.4.3 SURGICAL ABLATION

Cox and modified Cox-Maze surgical procedures have been used to treat AF for a couple of decades now [407]. The costs associated with these surgical procedures are related to sternotomy, thoracotomy, a more extended stay in intensive care, and periprocedural complications resulting in phrenic nerve damage, pneumonia, pleural effusions and wound infections [408-410]. Currently, the surgical maze procedure is mostly performed as a concomitant procedure in patients with AF who are undergoing CABG or surgery for valvular heart disease and can be perceived as cost-effective in selected settings [411]. Rankin et al. (2017) showed that the addition of surgical ablation to CABG was more costly at 1-year but cost effective at the 2-year follow-up with improved mortality in the US healthcare system setting [409,412]. More research into thoracoscopic surgical ablation is required at this point for it to be considered a cost-effective procedure in the long-term.

1.5.5 HEALTH AND QUALITY OF LIFE MEASUREMENTS

1.5.5.1 EUROPEAN HEART RHYTHM ASSOCIATION (EHRA) SCORE

EHRA score is a score based on symptoms driven by AF and ranges between I (mild symptoms) and IV (severe symptoms) [413]. EHRA score has been described in studies and has been validated to use for assessing AF symptoms[124,131,414-421]. Wynn et al. validated a modified EHRA score to allow for more specific distinction in symptomatic AF patients in the EHRA 2 score with 2b used as the threshold for consideration of treatment as shown in Table 1 [422].

Table 2: Modified European Heart Rhythm Association (EHRA) score.

Score	Symptom	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

1.5.5.2 ATRIAL FIBRILLATION EFFECT ON QUALITY-OF-LIFE (AFEQT) SCORE

AFEQT score is an AF specific score based on a questionnaire comprising 20 questions reviewing AF symptoms, daily function and AF treatment concerns. The questions are used to calculate the overall AFEQT score with each question having 7-point Likert responses ranging from most severe to no symptoms. AFEQT questionnaires are considered the most simplistic and easy for patients to understand. However, this score has not been extensively validated in literature although used very frequently in AF related studies [423,424]. AFEQT score is more sensitive than EQ5D and short form 36 (SF36) scores in identifying differences in specific AF-related quality of life (QOL) outcomes and is currently the most frequently used QOL measure in recent AF literature[18,21,124,155,189,261,422,425-428].

1.5.5.3 EQ5D SCORE

The EQSD is score derived from a series of scores developed by the EuroQol group. The EQ5D has two major components: five dimensions to patient's health; and an overall health score representing one week prior to visit. The five dimensions of health are mobility, mental health, usual activities, self-care, and pain/discomfort. There are Likert scales of the responses per dimensions and most commonly used are 3L (3 levels – no problems, some problems, extreme problems) or 5L (no problems, slight problems, moderate problems, severe problems, unable to perform). A large comparative study conducted by Janssen et al. (2018) concluded EQ5D-5L to be better than EQ5D-3L in measuring differences in quality of health and has recommended this score for multiple application including health economics

and clinical [429]. EQ5D-5L has been used increasingly in trials and studies identifying differences in QOL between treatments options in AF[18,189,416,430-432].

1.5.5.4 SHORT FORM HEALTH SURVEY (SF36) SCORE

The SF36 survey score has been used in the past to report quality of life of patients undergoing procedures. It consists of a measure on a scale between 0 and 100 in eight sections that include vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. SF36 has been validated in numerous studies involving a range of medical conditions[433-438]. Although used in AF studies, it is not AF specifically designed for AF related changes in quality of life and in recent times has not been frequently used in the literature reporting AF outcomes[18].

1.6 REDUCTION OF RISK OF THROMBOEMBOLIC EVENTS

1.6.1 ROLE OF ANTICOAGULANTS IN PREVENTION OF THROMBOEMBOLISM

Thromboembolic events can occur due to many factors such as blood stasis due to mechanical dysfunction, increased viscosity of blood due to an imbalance in the anticoagulation cascade, and intermittent arrhythmias such as AF [439-441].

Thrombus formation in the LA occurs predominantly in the LAA during AF but can also occur due to other factors such as the reduction in the LA contraction, shape of atrium and

appendage and other factors causing endothelial disruption [439,442-444]. Risk of thrombus formation is increased by advanced age, CHF, diabetes, vascular disease, and female sex [7,299,440,441]. Maintenance of SR and anticoagulation reduces the thromboembolic risk and can be achieved by using AADs, electrical cardioversion or ablation by any technique [440,445]. Despite prolonged periods of SR achieved with treatments, it is challenging to predict the next clinical AF episode that may cause thromboembolism resulting in transient ischaemic attack (TIA) and a cerebrovascular accident (CVA). Therefore, it is vital to assess the risk of potential stroke by using validated risk scores such as $CHADS_2$ and more recently CHA_2DS_2VASc score [64,446].

Anticoagulation can be achieved by targeting the coagulation cascade. Until recently, vitamin K antagonist such as warfarin was the mainstay of managing the risk of thromboembolism. Direct thrombin inhibitors and direct Xa inhibitor (such as dabigatran, apixaban, edoxaban, rivaroxaban) are a new class of anticoagulants with advantages of predictable anticoagulation, once or twice a day dosing and no regular dosing adjustments required [299,328,329,447]. Anticoagulation regimens need to be altered or taken into account when considering cardioversion, ablation strategies or other non-cardiac procedures. Recently, there has been a direction towards uninterrupted anticoagulation in ablation due to evidence of reduced risk along with a reduction of peri-procedure thromboembolism [372,448-454].

1.6.2 ROLE OF LEFT ATRIAL APPENDAGE CLOSURE AND EXCISION IN THROMBOEMBOLISM PREVENTION

Despite numerous advantages of anticoagulation, there are instances where anticoagulation carries a higher risk of bleeding [455-457]. Inability to prescribe anticoagulation can occur in patients with a history of significant or life-threatening haemorrhaging in the gastrointestinal tract or intracranial space [457,458]. In circumstances where anticoagulation is not an option, the thromboembolic risk can reduce by using devices to closure or occlude the LAA[457,458].

LAA can be closed internally by endovascular closure devices such as Watchman or externally by ligation using Lariat device, and LAA AtriClip™ deployed through a mini-thoracotomy or thoracoscopically [281,459-470]. Although these devices have been used in studies, their long-term efficacy in reducing thromboembolic risk needs to be further evaluated[471,472].

The acute success of LAA closure is dependent upon the ability to close the ostium of LAA appropriately [466,473]. There are variabilities in the anatomy of the LAA where the ostium is not circular and sometimes consists of multiple lobes [466,474-481]. In those circumstances, gaps can be left where the device has not entirely obliterated the ostium, or not all the lobes have been occluded resulting in high risk of thrombus in the LAA with higher embolic risk [466,482,483]. When appropriately deployed, there is evidence of electrical and mechanical isolation of the LAA using occlusive devices such as epicardial ligation and Watchman™ and with epicardial devices such as Atriclip™[484-487]. LAA closure is considered to be a cost-effective measure for high-risk patients and those unable to receive anticoagulation [369,488-492].

The risk of thromboembolism remains high due to underlying comorbidities, poor LA function, inability to take anticoagulation and endothelial dysfunction. Prothrombotic state persists along the walls of the LA and LAA, although this still needs to be evaluated in more extensive randomised control studies [493-498].

1.7 SUBSTRATE ANALYSIS OF LEFT ATRIAL SCAR AND LEFT ATRIAL FUNCTION USING IMAGING MODALITIES

1.7.1 LEFT ATRIAL VOLUME ASSESSMENT

LA dilation is the hallmark of electromechanical remodelling, particularly in patients with AF [499,500]. Greater dilation signifies more advanced disease process and higher failure rates following ablation [501-503]. LA dilation is useful in identifying patients that were at high risk of AF recurrence following ablation and offer the treatment to those who might benefit the most through maintenance of SR [503,Arya, Hindricks [504,505-507]. Restoration of SR causes a reduction in the LA volume termed 'reverse remodelling' which can be achieved by AADs, DCCV or ablation [508-510]. The reverse remodelling following ablation is not only due to the restoration of SR but also due to contraction resulting from the scar created by injured atrial tissue. [511,512]. This effect was reported in studies using CA [508,513,514], and it can occur in surgical treatments for AF.

Echocardiography is an essential diagnostic investigation used to assess LV and valvular functions [515]. Access to echocardiography is readily available worldwide and is the most common investigation utilised for assessment of cardiac structure and function [516-527]. However,

there are many limitations to echocardiographic techniques due to patient characteristics, operator skills, and technology available[528,529]. Patient characteristics such as the shape of the thorax, obesity, breast tissue and, musculoskeletal artefacts from ribs can result in reduced resolution of the acquired images during echocardiograms[526,527]. The quality of scan can improve with contrast, 3D echocardiography, and TOE.

Additionally, operator skills influence the quality of echocardiography assessments [517,518,530]. Association of structural heart disease and low functional state of the heart is associated with incidence and prevalence of AF [531]. LA dilation, LA diameter, poor LV function, valvular heart disease and cardiomyopathies can be assessed by echocardiogram and provide a useful screening tool for appropriate patient selection and predictability of success of ablation [516,531].

LA reverse remodelling has historically been measured using echocardiography and cardiac computerised tomography (CT). However, the high spatial resolution of cardiac magnetic resonance (CMR) imaging (MRI) supports more accurate measurements of cardiac chamber volumes and is therefore considered to be the gold standard imaging modality [530,532]. More recently, remodelling and reverse remodelling has been more accurately defined as the change in the shape of LA as opposed to volume termed LA sphericity. Both CMR and transthoracic echocardiogram (TTE) have been used to describe LA sphericity and its relationship to AF recurrence following ablation [533,534]. The RA dilation is an accompanying feature of LA dilation in LSPAF, and the reverse remodelling of RA is also poorly understood[535,536].

The current paradigm is that the larger the progressive atrial dilatation becomes with its consequent architectural changes, the lower the chance of restoration of SR through

ablation[97,501,504,511,537]. It is not uncommon for the decision to not pursue an interventional strategy, in otherwise symptomatic patients, to be based on LA chamber size parameters [501,504,538].

1.7.2 LEFT ATRIAL SCAR ASSESSMENT

Atrial fibrosis is a substrate for AF, and it increases in patients with persistent or LSPAF [539]. The current standard for assessment of atrial scarring is EAM developed in the late 1990s and early 2000, that is performed during an EP study to allow for encircling of PVs [18,540,541].

EAM was developed further to help define substrates for CFAE and creating lines to isolate abnormal regions [542-545]. Verma et al. (2005) described validating LA scar using 0.05mV as a cut-off for scar and 0.05mv – 0.5mv for low voltage range [546]. Voltage mapping is usually performed in SR, but some studies produced voltage maps in patients with AF [547,548]. The electrical activity of the LA is recorded using a mapping catheter before CA, with regions of scarring correlate with very low voltage (<0.05mV) or low voltage (<0.5mV)[549-551]. The main limitations of substrate assessment by electrophysiology study are its invasiveness, the use of ionising radiation for placing catheters in desired locations and the suboptimal accuracy, with reported errors of up to 15 mm in the localisation of scar tissue [552-554]. New 3D image integration modules to merge 3D mapping to fluoroscopic images and LA image acquisition before procedure using CT or CMR have reduced radiation to the patients and the operators [555-557].

LA fibrosis detection remains elusive due to many factors including CMR resolution, and myocardial factors that affect late gadolinium enhancement (LGE) and the protocols used to detect a high signal. Visualisation and quantification of LA scarring require objective, robust and accurate segmentation of the enhanced scar regions from the LGE on CMR images. LGE is an established non-invasive technique for detecting myocardial scar tissue [558]. With the segmentation and LGE technique, healthy and scar tissues are differentiated by their altered wash-in and wash-out contrast agent kinetics, which results in the identification of scar tissue seen as a region of high signal intensity and healthy tissue is not enhanced[559,560]. While 2 dimensional (2D) breath-hold LGE CMR is well-established for ventricular imaging, there is a growing interest in imaging the thinner-walled atria for identification of native and ablation scarring in AF patients [561-565]. Identification of LA scarring requires high spatial resolution, contiguous coverage and data acquired as a 3D volume during free-breathing with diaphragmatic respiratory-gating[566-568].

Structural and patient-related limitations include a thin atrial myocardium, artefacts from adjacent structures like aorta, oesophagus, increased BMI, MRI conditional implants, claustrophobia, allergies or severe renal disease not compatible with gadolinium administration[569-573]. The precise delineation of LA walls and PVs rule out confounding cardiac or extracardiac tissues that enhance with gadolinium e.g., the mitral valve and aorta, or the enhancement from non-heart structures [563,564,574-576].

Acquisition limitations include variations in the protocols to allow for appropriate roadmaps, variable algorithms for scar estimation, nulling of normal myocardium, translational shifts during respiration, cardiac rhythm (AF vs SR) and blood thickness [577,578]. Post-processing

limitations include manual versus automatic segmentation of the heart, software to delineate the blood pool against the endocardial surface of the atrium, co-registration of postprocessing images of the LA scar with CMR and voltage maps[559,564,566,579-583]. Moreover, varying contrast clearances in individual patients require manual calibration of contrast enhancement which can introduce error in scar estimation [584].

Attempts at validation of scar quantification with voltage maps have shown some promise [585]. LA scar can be studied in CMR acquired images in which atrial fibrosis can be delineated [586,587]. Higher degrees of LA fibrosis contribute to the recurrence of AF post-ablation [588]. However, these data and findings are not easily reproducible [589]. Better fibrosis imaging and assessment techniques are being developed and will provide accurate guidance of the pre- and post-ablation procedures to improve the long-term efficacy of an ablation modality [590,591].

Earlier studies utilising CMR for scar assessment assumed a fixed thickness of the LA wall although there is no evidence for this assumption. Re-orientation and interpolation of the MRI images during processing can result in partial volume effects and increase the variance of the wall thickness [577,592]. Inaccurate manual segmentation of the LA wall and PVs can further complicate the delineation of the atrial scarring. The inaccuracies of post-processing software are one of the reasons that atrial scarring identified by LGE CMR (enhanced regions) is thought to be inferior to the 'gold standard' EAM (low voltage regions) [593-595].

Fully automatic segmentation and quantification of the atrial scarring in LSPAF patients scanned by CMR LGE have not been previously assessed in detail. We proposed a fully automatic segmentation and quantification of atrial scarring identified by LGE for LSPAF

patients scanned by CMR [595]. Based on the CMR scar quantification a new threshold of LA bipolar voltage will be derived and used to quantify scar in bipolar voltage maps during AF and SR.

1.8 LEFT ATRIAL FUNCTION AS A PREDICTOR OF ATRIAL FIBRILLATION RECURRENCE

LA function comprises of parts of the atrial cycle and is reflected by three components: reservoir, conduit and contractile function[596-599]. The LA function can be measured through volume assessments, tissue Doppler velocities of atrial myocardium, strain and strain rate measurements obtained from TDI or speckle tracking/feature tracking[463,598-600 517,601,602]. These modalities can be applied to echocardiograms (TTE and TOE), CT and CMR. The specific measurements for assessing reservoir, conduit and contractile function using the modalities will be described in individual forthcoming chapters[598,600].

Reservoir function has also been reported as an expansion index and represents the maximum LA expansion representing atrial diastole[597,600,603]. Beginning of atrial diastole is represented on imaging by the closure of the mitral valve or electrically by the onset of QRS on ECG. End of atrial diastole or maximum LA expansion is represented by the opening of the mitral valve on imaging[603].

Conduit function has also been reported as passive LA emptying and represents the elastic recoil of the LA and pulmonary venous flow direct to the LV following mitral valve opening to the beginning of P wave on ECG [600,603].

The contractile function has also been reported as atrial booster function and pump function and represents active atrial contraction from the beginning of the P wave to the beginning of QRS [600]. It is represented on imaging by the beginning of atrial systolic contraction to the beginning of mitral valve closure. Electrically it represents the PR interval on ECG. The contractile function cannot be measured during AF as the atrial contraction is lost [600,603].

LA function assessment is affected by variables such as patient characteristics, operator skills and, technology [517,518]. Therefore, sufficient experience and appropriate training will help with acquiring useful quality data [517].

LA function in subjects with comorbidities and advancing age is reduced and starts before the AF manifests itself clinically [604-606]. Comorbidities such as diabetes mellitus, hypertension, LV dysfunction, increasing body mass index, and increasing age can impair LA function before onset of AF even without valvular heart disease. [604,607-611]. The reduced LA function overtime can lead to AF onset and propagate further LA dilation resulting in longer durations and severity of AF [612]. LA function can be measured by volume, Tissue Doppler imaging (TDI), strain and strain rate using 2D or 3D speckle tracking using transthoracic echocardiograms, transoesophageal echocardiograms, CT and CMR to derive reservoir, conduit and contractile function[600,613,614].

For each imaging modality, there are numerous vendors with different approaches to analysing TDI, strain and strain rate using specific offline software. Recently, there has been a surge in strain analysis using speckle tracking and ability to identify the rate of

deformation (strain) in longitudinal, transverse and radial planes [602,615,616]. Tissue Doppler imaging (TDI) and strain imaging of left atrium is shown to be a promising tool to identify reduced LA function and help identify patients most likely to benefit from AF treatments [617-620].

LAA is a part of the LA that lies anterior-laterally, and its contribution to the LA function is not known. LAA isolation and exclusion by endocardial occlude devices or epicardially do not show a detrimental effect on the LA function[460,463,470,621,622]. The formation of LAA and LA thrombus is closely related to the LAA function and associated comorbidities[463,621]. In AF, the LAA function is reduced and correlated with reduced LA function seen on TDI and strain imaging coexisting with LA scar [620,623,624].

Even though CT and CMR can also be used for functional assessments, but both have certain limitations: CT cannot readily provide useful functional information of the myocardium, while CMR is time and resource-consuming [518,625]. CMR has other advantages of detecting delayed enhancement of the LA which is reflected by strain and strain rate of the LA [625,626].

In AF, Transoesophageal echocardiogram (TOE) is individually performed to assess mitral valve, rule out thrombus in the LA before any procedures. Intraoperatively, TOE can be helpful to assist with transseptal punctures to access the LA via the right side of the heart, pulmonary vein assessment, LAA morphology and function assessment[627-629]. With improved imaging modalities within echocardiography such as velocity, TDI and strain, the LA and LAA function can also be readily measured [628,630-639].

1.9 ROLE OF GANGLIONIC PLEXI ABLATION IN REGULATION OF AUTONOMIC NERVOUS SYSTEM MODIFICATION AND MANAGEMENT OF ATRIAL FIBRILLATION

GP form an essential part of the intrinsic cardiac autonomic nervous system (ANS) [640]. The effects of ANS are the proarrhythmic effects of sympathetic activation or parasympathetic activation via the vagus nerve [640,641]. The changes at the level of the cell are a reduction in atrial cell refractoriness and action potential, which result in the substrate that allows re-entry mechanisms to ensure arrhythmia [642].

Advances in technologies to improve radiofrequency energy delivery and reduced size of surgical and CA tools have allowed for more prolonged and more sophisticated procedures [641,643-645]. The advent of minimally invasive thoracoscopic surgical AF ablation opened the possibility of ablating epicardial fat pad and PV antrum under direct vision using radiofrequency energy [281]. Studies show improved outcomes in patients in whom they combined PVI with GP ablation during 12 months follow up [285,644,646].

Tan et al. (2008) quantified sympathetic and parasympathetic innervation at PVs ostia and around GP clusters in animal models [647]. They showed that sympathetic and parasympathetic innervation coexist together in clusters. The GPs are located epicardially and are confirmed during epicardial ablation via direct visualisation and short HFS testing. As described above, HFS can stimulate neural bundles via a short and long duration stimulation for parasympathetic and sympathetic innervation [642].

The best interventional treatment for symptomatic LSPAF is yet to be defined. The encouraging results achieved with TSA in several cohort studies in persistent AF and LSPAF [643,644,648] were echoed by our pilot study results [191]. We suggested that the improved success is due to multiple factors like the direct visualisation of the ablation targets, ability to form contiguous lines by use of clamp, ability to test bidirectional blocks and identify targets. Results might be better with ablation at the PV antrum at the location of epicardial fat pads with reduced incidence of PV stenosis. However, it might be possible that the improved success was due to ablation of GP. GP ablation via thoracoscopic epicardial approach is more successful than endocardial CA [281].

1.9.1 COMPOSITION OF THE AUTONOMIC NERVOUS SYSTEM

The ANS is composed of parasympathetic and sympathetic components and forms part of the peripheral nervous system[649]. It subconsciously controls physiology, and the activity of its components varies throughout life. In new-born, the sympathetic activity is profoundly high and reduces with increasing age, while the parasympathetic activity increases [650]. There are numerous conditions which affect the development of the ANS and its function such as maternal consumption of alcohol, drugs, smoking or environmental factors such as temperature, body position, physical activity, psychological factors (stress) [650-653]. ANS affects the endothelial function of blood vessels, regulates vascular tone, resulting in changes in blood pressure and alterations in atherosclerotic changes over time [117,654-656].

1.9.2 ANATOMY OF GANGLIONIC PLEXI AROUND HEART

GP are dense areas of neurological synapses of the sympathetic and parasympathetic fibres that innervate the heart [657,658]. These structures have been recognised in autopsy studies since the 19th century, but their role has been poorly understood until recently [659,660].

1.9.3 MECHANISM OF ATRIAL FIBRILLATION ACTIVATION VIA GANGLIONIC PLEXI

The intrinsic cardiac ANS is critical in the initiation and maintenance of AF [661,662]. Intrinsic cardiac ANS consists of neural networks around the heart, and they congregate in clusters located in epicardial fat pads as GP. In the human heart, there is at least seven GP locations, and at least four are located on the epicardial surface around antrum of PVs [640,663-666].

Ablating GP at anatomical locations or having vagal mediated responses during ablation of the PV suggested that GPs was located nearby or being ablated[667,668]. During follow up of 12 months, up to 99% of the patients with a vagal response were free from recurrence of AF as compared to 74% of patients without vagal response. The results of ablating GP alone in other studies either by endocardial or epicardial approaches have not been promising with success rates in the range of 28-50% during mean follow up of 8.5 months [666,669]. However, GP ablation made a better impact on success when combined with PVI [285,640,643,670,671]. Results showed 65% - 85% of patients being free from atrial arrhythmias after one-year follow-up without the use of anti-arrhythmic drugs.

Several studies investigated cardiac autonomic nervous system denervation and modification on its own or in combination with CA, surgical maze or thoracoscopic ablation

[641,643,645,665,672-674]. Outcomes of ANS ablation, when compared to standard AF ablation alone, are favourable. Most of the studies have recruited patients with either PAF or a mixed cohort of varying types of AF, such as persistent and LSPAF.

AF ablation pilot study based on a European heart survey included >1200 patients with PAF were identified to have a significant autonomic contribution to the mechanism of trigger initiating AF. Results suggested that one-third of the cases were associated with ANS suggesting its significant role in the initiation and the maintenance of AF [675,676].

1.9.4 MEASURING AUTONOMIC NERVOUS SYSTEM ACTIVITY IN PATIENTS WITH ATRIAL FIBRILLATION

Testing and locating cardiac ANS can be achieved through high-frequency stimulation (HFS). HFS is usually 20 Hz, 10-150 mV and with a pulse width of 1-10ms. Stimulation of parasympathetic and sympathetic systems elicits a rapid response (2-4 seconds) and delayed (8-10 seconds) response, respectively [640].

Testing of ANS comprises of 3 components; Sudomotor (testing sweating by electrical stimulation or heat), cardiovagal (deep breathing and Valsalva manoeuvres), and adrenergic assessment (Valsalva and tilt testing) [650,677,678]. The parameters tested are heart rate variability (HRV), Baroreceptor reflex and BP response [678]. HRV can be functionally assessed by time and frequency domain methods [650]. Time-domain is used to analyse long recording conditions such as circadian rhythm or ambulatory conditions. The frequency domain is used to analyse short duration, such as 5 minutes of ECG recordings in standardised conditions [650].

Time-domain methods utilise R-R interval on ECG and standard deviations of R-R intervals to represent sinus node and AV node autonomic regulations[650,679]. Frequency domain measures very low frequency (VLF), low frequency (LF) and high frequency (HF) of QRS complexes on ECG and is illustrated on a plot using spectral analysis [679,680].

At present, GP can be located by either the predefined anatomical location or by HFS [640,642,671,680]. The effects of parasympathetic stimulation include bradycardia, hypotension and AV node block [642].

1.10 LIMITATIONS IN CURRENT STANDARD TREATMENTS IN MANAGEMENT OF ATRIAL FIBRILLATION

The major limitation in treating AF remains AADs toxicity, their pro-arrhythmic effects, and lack of symptom control in the rhythm control strategy [681]. DCCV is commonly used to establish improvement in symptoms by restoring SR and evaluating this improvement to aid the further choice of treatment, i.e. consider rhythm control instead of the rate control strategy. DCCV and subsequent longer duration of freedom from AF is a predictor of the success of future ablation strategies [165,682,683]. Failure to maintain SR can suggest underlying advanced substrate that promotes AF [165,682]. DCCV has poor success in the long-term maintenance of SR with concomitant use of AADs before or post-ablation recurrence [684].

Despite advances in technologies in mapping, CA techniques, the maintenance of freedom from AF after ablation remains between 50-80% at one year follow up [685]. AF substrate modification by targeting CFAE was initially thought to have some success albeit from

excessive ablation and resulting in atrial tachycardia initiation due to formation of scar [685,686]. Long-term success in ablation of persistent AF and LSPAF has been a significant limitation on allowing electrophysiologists to offer ablation for symptomatic AF [686-688]. Linear lesions can reduce instances of atrial tachycardia (AT) through modification of atrial substrate, although in some cases, it can cause AT using gaps through incomplete lines[686,689].

The high recurrence rates of AF following ablation is due to [31,263,503,550,590,690-695]:

(1) difficulty in identifying the potential non-responders to ablation

(2) inability to establish the ideal ablation strategy for each patient

(3) limitations in the information about the location and extent of the atrial scar before, and after the procedure for instances of redo CA.

(4) Ineffective treatments for comorbidities associated with worse outcomes such as diabetes, obesity, metabolic syndrome, CHF and untreated ischemia.

(5) A higher degree of atrial fibrosis makes the likelihood of AF recurrence higher.

1.11 SUMMARY OF LITERATURE REVIEW, AIMS AND HYPOTHESIS OF THE THESIS

Summary of literature review and identifiable gaps in the knowledge that forms the basis of this thesis and hypotheses are outlined below:

1. Prevalence and incidence of AF are increasing predominantly due to rise of comorbidities and risk factors with changing lifestyles and an increasingly ageing population. In persistent AF and LSPAF, the success of ablation strategies is challenging due to a complex cascade of neurohormonal remodelling resulting in

LA dilation and fibrosis. The jury is still out on how to achieve and maintain sinus rhythm over medium to long-term follow in symptomatic patients with LSPAF. The cornerstone to all management of AF remains pulmonary venous isolation. The success of conventional catheter ablation is suboptimal in non-paroxysmal AF with variable results after targeting CFAE; Individual linear lines such as roofline, inferior line, mitral line (anterior, lateral or posterior) in combination with wide-area circumferential ablation (WACA) around the pulmonary veins. Combining the lesion sets in CA with LAA exclusion by Atriclip™ (in TSA) holds promise but have not been tested in a randomised control trial for the population of LSPAF.

The main hypothesis of the thesis is that TSA is more effective in maintaining SR when compared to CA in a randomised control study over 12 months.

In chapter 3, I aim to explore the efficacy of TSA compared to CA as a first-line ablation strategy in patients with symptomatic LSPAF by enrolling in the CASA-AF randomised control trial. The primary outcome of the study defined as freedom from atrial arrhythmias lasting longer than 30seconds measured by ILR over 12 months follow up. Secondary endpoints include clinical success, safety outcomes, changes in symptoms and quality of life scores. Clinical success is defined as AF/AT burden reduction≥ 75% each month over 12 months following CA and TSA. The safety endpoint was identified as a serious adverse event that requires hospitalisation or another intervention to manage the adverse event, and permanent injury or death. Symptom changes will be evaluated using the EHRA

symptom score. The AFEQT score and EQ5D-5L score will measure the quality of life scores.

2. Symptomatic LSPAF patients are becoming increasingly difficult to treat. TTE most commonly measures cardiac structure and function and with recent technological advancements, reduced LA function can be more accurately measured by 2D strain imaging compared to volume changes and TDI. In addition to pulmonary venous electrical isolation, targeting CFAE ablation, adding linear lines (roofline, inferior line, mitral line) has not shown to have promising results to treat persistent and LSPAF.

   I hypothesised that there is local LA functional change from linear lesions that are delivered in TSA and CA, and LAA exclusion using Atriclip™ in TSA can be measured by advanced echocardiography. In addition to local LA function, global LA function measured by volume, TDI and strain imaging in LSPAF will predict patients that will benefit from ablation strategy and are more likely to maintain SR long-term.

   In chapter 4, I aim to explore the impact of linear lesions and LAA exclusion on local LA function and global LA function. I aim to evaluate the relationship of local and global atrial function with maintaining SR in a sub-study of the CASA AF trial using the volume-based function and advanced echocardiography techniques such as TDI and 2D speckle tracking strain.

3. Change in LA volume termed LA reverse remodelling has been considered to be a predictor of SR maintenance in patients with PAF and persistent AF. However, this has not been investigated in LSPAF treated with CA or TSA. In addition, the risk of pulmonary vein stenosis following TSA has not been systematically evaluated. Measuring RA volume using CMR is more accurate than TTE using contiguous stacks instead of estimating using biplane Simpson method or area-length method. RA volumes in LSPAF have not been thoroughly investigated in patients with LSPAF.

   I hypothesised that atrial reverse remodelling in LSPAF is seen after both TSA and CA but is not a predictor for SR maintenance. Pulmonary vein stenosis will likely be less in the TSA group due to direct visualisation of the pulmonary veins as opposed to a 3D computer-generated model of LA used in CA.

   In chapter 5, I aim to investigate volume and LA function changes and pulmonary vein diameter assessment using CMR and evaluate association with AF recurrence in patients enrolled in the CASA AF trial.

4. There have been significant advancements in scar estimation by non-invasive methods such as imaging and in particular CMR with delayed enhancement suggestive of fibrosis. The degree of LA fibrosis has not been measured in the LSPAF, and the extent of fibrosis created by TSA has not been evaluated. Moreover, the post image acquisition processing is not always reproducible in all tertiary centres around the world and are limited to only a handful of high

volume with extensive publications in the area of LA scar estimation such as University of Utah, Leipzig University, and Barcelona Hospital Clinic. We developed a new automatic segmentation method of quantifying LA scar using ground truth and training of data set using deep learning methods. The deep learning method has been published, and we aim to apply this method on CMR images of the patients enrolled in the CASA AF trial.

I hypothesised that TSA will have less scar, quantified by CMR compared to CA likely due to direct visualisation of the area of ablation with the use of bipolar clamps resulting in straight linear contiguous lines as opposed to CA. Lesions in CA are delivered on the endocardial surface of the LA via a floating catheter with variable levels of contact force resulting in a more substantial area of atrial fibrosis as the heart is continuously beating. I also hypothesise that a greater extent of LA scar will result in lower freedom from atrial arrhythmias.

In chapter 6, I aim to estimate LA scar by applying a locally developed software using deep learning methods that will allow for automatic LA segmentation and LA scar quantification in patients enrolled in the CASA AF trial.

5. GP ablation for management of AF in isolation has not been as effective as in combination with WACA. GP ablation remains a target to consider amongst clinicians as part of an ablation strategy. Moreover, the durability and clinical impact of GP ablation over the short and long term are not fully understood.

I hypothesised that GP mapping by high-frequency stimulation and targeted GP ablation performed in the TSA group will result in more selective parasympathetic blunting compared to the CA group where GPs were not selectively ablated. I also hypothesise that increase in parasympathetic activity during the follow up is associated with AF recurrence following ablation.

In chapter 7, I aim to assess the impact of targeted GP ablation on the activity of the autonomic nervous system by measuring the daily HRV recorded on ILR. I also intend to establish the trends of HRV over one year follow in patients who received GP ablation as part of TSA compared to CA, where GPs were not explicitly targeted.

CHAPTER 2

COMPARISON OF CATHETER ABLATION VERSUS THORACOSCOPIC SURGICAL ABLATION (CASA-AF) RANDOMISED CLINICAL TRIAL

2.1 METHODS

CASA-AF is a prospective, multicentre, randomised clinical trial (RCT) to assess the effectiveness, safety and cost-effectiveness of TSA compared to CA (usual care) in patients with LSPAF. In this thesis, we will aim to look at the effectiveness and safety of the CASA AF RCT. CASA-AF RCT was conducted over four tertiary specialist NHS hospitals in England (Royal Brompton Hospital, Harefield Hospital, Liverpool Heart and Chest Hospital and Brighton Hospitals) with proven expertise in both interventions. The protocol followed the guidance of the SPIRIT 2013 statement and has been published in peer reviewed literature [696-698].

2.1.1 PRIMARY OUTCOME

The main objective of this trial was to identify the most effective ablative intervention for treating LSPAF. The primary hypothesis of the study is that TSA is more effective than percutaneous CA in achieving freedom from atrial arrhythmia.

The primary outcome in the study was freedom from atrial arrhythmia after a single ablation procedure and without AADs during study follow up. Follow up was defined as the

period after three months and up to 12 months after the ablation. Blanking period is the period from the index ablation to the end of the three months after ablation. Data was collected by the ILR throughout the follow-up period to detect the recurrence of atrial arrhythmias defined as AF/atrial tachycardia (AT) ≥ 30 seconds.

2.1.2 SECONDARY OUTCOMES

The most important secondary outcome was the safety of the two interventions. The safety end-point in this trial was an intervention-related major complication, defined as permanent injury or death, or required unplanned intervention for treatment, or that prolongs unplanned hospitalisation for more than 48 hours.

In addition, for the thesis, we evaluated:

- the secondary outcome, defined as freedom from atrial arrhythmias following multiple procedures without AADs during 12 months' follow-up
- the clinical success of the two interventions by comparing the AF burden (≥ 75%) reduction over the follow-up period in each treatment arm
- changes in LA size and function following ablation using transthoracic echocardiography modalities such as TDI and 2D speckle tracking.
- Changes in atrial size and volumetric function following ablation using CMR imaging
- the effects of arrhythmia interventions on patients' symptoms and quality of life through changes in EQ-5D-5L and AFEQT scores [428].
- The quantification of LA scar using a new automatic segmentation algorithm on CMR and correlation with bipolar voltage maps during AF and SR.

- Effect of GP ablation on the autonomic modulation in patients with LSPAF.

2.1.3 PATIENT SELECTION

Adults with symptomatic LSPAF considered for treatment (DCCV or CA) at the participating trial centres underwent eligibility screening and inclusion in the CASA AF RCT[698]. The list of inclusion and exclusion criteria for the CASA-AF RCT is in Table 3.

Table 3: Eligibility Criteria in the CASA-AF Trial

Inclusion criteria
• Age ≥ 18 years • Long-standing persistent AF (>12 months' duration) • EHRA symptom score >2 • Left ventricular ejection fraction ≥ 40% • Suitable for either of the ablation procedures
Exclusion criteria
• Left-sided valvular heart disease with severity greater than mild • Contraindication to anticoagulation • Thrombus in the left atrium despite anticoagulation in therapeutic range • Cerebrovascular accident within the previous 6 months • Previous thoracic or cardiac surgery (including surgical interventions for AF) • Prior left atrial catheter ablation for AF

- Unable to provide informed written consent
- Active malignancy, another severe concomitant condition or
- presence of implanted cardiac devices that would preclude patient undergoing study-specific procedures *
- Pregnant or breast-feeding, or women of childbearing age not using a reliable contraceptive method.

*Footnote 3: Following consent, if there was a concern with valvular heart disease, further tests were undertaken before inclusion into the study such as TOE. If there was a mass noted on CMR, then further imaging like CT thorax and abdomen was performed before being considered eligible and before randomisation. * if patients could not have a CMR due to cardiac devices, then a CT heart was requested to ensure that the atrial volumes and anatomy of the PV was assessed before randomisation.*

The participating sites referred the patients once the consultant cardiologists at their respective sites had identified them in the outpatient clinics or through DC cardioversion and ablation waiting lists. Once referred, the patients were assessed for inclusion in the trial by the research team. The study was aimed to recruit 120 patients within the designated timeline of July 2015 to June 2017. Patients were allowed to withdraw from the study at any time with no explanation required during the follow-up period. Any withdrawn patients were not replaced as the levels of attrition had formed part of the sample size calculation. The RCT had to undergo an extension of study due to unexpected slower recruitment in the study, and two further centres (Liverpool Heart and Chest Hospital and Brighton and Sussex University Hospitals NHS Trusts) were selected as trial sites.

2.1.4 STATISTICAL ANALYSIS

All statistical analyses were based on intention to treat, and the data analysed was from all randomised participants. We will also perform sensitivity analyses to explore the impact of missing data, non-compliance, the crossover of the arms and withdrawals from the study. International business machines (IBM) SPSS Statistics version 25 (IBM corporation, Armonk, New York, USA) was used to perform the analysis.

Sample size (n = 120) was calculated based on the data from our pilot study showing freedom for AF/AT at six months in the surgical group in 76% versus 44% in the catheter group [191]. Using these results, a sample size of 48 per group was required to detect a difference in the primary outcome with 90% power and 5% significance level. There is a margin of error of 25% which includes a 10% drop out rate.

The primary outcome of the trial is the proportion of LSPAF patients undergoing ablation that are free from atrial arrhythmias (defined as a single episode of ≥ 30seconds) within one year after a single ablation procedure. 'Arrhythmia free' patients were identified through ILR data assessments performed monthly by a single-blinded cardiac physiologist. Chi-squared test was used for comparison between the trial arms. A logistic regression model was developed to estimate the probability of being free from AF at one year by either procedure. The primary measure to be reported is the adjusted odds ratio of being 'AF free' for the surgical group.

The recurrence of AF and duration of AF freedom was analysed using Kaplan-Meier survival curve. Binary secondary outcomes (reduction in arrhythmia burden, freedom from arrhythmia following multiple procedures) was analysed in the same manner as the primary outcome using a combination of Chi-squared test and logistic regression. Freedom from arrhythmia following multiple procedures was analysed using Kaplan-Meier survival curve. Kaplan-Meier survival curve was also used for sensitivity analysis to evaluate per-protocol analysis, and for patients who withdrew from either arm. A simulation was performed on the ILR data to mimic one month Holter recordings and 24-hour recordings every three months. The simulated data were used for sensitivity analysis to assess differences in recording atrial arrhythmias and its impact on survival curves. Repeated measures analysis was conducted on variables that were measured at baseline and follow up.

Ordinal data were analysed by the Chi-squared test and presented as a total number between two groups (CHA_2DS_2VASc, HAS-BLED, anticoagulation). Continuous data were analysed by either Student's *t*-test or Mann-Whitney test and presented as mean $\pm$ SD, mean (95% confidence interval) or median (interquartile range –IQR) depending upon the distribution of obtained data. A $P<0.05$ was considered significant.

2.2 TRIAL SCHEDULE

Patients considered eligible to take part in the study were provided with a Patient Information Sheet (PIS) and given opportunities to discuss details of trial and enrolment in the CASA-AF RCT. They were encouraged to discuss the information with their family, friends and general practitioners before deciding to participate in the trial. When they

confirm their interest in taking part, a hospital appointment was arranged for them to sign an informed consent form and to complete baseline assessments. Participants' progress through the study is shown schematically in Figure 2.

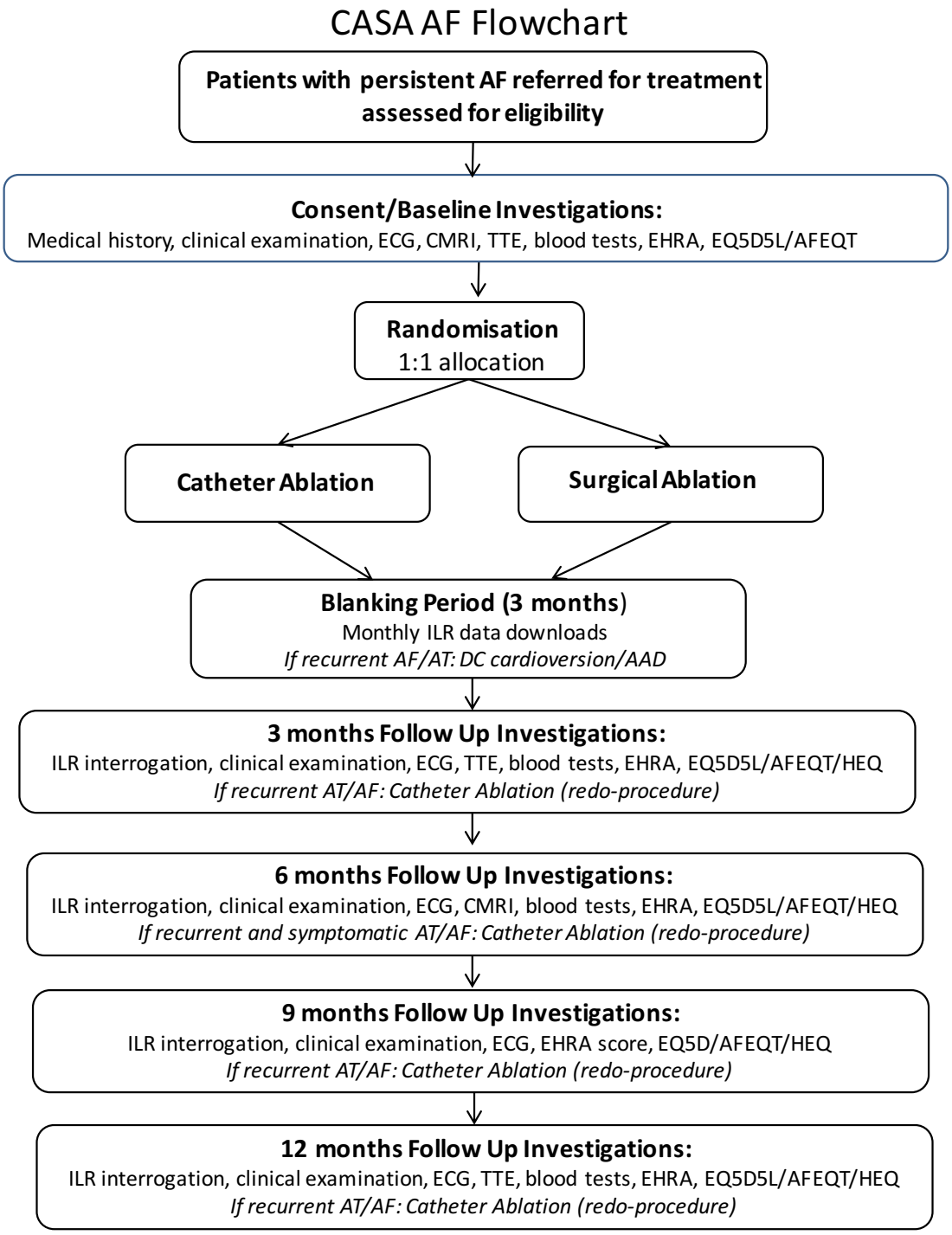


Figure 2: Schematic representation of CASA-AF study design

Footnote 4: AAD – antiarrhythmic drug, AF – atrial fibrillation, AFEQT – Atrial Fibrillation Effect on QualiTy of life, AT – atrial tachycardia, CMR – cardiac magnetic resonance, ECG - electrocardiogram, EHRA – European Heart Rhythm Association, EQ5D-5L – European Qol group 5 dimension – 5 level questionnaire, HEQ – health economic questionnaire, ILR – implantable loop recorder.

2.3 BASELINE STUDY VISIT

As part of the baseline visit, ECG was performed to ensure the patients were still in AF. Once AF was confirmed any further discussions or queries were discussed with the centre's trial team. A consent form was signed if the patient agreed to take part in the study. The team then collected blood samples for routine haematology, biochemistry and coagulation assessments. Routine haematology and biochemistry assessments included full blood count, electrolytes, renal function tests, coagulation profile, liver function tests, thyroid function tests, C-reactive protein, tests for diabetes (HbA1C) and lipid profile (HDL, LDL). Biomarkers were obtained but not analysed in this thesis and are for future analysis.

TTE and CMR assessment were performed to ensure that patients do not have reduced left ventricular (LV) function, valvular disease or other pathologies that meet the exclusion criteria. Other incidental findings during these preliminary tests such as LA or LV thrombus, suspicion of significant valvular disease, malignancy was investigated further. Another imaging modality such as TOE and CT of the thorax and the abdomen were requested to

ensure they met the eligibility criteria.

Additional clinical and study data collected at baseline included assessment of cardiovascular risk, quality of life, past medical and surgical history, current medications list, EHRA symptoms score, and a generalised clinical examination by one of the designated team members (Figure 3). Although a Health economics questionnaire was completed to assess the usage of health care systems during the follow-up period (Figure 3), it will not be analysed as part of this thesis.

Tests/ Data Collection	Baseline	Treatment Allocation	Index Ablation	Blanking period	Months after index ablation											
				Post-operative surveillance	1st FUP			2nd FUP			3rd FUP					4th FUP
				1	2	3	4	5	6	7	8	9	10	11	12	
Registration (demographics)	X															
Eligibility	X															
Medical History (significant conditions not related to LSPAF)	X															
Cardiac Risk History (medical conditions associted with AF)	X															
Cardiac Risk Scoring (CHA_2DS_2VASc, HASBLED)	X															X
Concomitant Medication	X		X			X			X			X				X
Current Anti-Coagulant Therapy	X		X			X			X			X				X
Arrhythmia Characteristics (diagnosis date, prior history of cardioversion, other arrhythmias, other ablations)	X															
EHRA AF Classification	X					X			X			X				X
Clinical Examination (blood pressure, heart rate, weight)	X					X			X			X				X
Haematology & Biochemistry assessments	X					X			X							X
Biomarkers	X					X			X							X
12 lead ECG	X					X			X			X				X
Transthoracic Echocardiogram	X					X										X
Cardiac Magnetic Resonance	X								X							
EQ5D-5L Questionnaire	X					X			X			X				X
AFEQT Questionnaire	X					X			X			X				X
Allocate to treatment		X														
Health Economics Questionnaire						X			X			X				X
Adverse Events			X	X		X			X			X				X
ILR Interrogation (primary outcome)				X	X	X	X	X	X	X	X	X	X	X		X
Transoesophageal Echocardiogram			X													
Catheter Ablation			X													
Surgical Ablation			X													
Discharge			X													
DC Cardioversion (if needed)				X	X	X			X			X				X
Clinical Catheter Ablation (if needed)						X			X			X				X

Figure 3: Schedule of Enrolment, Tests and Assessments in CASA-AF Study (SPIRIT figure)

2.4 RANDOMISATION

Patients with confirmed eligibility for participation at baseline assessments were assigned to the treatment group by a computer-generated sequence in a 1:1 ratio using minimisation. A secure 24-hour bespoke web-based system hosted by the King's Clinical Trials' Unit provided team members with access to the allocation system where they enter participant's unique study identifier (PIN), initials and date of birth in an electronic online form. Also, the system uses the study site code, participant's sex and the size of the left one atrium (< 50 mm, >50 mm) as stratifying variables. Allocation is concealed, but blinding was not possible in this trial due to the apparent intervention differences between the two groups. However, the primary outcome assessor was blinded to the treatment arms and only had access to the ILR data.

2.5 ANTICOAGULATION PROTOCOL

According to the guidelines at the time of enrolment [299], it was recommended that patients randomised to CA remained on uninterrupted warfarin treatment unless the operator outlines a different strategy. If patients were treated with NOAC, they could be converted to warfarin treatment for four weeks before the CA procedure, continue with NOACs or stop the therapy 24-36 hours before the ablation procedure, depending on the type of NOAC and clinician's preference. This was individually discussed before all procedures to ensure there was no breach of study protocols.

For patients randomised to TSA, it is current practice to stop warfarin therapy five days

before the procedure and have anticoagulation bridging with enoxaparin at a dose of 1.5 mg/kg once daily for three days with no anticoagulation a day before they had the procedure. If patients were on a NOAC, it was discontinued 2-5 days before surgery depending upon the name of the NOAC and creatinine clearance.

2.6 ABLATION PROTOCOL

2.6.1 CATHETER ABLATION PROTOCOL

Patients were brought into the procedure room and anaesthetised using GA. TOE will exclude LA thrombus under GA before venous access is obtained. TOE also guided transseptal puncture. Patients were heparinised to maintain an activated clotting time between 300 - 350 seconds. The CARTO® three-dimensional electroanatomical mapping (EAM) system (Biosense Webster®, Diamond Bar, California) was used to create the LA geometry with a twenty-pole circular mapping catheter (Lasso 2515 NAV, Biosense Webster®, USA). Simultaneous bipolar voltage maps were created using CARTO® CONFIDENSE™. The bipolar voltage maps were created in AF and SR once the patient is cardioverted.

CA was conducted by using THERMACOOL® SMARTTOUCH™ 3.5mm irrigated-tip catheter (Biosense Webster®, Diamond Bar, California). A stepwise ablation strategy was used to isolate the PVs at the antral level electrically, then LA roof and the posterior/inferior line below the right and left inferior PVs (to create a ‘box lesion’) were created. A lateral mitral isthmus line (MIL) was performed and, finally, ablation at the cavotricuspid isthmus (CTI)

ablation was performed in the right atrium (Figure 4). After a waiting period of 30 minutes had elapsed, the electrical isolation of the PVs was confirmed through testing for both entrance and exit blocks with the circular sensing catheter (LASSO®). Differential pacing manoeuvres assessed the integrity of the linear lesions. Further ablation was performed to achieve bi-directional block across the linear lesions if a gap was present. If AT occurs at any point, it was mapped and ablated when possible [699]. An ILR was implanted at the end of the procedure once the activated clotting time (ACT) has normalised following heparin reversal with intravenous protamine. Patients were then extubated in the cardiac catheterisation laboratories upon recovery by the anaesthetist.

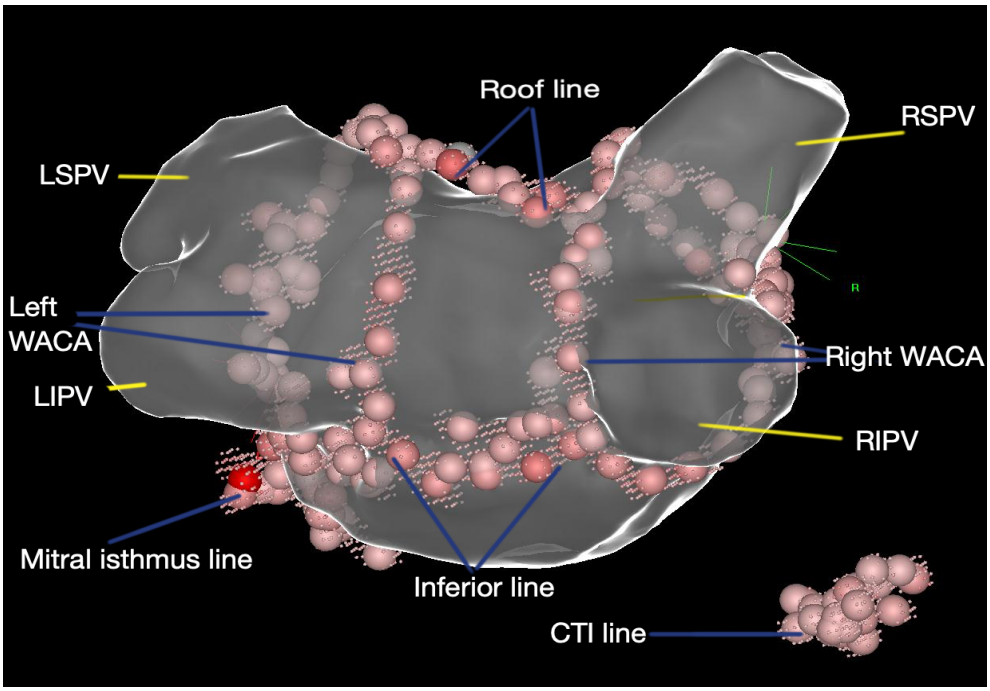


Figure 4: Lesion set for catheter ablation used in CASA AF RCT Trial. CTI – cavotricuspid isthmus line, LIPV – left inferior pulmonary vein, LSPV – left superior pulmonary vein, RIPV – right inferior pulmonary vein, RSPV – right superior pulmonary vein, WACA – wide area circumferential ablation.

2.6.2 THORACOSCOPIC SURGICAL ABLATION PROTOCOL

TSA consist of a totally thoracoscopic video-assisted surgical technique with the additional collaboration of an electrophysiologist for testing of ablation lesions.

Under GA, the patient was placed in the supine position with both arms lifted above his head and support underneath the spine to improve the exposure of lateral chest.

After draping and prepping transoesophageal echocardiography was performed to exclude the presence of any LA thrombus. Once LA thrombus was excluded, the procedure proceeded with selective single lung ventilation. Right video assisted thoracoscopic surgery was performed first, positioning a 5-mm port in the fourth intercostal space at the mid-axillary line. Once it was verified that there is no lung parenchymal adhesion to prevent the feasibility of the procedure, carbon dioxide insufflation was started. A second 8mm port was placed in the third intercostal space at the anterior axillary line and a third 10mm port at the sixth intercostal space between anterior and the posterior axillary line.

PVs and LA antrum were exposed by pericardiotomy, and blunt dissection using Lumitip™ dissector into the transverse and oblique sinus. The pericardiotomy was performed anterior to the phrenic nerve and retracted with sutures (Figure 5).

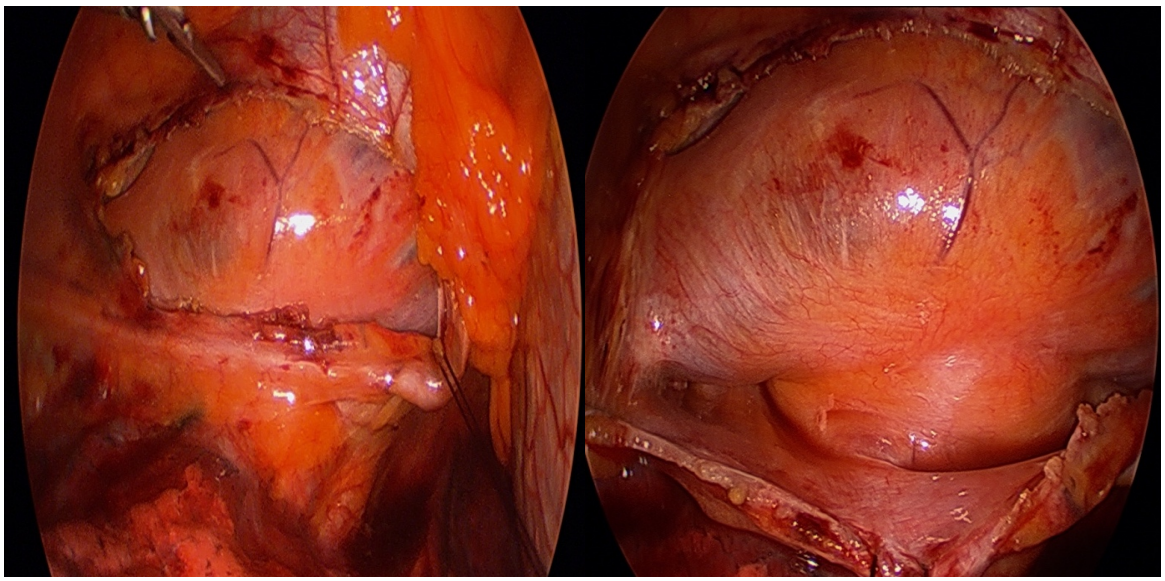


Figure 5: Phrenic nerve and exposure of right atrium anterior to it on the right-side approach.

Following dissection into the oblique sinus, the Sondergaard's groove is exposed in order to have a good surface of contact between the atrium and the ablator (Figure 6).

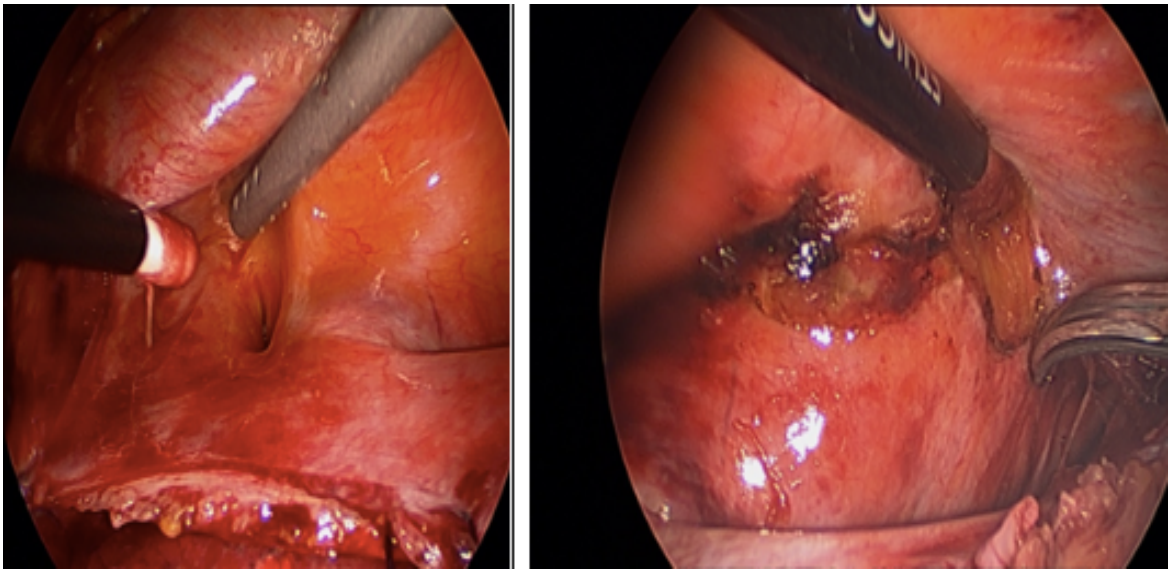


Figure 6: Oblique sinus and dissection of Sondergaard's groove

The pre-procedure activity of atrium and PVs are mapped using the isolator linear monopolar pen (AtriCure®, Inc., West Chester, Ohio, USA),(Figure 7, Figure 8).

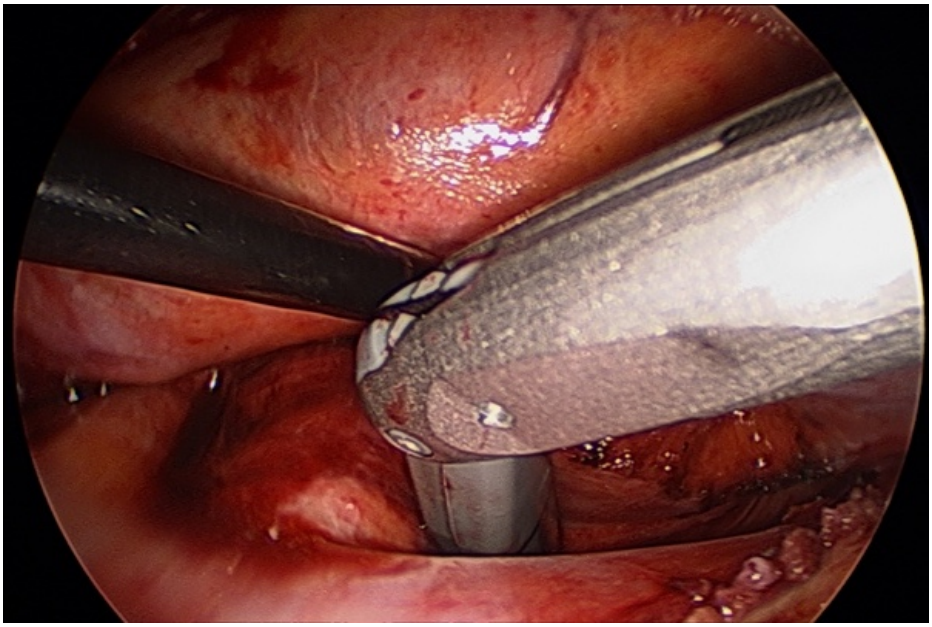


Figure 7: Preablation mapping of the right inferior PV

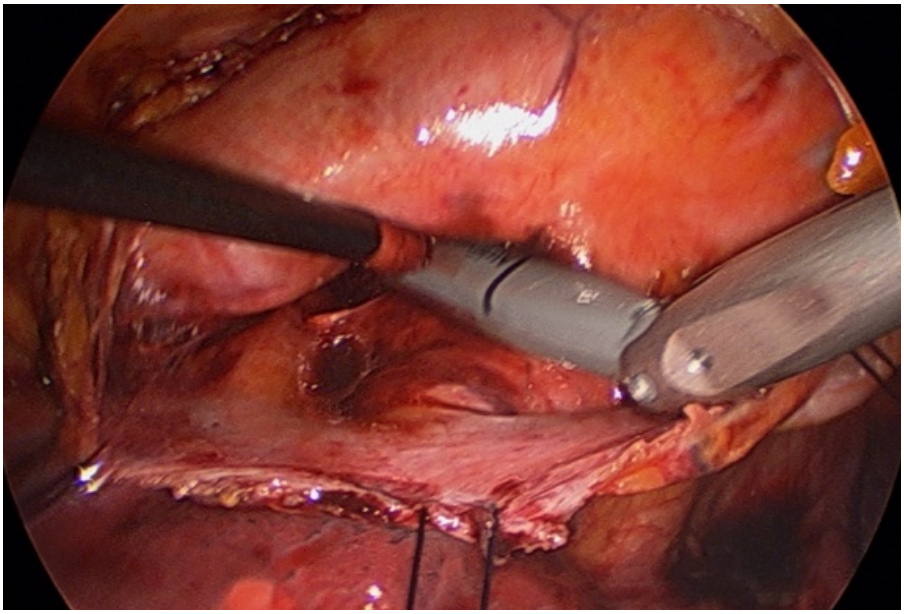


Figure 8: Preablation mapping of right superior PV

The Wolf™Lumitip™ dissector (AtriCure®, Inc., West Chester, Ohio, USA) is then used to encircle the right superior and inferior PV passing a guiding band under the PV through the oblique sinus (Figure 9). The rubber band is connected to AtriCure Isolator Synergy™ surgical ablation clamp (AtriCure®, Inc., West Chester, Ohio, USA) and is used as a guide to position it around the PV antrum. Pulmonary venous isolation (PVI) was performed from the epicardial surface using the bipolar RFA clamp and overlapping applications around LA antrum. Radiofrequency energy with the clamp was delivered until an impedance drop was seen within 5 seconds of the application. 5-10 applications are performed in order to achieve transmural lesions (Figure 10, Figure 11).

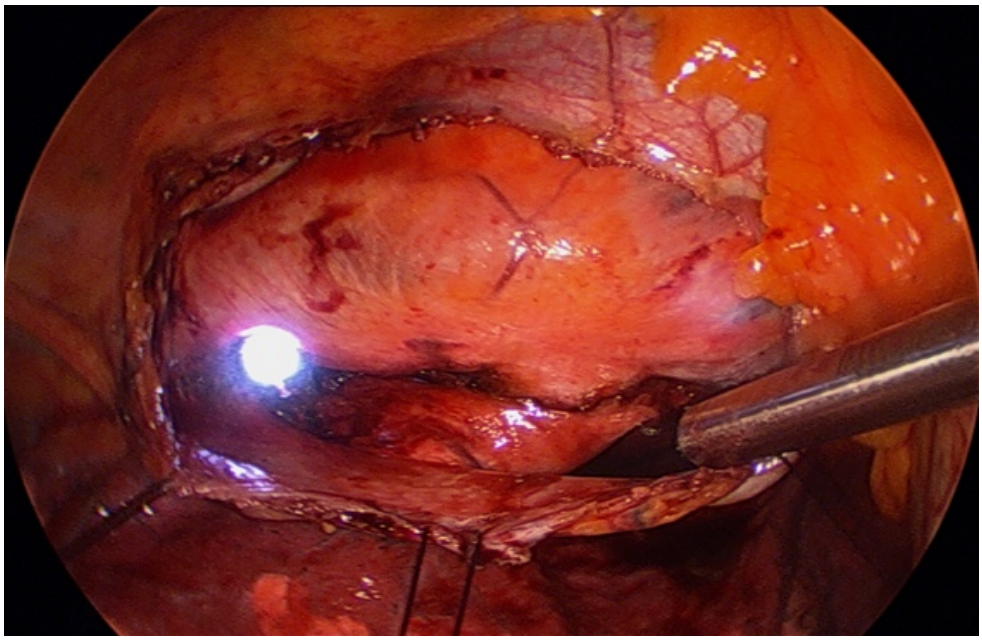


Figure 9: Dissector encircling the right superior and inferior PVs

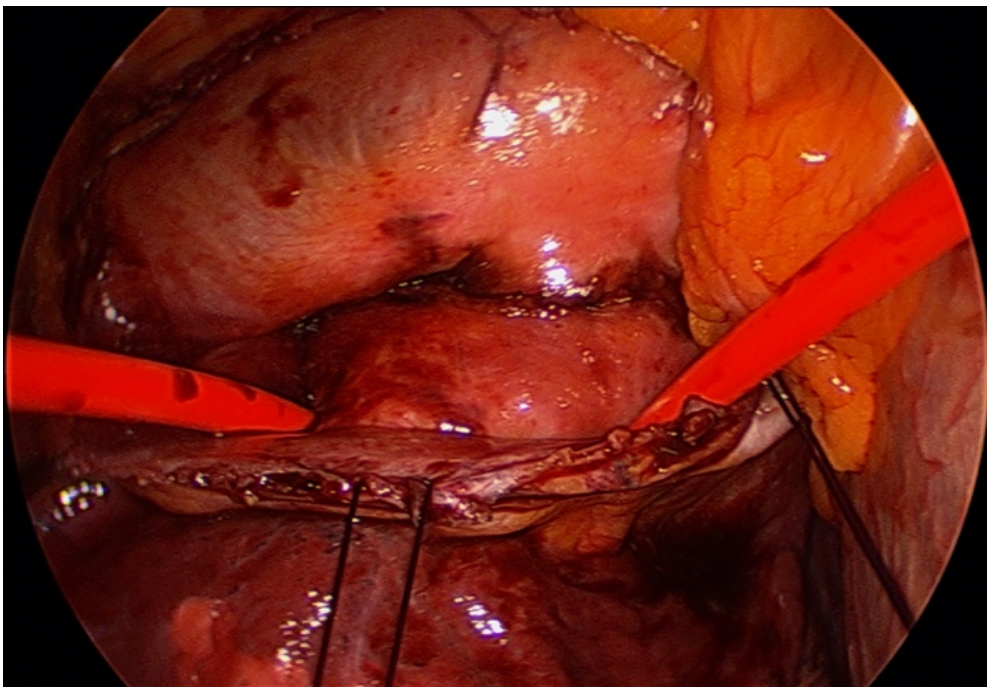


Figure 10: Delivery of right-sided clamp

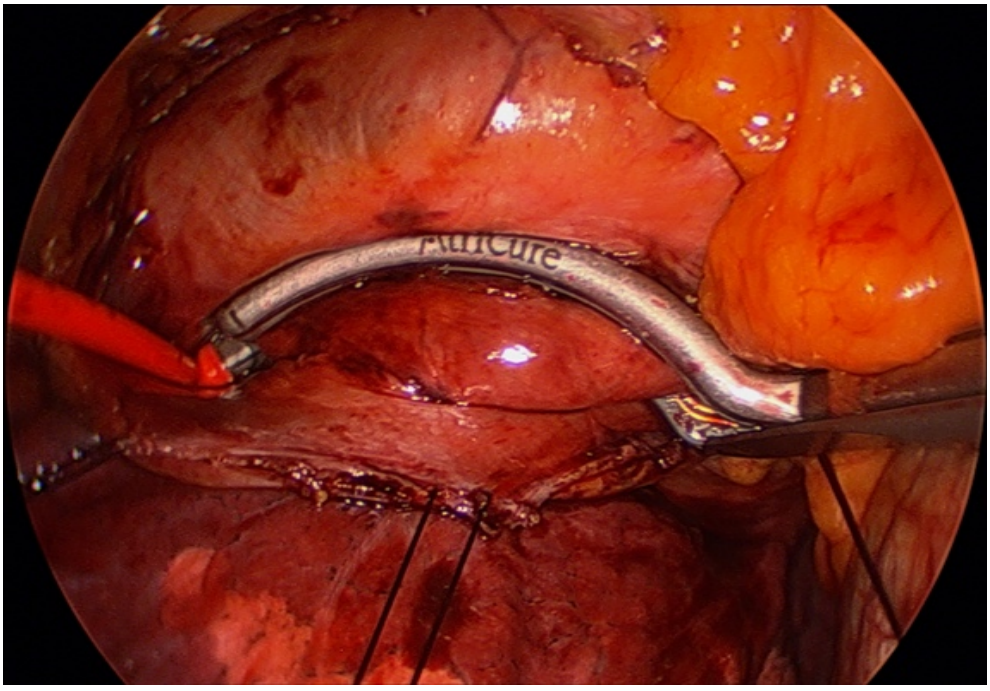


Figure 11: Ablation of right-sided atrial antrum using a clamp

An isolator 20mm linear monopolar pen (AtriCure®, Inc., West Chester, Ohio, USA) is used to create roofline and an inferior line of the box lesion (Figure 12, Figure 13, Figure 14).

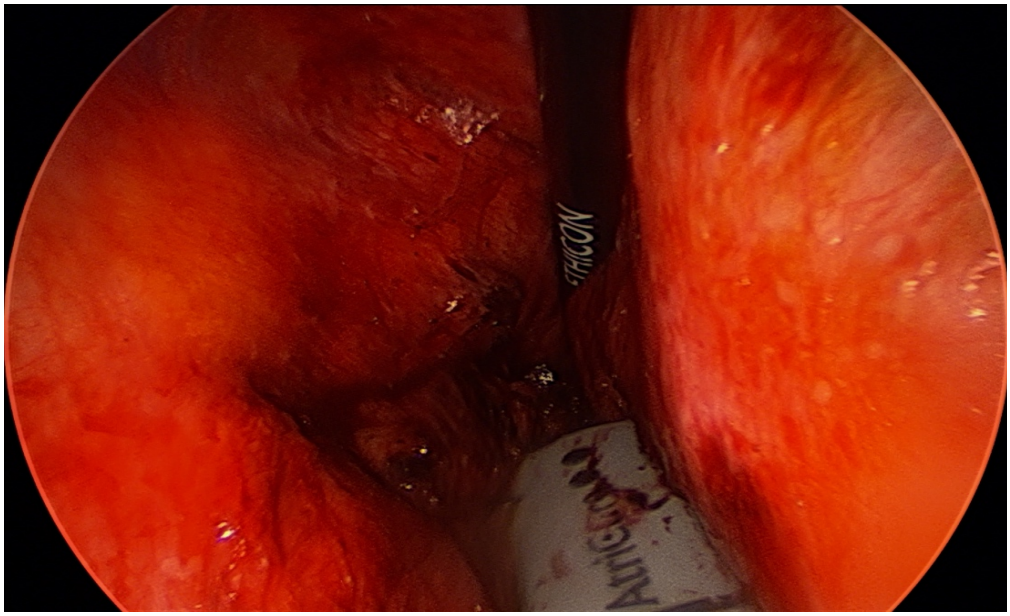


Figure 12: Superior line ablation

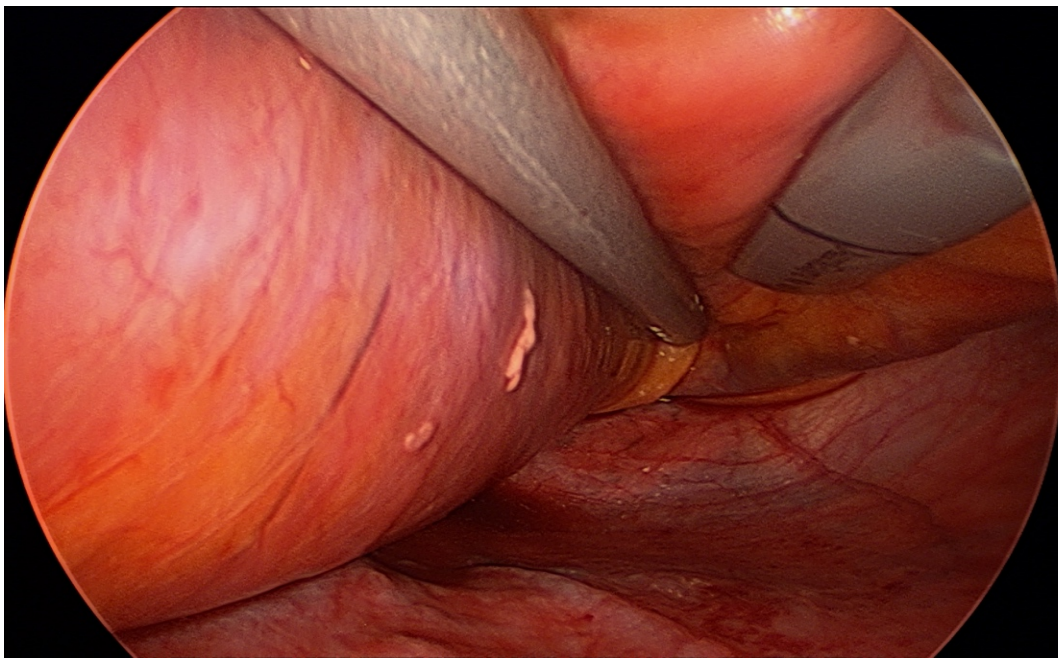


Figure 13: Inferior line ablation

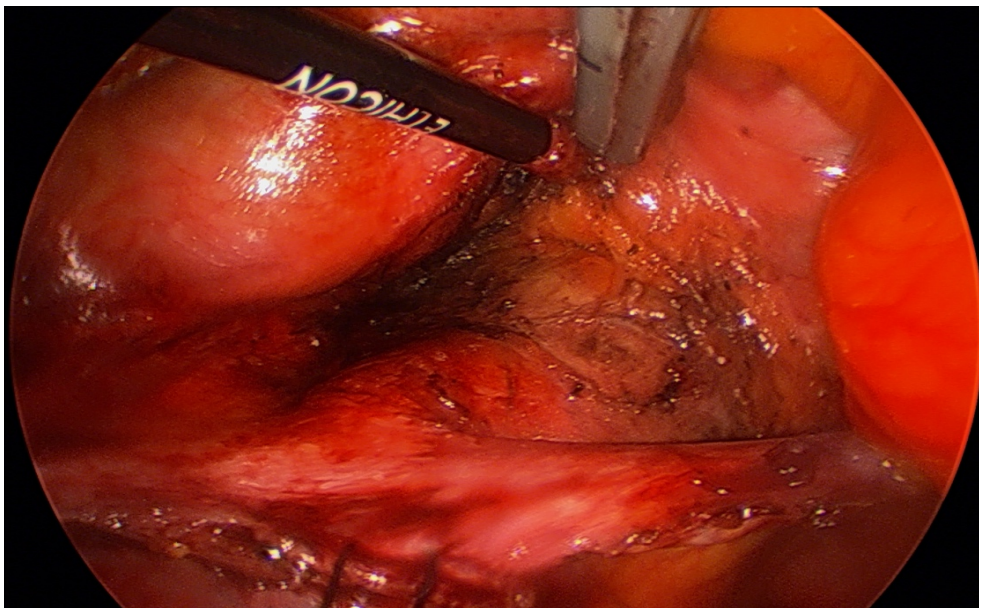


Figure 14: Superior line lesions adjoining right-sided PV lesions.

The result of the isolation of the right PVs is verified using the 20mm isolator linear pen and confirming PV entrance block (Figure 15).

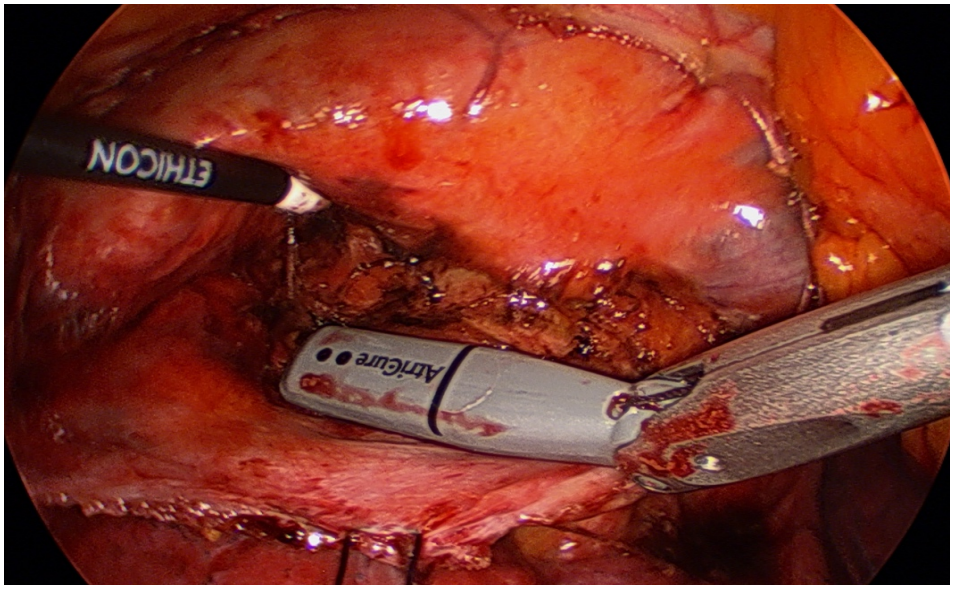


Figure 15: Post ablation sensing to ensure entrance block into PVs proximal to the ablation line

Finally, the GPs were identified at pre-defined anatomical locations using HFS for 5 seconds (60ms burst, 25mA current and pulse width 2ms) with resulting reduction in heart rate >50% or asystole 2 seconds. The HFS was delivered using the Atricure® Isolator® multifunctional pen. GPs were ablated using the AtriCure® Isolator® linear pen at the positively identified locations and retested to ensure they are not excitable (Figure 16, Figure 17).

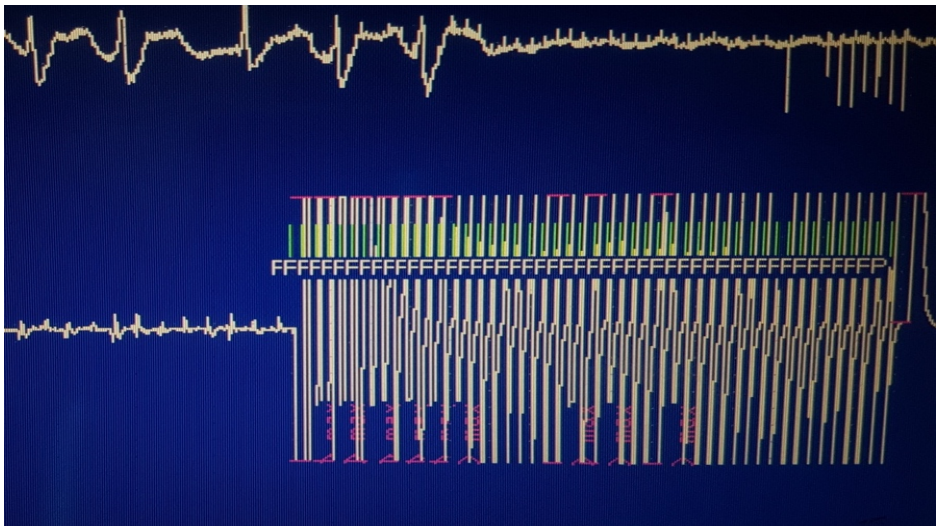


Figure 16: Positive high-frequency stimulation of ganglionic plexus resulting in asystole.

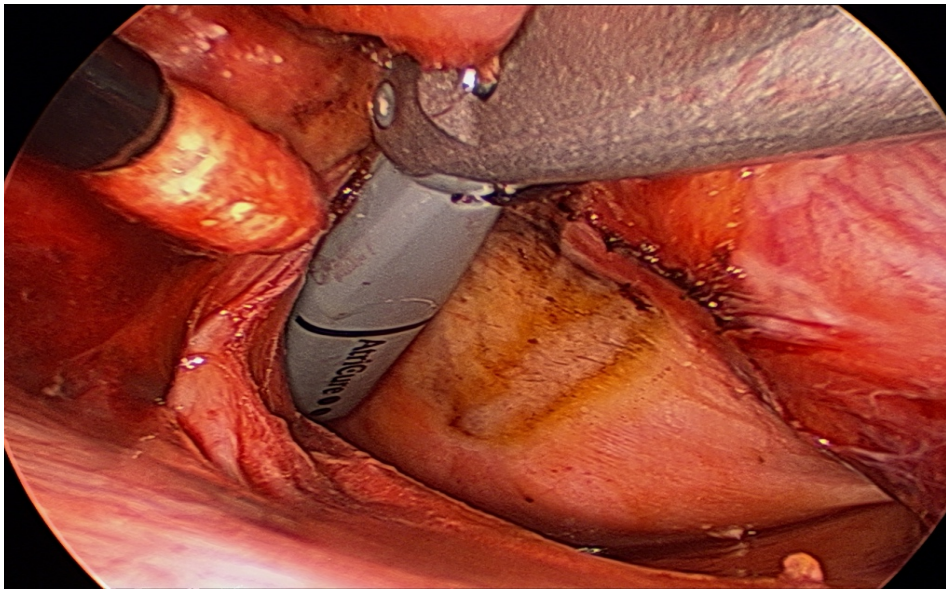


Figure 17: Ablation of Ganglionic plexi at the site of positive testing

The right lung was then inflated, and the procedure carried on from the left side of the chest. A similar arrangement of right-sided ports was inserted along the mid-axillary line. The pericardium was opened on the left side posteriorly to the phrenic nerve to allow for access to the left PVs and LAA. The ligament of Marshall was identified and divided or cauterised.

After mapping left PVs activity, AtriCure® Isolator® Transpolar clamp was used to perform PVI on the left side, and the Isolator® linear monopolar pen was used to complete the box lesion at the superior and inferior box line (Figure 18, Figure 19).

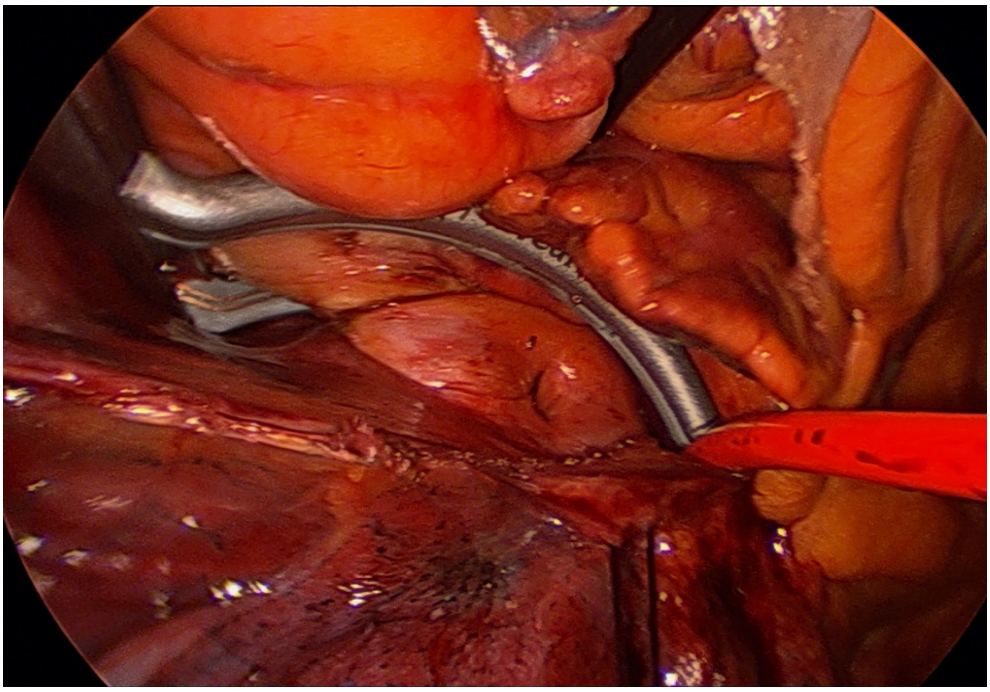


Figure 18: Left-sided PV antrum ablation

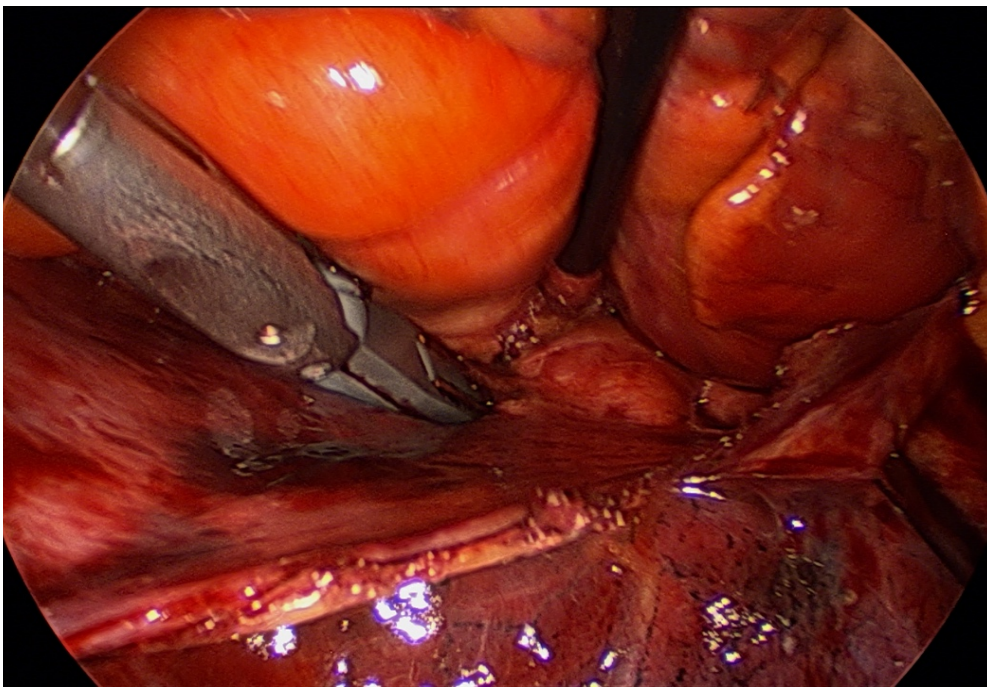


Figure 19: Inferior line and superior line join to the left-sided PV lesions

After confirmation of the lesions, external DCCV was performed and subsequently entry and exit blocks confirmed at the level of individual PVs, and posterior wall isolation (PWI) is confirmed through sensing and pacing at the level of the box lesion. Finally, after confirming the LAA size, AtriClip™ LAA excluder system (AtriCure®, Inc., West Chester, Ohio, USA) was deployed at the base of the LAA, and the position confirmed on the TOE before deployment. Once deployed on the LAA, TOE was performed to ensure there was no leakage before the complete withdrawal of the delivery system. The right pericardium was closed with 2 or 3 sutures to prevent possible herniation, and the left and right basal pleural drains were positioned.

Details of the operation have been described previously by Yilmaz and others [280,281,700]. In this trial, the protocol additionally mandated the presence of a cardiac electrophysiologist in

theatre during surgical ablation to ensure conduction block is tested and achieved for all lesions, as this has been associated with a trend towards better outcomes [191]. Cardiac surgeons participating in this study needed to be experienced in video-assisted thoracoscopic surgery and to have conducted at least 20 thoracoscopic ablations for AF as the primary operator before participating as an operator in the study.

Roof-line and an inferior line connecting the contralateral superior PVs were created by using the Isolator® multifunctional pen to isolate the posterior wall. (Figure 14). If AF persists, DCCV will restore SR. Posterior wall isolation was confirmed by sensing and pacing manoeuvres verify electrical isolation in SR. There is emerging evidence of improved outcomes with LAA exclusion [701]. Hence, the LAA will then be excluded using the AtriClip™ (AtriCure) to achieve mechanical and electrical isolation. The ILR was implanted at the end of the procedure and patients were extubated in the operating theatre.

Electrophysiological testing of the lesion set in TSA:

The attending electrophysiologist confirmed electrophysiological testing in the operating room. All PVs were tested pre-ablation using a surgical pen to ensure they were connected at the beginning of the ablation. Post-ablation, PVI was evaluated by testing at ten sites per patient. If PV appeared silent, a multipolar electrophysiology catheter was wrapped around the PV to test for circumferential isolation and in the posterior wall to test PWI (Figure 20).

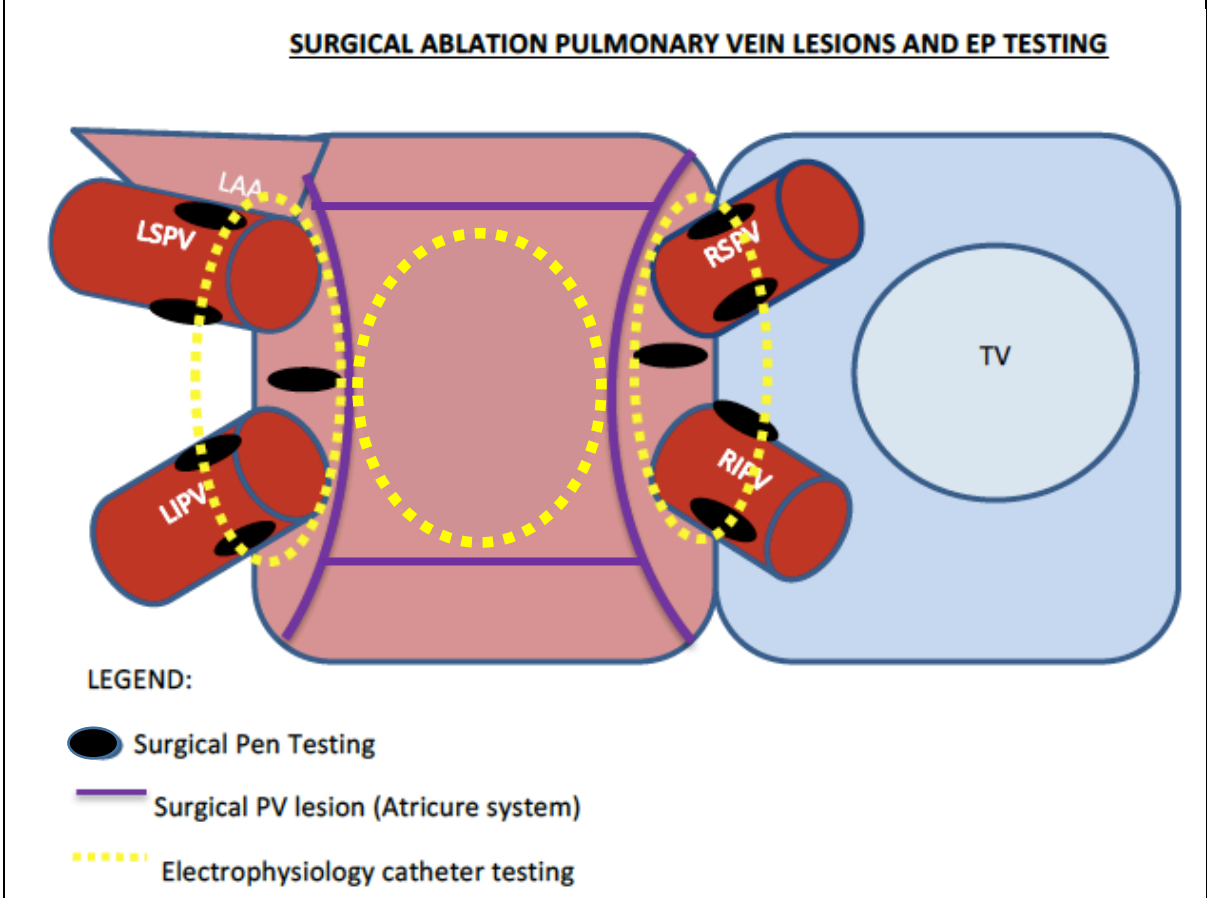


Figure 20: TSA with PV lesions and testing of isolation with multipole EP catheter and multipurpose surgical pen

Footnote 5: RIPV – right inferior pulmonary vein, RSPV – right superior pulmonary vein, LIPV – left inferior pulmonary vein, LSPV – left superior pulmonary vein, PV – pulmonary vein, TV – tricuspid valve

2.7 CARDIAC RHYTHM MONITORING PROGRAMMING AND PROTOCOL

Continuous cardiac monitoring using implantable loop recorders is shown to have overall high accuracy and excellent diagnostic yield in identifying AF/AT compared to non-invasive, intermittent cardiac monitoring[702,703]. The Medtronic Reveal LINQ ™ (Medtronic, Minnesota, USA,) ILR was chosen as it was at the time the smallest, latest generation of ILRs available with the most reliable remote monitoring system that helps minimise data loss[704,705]. It was inserted at the end of the index ablation procedure subcutaneously in left parasternal location along the anterior chest wall.

The sensitivity of the R wave was adjusted after implantation to ensure that there is no under-sensing or T wave over-sensing. The ILR is paired with a transmission module that is taken at home called the CareLink™ and communicates via the satellite to the CareLink™ network. Patients were asked to perform manual downloads twice a week at the beginning of their follow up to ensure that there were no episodes of arrhythmia missed. The download frequency was adjusted to more frequent for individual patients when the ILR's memory was filling too frequently.

Reveal LINQ™ is a highly sensitive and programmable device to detect the occurrence of AF and AT lasting 30 seconds or more [705,706]. Along with the critical primary outcome rhythm data, the ILR will also capture significant life-threatening arrhythmias such as asystole, ventricular tachycardia and bradycardia. Programming parameters of the device are summarised in Table 4. It has the capacity to record up to 30 minutes of data automatically. Each automatically detected event consisted of 2 minutes (15 episodes) of recording, and

any symptom triggered event consisted of 7.5 minutes (4 episodes) recordings or a combination of both equalling 30 minutes.

Table 4: Programming parameters for Reveal LINQ™ ILR

Programming Feature	Parameter programmed	Duration for detection
Indication	Post AF Ablation	
AT/AF	Both ON	
AT	Rates ≥ 100 /min	
Tachycardia	>162 /min	48 beats
Asystole	4.5 seconds	
Bradycardia	<40/min	8 beats
Patient symptom capture	7.5 minutes	4 episodes

Footnote 6: AF – atrial fibrillation, AT – atrial tachycardia

The patients are registered on Medtronic CareLink™ network following ILR insertion. Instructions were provided to perform manual data downloads using their home monitoring equipment. Data transfer to the CareLink™ server from the ILRs takes place over mobile phone networks. Patients are asked to perform manual data downloads once a week or more frequently depending on the burden of collected data in individual cases.

CareLink™ Network server access was provided to designated personnel to monitor ILR data uploads for their patients. A few dedicated cardiac physiologists were part of a core lab, blinded to treatment allocation, analysed the downloaded data regularly to produce

monthly heart rhythm assessment reports for each patient. A panel of three experts is nominated to adjudicate in cases where the heart rhythm is assessed as ambiguous by the cardiac physiologist.

The ILR had the capability of recording cardiac data including average daily heart rate, HRV, duration of AF, ventricular rates during atrial arrhythmias, and daily physical activity. The data were shown in a graph form and data was extracted using a digitization method to give numerical values for analysis. This is explained in detail in chapter 7 and used to analyse impact of GP ablation on the ANS.

2.8 POST OPERATIVE MANAGEMENT

2.8.1 ANALGESIC

Participants in the surgical ablation arm received intercostal nerve block at each port site (Bupivacaine or similar agents; dosage depended on patient characteristics and tolerance and was adjusted by the anaesthesiologist), paracetamol, codeine and tramadol if appropriate. In the first 24 hours' post-procedure, the patients were on patient-controlled analgesia using fentanyl or morphine or other opioids depending on the anaesthetist's recommendations and current clinical practice.

A day after surgery, if patients have a normal renal function and were able to tolerate oral medication, non-steroidal anti-inflammatory drugs were prescribed for one week with or without opiates. On discharge, the patients were given a supply of analgesics, including

acetaminophen for 28 days to be taken as needed. Participants in the CA arm were treated with acetaminophen and codeine as required.

2.8.2 ANTIBIOTIC

In both treatment arms patients received one dose of antibiotic on the induction of anaesthesia, one dose at the end of the procedure, and five days post-operatively, depending on local practices. Any signs of infection were treated with conventional empiric antibiotic regimen according to local antimicrobial practices.

2.8.3 ANTIARRHYTMIC MEDICATION

AADs were prescribed If the patient were taking them before the ablation and if arrhythmias occurred during the day of the procedure or post-procedure while in hospital. ß-blockers or CCB were continued to suppress atria ectopics that might lead to post-operative AF. Treatment with AADs ceased within the three month blanking period.

2.8.4 ANTICOAGULATION

After a minimum of 3 hours following ablation, patients received anticoagulation if there are no contraindications or haemorrhagic complications from the procedure. Anticoagulation in the surgical group received enoxaparin (1.5mg/kg once daily) or other heparin derivatives to ensure rapid reversal if needed. Once chest drains were removed, the patient's usual anticoagulation (warfarin or NOAC) was restarted and continued for the duration of the trial

follow up. Anticoagulation in the catheter group was continued uninterrupted and continued for the duration of the trial follow up.

2.9 FOLLOW UP

Details of the assessments during study participation are given in Figure 3 as per SPIRIT 2013 recommendations. Recurrence of symptomatic AF during the blanking period was treated with DC cardioversion with or without the use of AADs depending on patient tolerances and comorbidities. Patients were offered redo CA if the AF recurs at a later point in the follow-up period, as shown in Figure 2.

2.10 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All adverse events occurring during the course of the trial were collected, documented and recorded by the research team at each trial centre. Patients were advised to contact the research team if they have any health concerns during the study follow up.
The research teams ensured that known complications, as well as unexpected events/reactions, were documented in patients' study files as well as their medical notes. The teams followed agreed protocol for timely reporting of all serious adverse events, which involved written notification to the chief investigator and the study sponsor as soon as possible.

All adverse events and their classification were regularly reviewed by the members of the DMC which met twice a year. Towards the end of the follow up period we additionally

convened an independent expert group to review adverse events in the study. The group consisted of two cardiothoracic surgeons and one EP consultant. They familiarised themselves with the protocol and each was sent a subset of adverse events to classify on their own. The group was blinded to the treatment allocation of the patients whose anonymised data were reviewed. We then scheduled a meeting in person with the trial management group to discuss and classify 40 events. The aim of the meeting was to ensure that every serious adverse event was identified as such and that its relatedness to the study procedure was ascertained. A consensus was used in cases where unanimous decision was not reached. The study protocol defined serious adverse events as those resulting in hospitalisation and leading to permanent injury or death.

Table 5 shows a list of expected complications from the ablative procedures. Recurrence of AF and subsequent hospital admission for DC cardioversion or percutaneous CA will not be treated as serious adverse events in the trial but were recorded and reported with the results.

Table 5: Known Complications Associated with Ablative Procedures in CASA-AF Study

Adverse Events	Serious Adverse Events
Bruising, hematoma, vascular injury not requiring intervention	Vascular complications requiring blood transfusion or intervention
Pericardial/pleural effusion (observation only)	Symptomatic pericardial/pleural effusion or requiring intervention
Broken rib	Stroke/transient ischemic attack
Pneumothorax requiring observation	Pneumothorax requiring chest drain
Infection (i.e. pneumonia)	Empyema
Pulmonary oedema	MI
Temporary phrenic nerve damage	Permanent phrenic nerve damage
Pain near surgical sites	PV stenosis (>50% reduction in diameter from baseline)
	The requirement to insert PPM (with or without prior conduction tissue damage)
	Cardiac trauma requiring surgical intervention
	Radiation induced skin damage
	Oesophageal atrial fistula
	Death

Footnote 7: MI – myocardial infarction, PPM – permanent pacemaker, PV – pulmonary vein

2.11 EVALUATION OF ATRIAL AND VENTRICULAR FUNCTION

LA size and function were evaluated using two main imaging modalities; CMR and echocardiography. The LA size was measured by CMR at baseline and at 6 months, while transthoracic echocardiograms were performed at baseline, 3 months and 9 months. In CMR, the LA volume was calculated by using biplane Simpson's method while RA volumes were calculated by measuring the endocardial delineation of the RA in each individual slice of acquisition. In TTE, the LA volume was calculated by using biplane Simpson's method. Maximum and minimum volumes of the LA and RA were used to calculate the emptying fraction of the atrial chambers (LAEF and RAEF). The volumes of the atria during follow up were compared to baseline volumes to evaluate the impact of ablation and restoration of sinus rhythm on the atria. In cases where the atria shrunk during follow up, it was termed reverse remodelling. Patients with very poor acoustic windows and those in AF during the follow up scans were excluded from analysis. This is explained in detail in chapter 4 and chapter 5.

LA function can also be calculated by using other imaging modalities such as tissue Doppler imaging, and strain was also used to derive three aspects of LA function during the cardiac cycle. The three aspects of atrial function are termed reservoir function (LA expansion from minimum LA size), conduit function (LA function during passive ventricular filling) and contractile function (LA function during active contraction of the atria). Impact of two ablation techniques on the atria was measured at baseline, 3 months and 12 months. The atrial function is described in detail in the chapter 4. Patients with very poor acoustic windows and those in AF during the follow up scans were excluded from analysis. TomTec

was used to measure strain on 2D images to allow centres to be independent of vendor software used in individual institutions. This is explained in detail in chapter 4.

CHAPTER 3

SUCCESS OF THORACOSCOPIC SURGICAL ABLATION COMPARED TO CATHETER ABLATION – CASA AF RCT

The primary objective in this trial is to establish which of the two ablative techniques is more effective in treatment of long standing persistent atrial fibrillation (LSPAF).

The primary efficacy end point is measured by the proportion of patients who require a single intervention to remain AT/AF free during the 12 months follow up following ablation (starting from the end of the blanking period) without needing AADs. Recurrence is established from the ILR data with episodes of AT/AF lasting ≥30 seconds.

Additionally, the study aimed to evaluate the secondary efficacy endpoint of each procedure defined as reduction in the burden of AT/AF by ≥75% and their safety.

Management of AF with rhythm control strategy becomes increasingly challenging beyond paroxysmal AF due to underlying neurohormonal imbalances leading to remodelling of the atria resulting in atrial dilation and fibrosis. Details of the background information on atrial fibrillation were provided in chapter 1. In order to investigate the most effective ablation modality for LSPAF, we completed a randomised control trial called CASA-AF that was designed to compare success in maintaining sinus rhythm following ablation between catheter ablation and thoracoscopic surgical ablation [698]. Details of the ablation lesion sets and the methodology of the trial and substudy of atrial function are described in detail in chapter 2.

3.1 RESULTS

One hundred and twenty patients with LSPAF recruited from 4 sites in England (Royal Brompton Hospital, Harefield NHS Hospital Trust, Liverpool Heart and Chest Hospitals, and Brighton University Hospitals) were enrolled in CASA AF trial and randomised in 1:1 ratio to CA or TSA. The recruitment of the study took place from August 2015 to June 2018, and the participants were followed up for one year after ablation. The eligibility criteria are listed in Table 3. A CONSORT diagram below shows the outcomes of screening and randomisation and progress of the participants through the study (Figure 21)

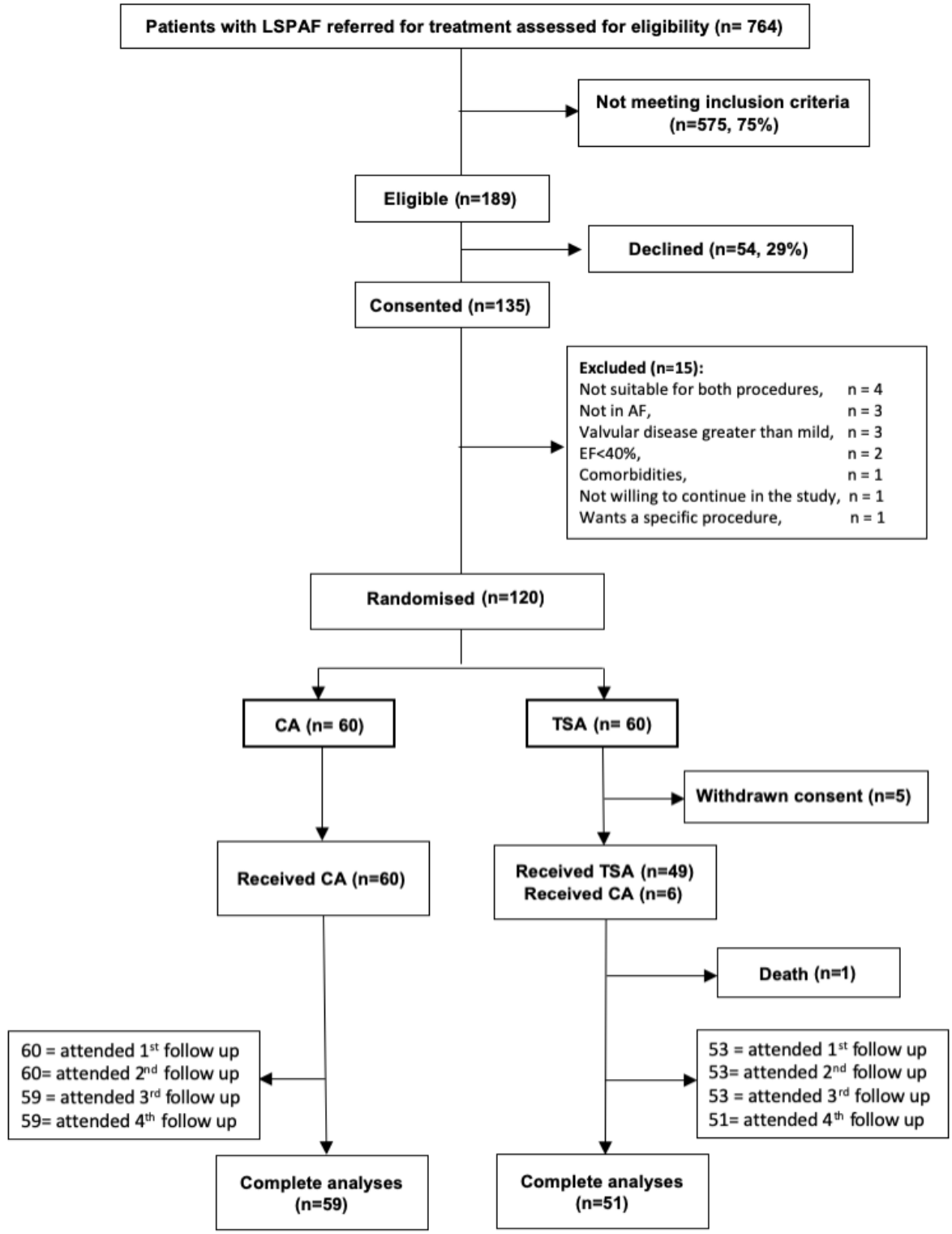


Figure 21: Consort diagram of the CASA AF Trial

Footnote 8: CA – catheter ablation, TSA – thoracoscopic surgical ablation. Five patients withdrew from the trial and were treated according to clinically determined management.

Baseline characteristics of the study participants are outlined in Table 6.

Table 6: Baseline characteristics of patients randomised to receive CA or TSA as part of the CASA AF RCT

Parameters	**CA (60)**	**TSA (60)**
Age mean ± SD	61.3 ± 10.1	64.2 ± 8.9
Male n (%)	45 (75)	44(73)
AF duration, (days)	751 ± 379	906 ± 433
LVEF (%)	56.2 ± 7.1	56.2 ± 7.7
DCCV		
0	3 (5)	6 (10)
1	37 (61.7)	36 (60)
2	12 (20)	15 (25)
3	4 (6.7)	2 (3.3)
4	4 (6.7)	1 (1.7)
LA volume (CMR) ml/m^2 ± SD	63.2 ± 14.9	68.1 ± 18.5
LA volume (TTE) ml/m^2 ± SD	51 ± 14.4	52.5 ± 16
Hypertension, n (%)	22 (36.7)	31 (51.6)
Diabetes, n (%)	4 (6.7)	5 (8.3)
Dyslipidaemia, n (%)	33 (55)	33 (55)
Stroke / TIA, n (%)	0	4(6.7)
COPD/Asthma, n (%)	6 (10)	13 (21.7)

Chronic kidney disease, n (%)	5(8.3)	4(6.6)
Coronary artery disease, n (%)	7 (11.7)	6 (10)
Thyroxine, n (%)	2 (3.3)	3 (5)
Betablockers, n (%)	51 (85)	47 (78.3)
Calcium channel blockers, n (%)	5 (8.3)	8 (13.3)
Digoxin, n (%)	17 (28.3)	13 (21.7)
ACE/ARB, n (%)	26 (43.3)	28 (46.7)
Statin, n (%)	27 (45)	26 (43.3)
Amiodarone, n (%)	2 (3.3)	5 (8.3)
Sotalol, n (%)	1 (1.7)	2 (3.4)
Flecainide, n (%)	2 (3.3)	0
CHA_2DS_2VASc score, (n)		
0	18	12
1	21	18
2	8	16
3	9	3
≥4	4	11
HAS-BLED score, (n)		
0	12	12
1	24	16
2	17	22
≥3	7	9
Anticoagulation (n)		

Apixaban	20	16
Rivaroxaban	16	22
Dabigatran	5	2
Edoxaban	3	1
Warfarin	16	18
Baseline to randomisation, (days)	23.1 ± 32.8	28.7 ± 39.7

Footnote 9: ACEi -angiotensin converting enzyme inhibitor, AF – atrial fibrillation, ARB- angiotensin receptor blocker, CMR – cardiac magnetic resonance imaging, COPD – chronic obstructive pulmonary disease, DCCV – direct current cardioversion, LA – left atrium, LVEF – left ventricular ejection fraction, ml/m^2 – millilitres per meter squared, n – number of patients, SD – standard deviation, TIA – transient ischemic attack, TTE – transthoracic echocardiogram

Study participants were required to complete a number of baseline assessments before being randomised in the study which took on average 26.7 (±36.4) days, similar in both arms. Baseline characteristics of TSA group were minimally different compared to CA group as shown in Table 6 in patients having hypertension (51.6% vs. 36.7%, p = 0.04), stroke/TIA (6.7% vs. 0%, p = 0.04), COPD (21.7% vs.10%, p = 0.04) and AF durations (906 days vs 571 days, p =0.04). Incidental findings at baseline requiring further investigations were responsible for increased time between baseline assessments and randomisation, which was on average 23.1 ± 32.8 days in CA and 28.7 ± 39.7 in TSA arm. The time between randomisation and receiving the procedure was 49.5 ± 38 days vs 74.3 ± 46.7 days for CA vs TSA respectively, p<0.0001. The delays were more pronounced in TSA arm and were due to frequent cancellations of the TSA procedure in order to deal with more urgent clinical cases.

Two patients were not suitable for TSA and three did not want to proceed with the ablative treatment following randomisation, so they were excluded from the survival curve analyses. Six patients in the TSA group had severe adhesions between myocardium and pericardium and surrounding structures, resulting in abandonment of the TSA procedure prior to any ablations being delivered as the risk of cardiac perforation or tear was too high. These six patients subsequently received CA, but their data are analysed as per intention to treat. A per protocol analysis was also performed as part of sensitivity analysis.

3.2 ACUTE PROCEDURAL RESULTS

Mean overall procedure duration in the CA arm was 229 ± 48.4 minutes, and in the TSA group was 278.6 ± 64 minutes ($p<0.0001$). The delivery of lesion set in the TSA arm was quicker (20.5 ± 9.2 min) when compared to CA (70.9 ± 28.4 min) group, $p<0.0001$.

Ablation using wide area circumferential ablation (WACA) encircling the PVs took significantly less time in the TSA group as compared to the CA group (140 ± 130.2 seconds vs. 990 ± 484 seconds, <0.0001) as shown in Table 7. There was no difference in the additional lines of the roof and inferior lines (roof line: 371.6 ± 261.5 seconds vs 364.8 ± 232.8 seconds, $p=0.88$; inferior line: 361.6 ± 263.6 seconds vs 394.8 ± 217.2seconds, $p=0.45$) between CA and TSA groups. The power required to execute all lesions was significantly lower in TSA arm. Total fluoroscopy time in CA was 26±44.6 minutes. Lesions completion was confirmed with bidirectional block across each of the lesions (Table 7).

Table 7: Procedure details for the index procedure for both TSA and CA groups

Parameter		CA (n = 60)	TSA (n = 55)	P value
Procedure time, minutes (mean ± SD)		229 ± 48.4	278.6 ± 64	<0.0001
Ablation time, minutes (mean ± SD)		70.9 ± 28.4	20.5 ± 9.2	<0. 0001
Fluoroscopy time, minutes (mean ± SD)		26 ± 44.6	0	<0.0001
Right WACA	Duration, seconds (mean ± SD)	990 ± 484	140 ± 130.2	<0.0001
	CF, grams (mean ± SD)	13.4 ± 3.2	n/a	
	Power, watts (mean ± SD)	31.7 ± 5.2	16 ± 3.6	<0.0001
Left WACA	Duration, seconds (mean ± SD)	963 ± 361	126.6 ± 84	<0.0001
	CF, grams (mean ± SD)	12.7 ± 3.2	n/a	
	Power, watts (mean ± SD)	32.3 ± 5.2	16.4 ± 3.3	<0.0001
Roof line	Duration, seconds (mean ± SD)	371.6 ± 261.5	364.8 ± 232.8	0.88
	CF, grams (mean ± SD)	18.9 ± 12.7	n/a	
	Power, watts (mean ± SD)	31.4 ± 6	19 ± 1.5	<0.0001
Inferior line	Duration, seconds (mean ± SD)	361.6 ± 263.6	394.8 ± 217.2	0.45
	CF, grams (mean ± SD)	17.8 ± 12.5	n/a	
	Power, watts (mean ± SD)	32.1 ± 14.4	19.2 ± 2	<0.0001
MIL	Duration, seconds (mean ± SD)	832.7 ± 648.6		
	CF, grams (mean ± SD)	15.8 ± 2.9		
	Power, watts (mean ± SD)	31.9 ± 5		
CTI line	Duration, seconds (mean ± SD)	553.8 ± 307		
	CF, grams (mean ± SD)	14.4 ± 14		

	Power, watts (mean ± SD)	36 ± 4.9		
Isolations	Right WACA, n (%)	57 (95)	52 (95)	1
	Left WACA, n (%)	57 (95)	53 (96)	0.98
	Roof line, n (%)	46 (77)	50 (91)	0.04
	Inferior line, n (%)	55 (92)	46 (84)	0.19
	MIL, n (%)	45 (75)		
	CTI line, n (%)	56 (93)		

Footnote 10: CA – catheter ablation, CF – contact force, CTI - cavotricuspid isthmus, MIL - mitral isthmus line, min – minutes, TSA – thoracic surgical ablation, WACA – wide area circumferential ablation

Acute procedural success defined as restoration of SR and completion of lesion sets was achieved in 56(n=60) in the CA arm and 49(n=55) in the TSA arm (93.5% vs. 89.1%, p 0.42).

In CA group electrical isolation of the left and right pulmonary veins, and cavotricuspid isthmus line was achieved in 98% of the patients (58/60). Electrical isolation of the mitral valve isthmus and box lesion was achieved in 82% of patients (49/60).

Of 60 patients randomised to TSA group 55 underwent treatment. Six of them had to be treated by CA due to lung or cardiac adhesions. Of 49 patients who completed TSA treatment, two did not have the complete lesion sets ablated: one patient did not have left

PV isolated and LA appendage occluded due to its unfavourable anatomical features. One other patient did not have their LA appendage ligated for the same reason.

Electrical isolation in surgical ablation group, tested with surgical pen, was achieved in 96 % of the patients (47/49) for left pulmonary vein, 92% (45/49) for right pulmonary vein and 88% (43/49) for box lesions. Isolation of GP was based on positive identification (vagal response) using high frequency stimulation. Coronary sinus GP was ablated in 71% (35/49) of patients, right inferior GP in 35% (17/49) and right superior GP in 29% (14/49) of patients as shown in *Figure* 22 . At the end of the procedure there was abolition of vagal response in all of the GPs.

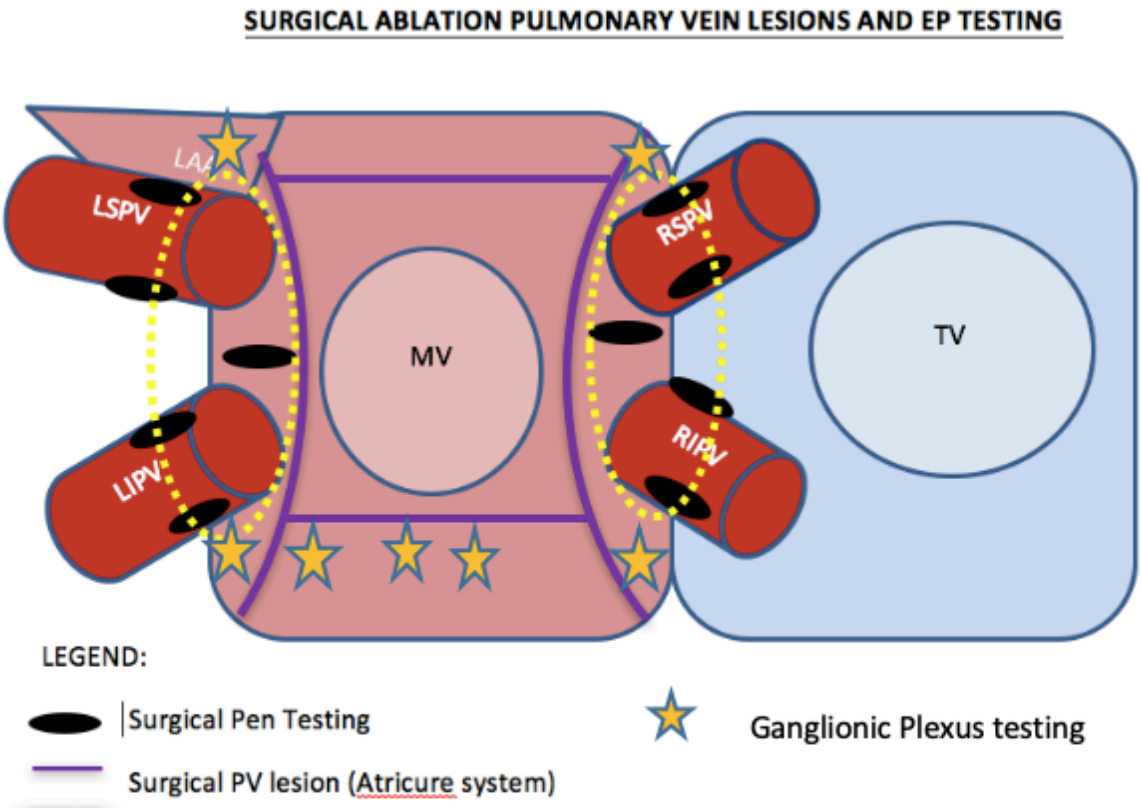


Figure 22: Surgical pen testing and multipole electrophysiology catheter testing of the lesion set delivered in TSA.

The time and power required to ablate ganglionic plexi in TSA group are shown in Table 8.

Table 8: Details of GP lesions in patients undergoing surgical ablation (median, IQR).

Ganglionic plexus	**Patients with positive test (n)**	**Number of lesions** (mean ± SD)	**Ablation time minutes** (mean ± SD)	**Power, Watts** (mean ± SD)
Left superior	2	2.5 (2.2-2.8)	0.8 (0.7-0.8)	20 (20 - 20)
Left Inferior	2	7 (6.5-7.5)	0.8 (0.8-0.9)	20 (20-20)
Right Superior	14	2.5 (2-7.5)	0.8 (0.6-1.6)	19.2 (17.5-20)
Right Inferior	17	4 (2-8)	1 (0.5-1.5)	20 (17-20)
Right Posterior	7	4 (4-11.5)	1 (0.7-2.1)	20 (19.8-20)
Coronary Sinus	36	11 (6.8-16.2)	1.7 (1.1-2.6)	20 (15.2-20)
Left Bifurcation	1	4	0.5	20
Right Anterior	1	2	0.4	20

Electrophysiological testing in SA arm was intended to be done by two methods, firstly by multipoint testing using the surgical pen and then by multipolar electrophysiological catheter. In our trial this proved to be a very demanding process which was attempted in 11 patients but was successful in only 8. This was largely due to anatomical features which increased the risk of serious complications (for example enlarged superior vena cava). In patients where we were able to conduct electrophysiological testing using both methods,

multipolar catheter identified only one additional site of PV connectivity compared to surgical pen, so we abolished this testing in the remaining procedures.

In the TSA group, the patients spent more time in high level care compared to the CA group as shown in Table 9. Left atrial appendage ligation was not performed in two patients due to short anatomical neck and cauliflower anatomy. SR was established in all surgical cases by DCCV at the end of the procedure.

Patients in the TSA group spent significantly longer in the hospital than CA group post-operatively (6.6 ± 2.9 days vs 2.3 ± 1.9 days, p<0.0001). The length of stay of 2.3days for the CA group was related to the logistics of admitting the patient a night before and keeping them at least one day post-procedure to ensure the research team identified all complications before discharge.

Table 9: Post-operative period prior to discharge following index procedure

Parameters	**Unit**	**CA (60)**	**TSA (55)**	**P value**
Acute success	n (%)	56 (93.3)	49 (89.1)	0.42
Length of stay in hospital	Days, mean ± SD	2.3 ± 1.9	6.6 ± 2.9	<0.0001
Intensive care unit	Days, mean ± SD	0	1.4 ± 0.9	<0.0001
High dependency unit	Days, mean ± SD	1	2.6 ± 1.7	<0.0001
Recovery unit	Days, mean ± SD	1.2 ± 0.4	2.3 ± 2.2	0.001

Footnote 11: CA – catheter ablation, CF – contact force, CTI - cavotricuspid isthmus, HDU - high dependency unit, ICU - intensive care unit, MIL – mitral isthmus line, LOS - length of

stay, SD – standard deviation, TSA -thoracoscopic surgical ablation. Acute procedural success was defined as bidirectional block in the lesion set delivered for the ablation procedure and the end of the case

Only one person needed treatment in the high dependency unit following CA whereas ten patients from TSA arm were admitted to intensive care for 1.4 ± 0.9 days, and 39 were admitted to the high dependency unit for 2.6 ± 1.7 days. Seven patients needed DCCV before discharge from hospital following TSA. Nineteen patients required DCCV in the blanking period to restore SR (*Figure* 23).

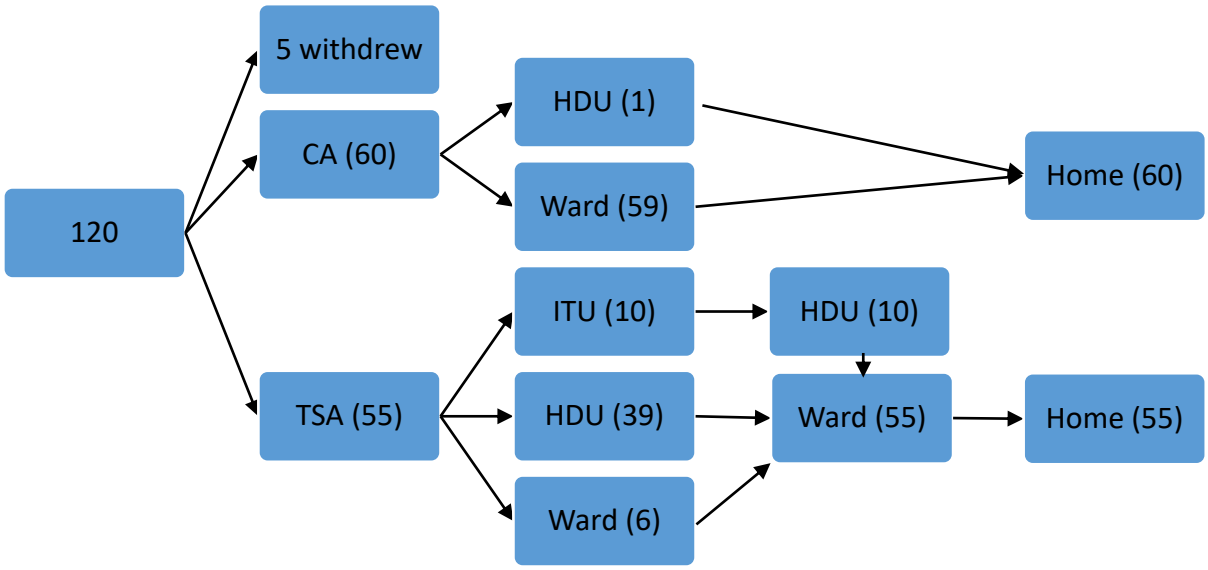


Figure 23: Patients treatment and flow in the hospital prior to discharge

Footnote 12: CA – catheter ablation, HDU – high dependency unit, ITU – intensive care unit, TSA – thoracoscopic surgical ablation.

3.3 BLANKING PERIOD

Blanking period was set to 90 days following ablation within which time any arrhythmia was to be treated with amiodarone or DCCV. Twenty-one patients (35%) from CA and 19 patients (34.5%) from the TSA group received DCCV in the blanking period to restore SR, p =0.96.

Amiodarone therapy was prescribed for 17 patients and discontinued at the end of the blanking period in 14 patients with 3 patients continuing Amiodarone as a consequence of frequent symptomatic paroxysms of AF.

Patients had study assessments every three months following ablation (as described in Chapter 2) and their heart rhythm was reviewed from the ILR data on a monthly basis by a cardiac physiologist blinded to procedure allocation.

3.4 PRIMARY OUTCOMES

The primary outcome was defined as freedom from atrial arrhythmia after a single ablation procedure without AADs during the follow-up period (Chapter 2.1.1). Primary outcome analyses are based on ITT analysis of the data from 115 patients who underwent ablation, 60 in CA and 55 in SA arm. Similar proportion of patients in both arms had additional ablation during follow up: 9/60 (15%) in CA and 10/55 (18%) in TSA group, p =0.65. At the end of the 12 months' follow up excluding blanking period, 26.7% of patients in the CA (16/60) arm and 29.1% patients in SA (16/55) were free from AT/AF after one procedure and without AADs, p=0.95 (Figure 24).

Four patients in the follow-up period were given DCCV to restore SR. Eight patients from the TSA group and eight patients from the CA group were offered redo CA due to ongoing symptoms with EHRA score > 2. Kaplan Meier survival log-rank analysis showing recurrence to first atrial arrhythmias following the blanking period to 12 months follow up (Figure 24). There was no difference in freedom from atrial arrhythmias after initial ablation strategy without AADs between TSA and CA (29.1% vs 26.7%, Log Rank test p=0.95), with HR = 1.013 (95% CI = 0.66 – 1.56, p=0.95).

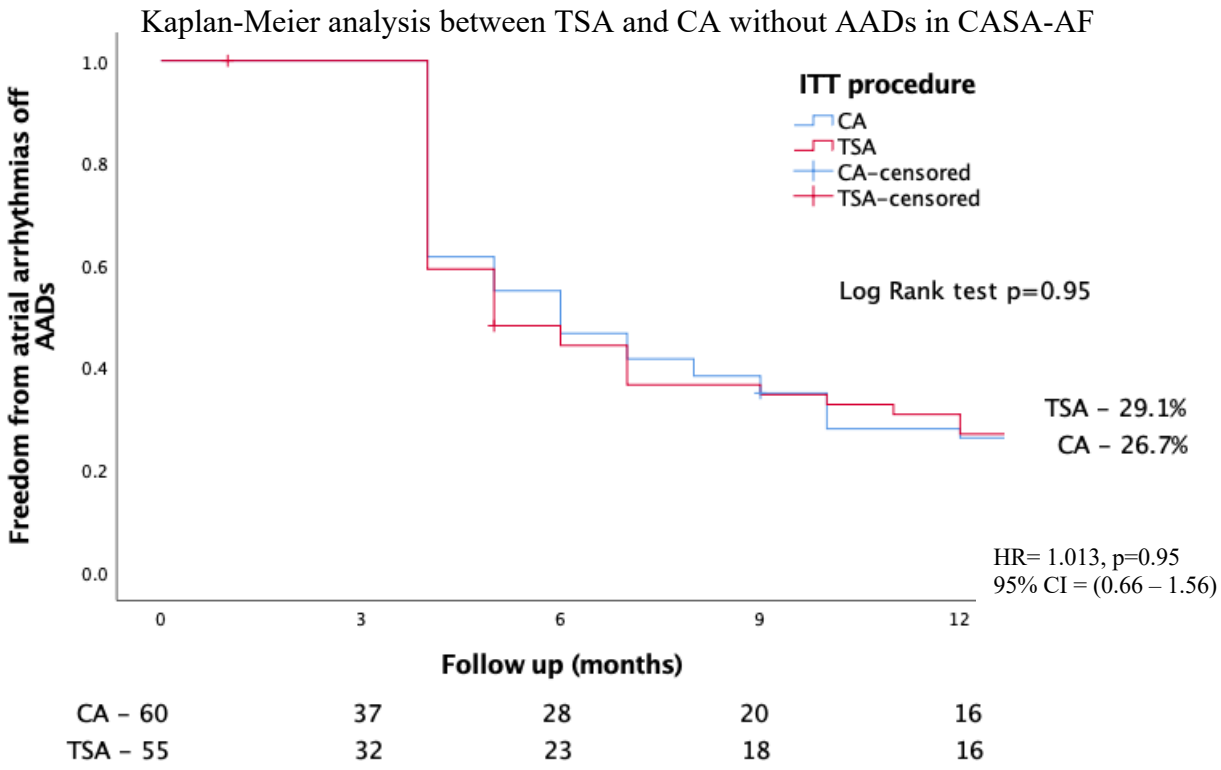


Figure 24: Kaplan-Meier plot of survival free from atrial arrhythmias from the end of the blanking period to the 12 months follow up between TSA and CA.

Footnote 13: AADs – antiarrhythmic drugs, CA – catheter ablation, CI – confidence interval, HR – hazard ratio using cox regression analysis, ITT – intention to treat analysis, TSA – thoracoscopic surgical ablation

3.5 SENSITIVITY ANALYSIS OF PRIMARY OUTCOMES

There was attrition in the TSA arm due to 5 withdrawals prior to ablation and also 6 patients crossed over to CA arm. We therefore conducted sensitivity analyses to ensure the results are robust: first we included patients who withdrew from the study before undergoing ablation (intent to treat analysis - ITT) and then analysed the data by excluding those who did to have the procedure they were randomised to (per protocol analysis - PPA).

ITT sensitivity analysis was also evaluated according to 1 week ILR data extracts every three months during the follow-up period (thus mimicking 1 week Holter monitor data).
In PPA, there was no statistically significant difference between the two groups although pair estimates favoured CA rather than TSA. Including patients who withdrew from the study in the TSA, the group did not affect the Kaplan-Meier survival plot as shown in Figure 25.

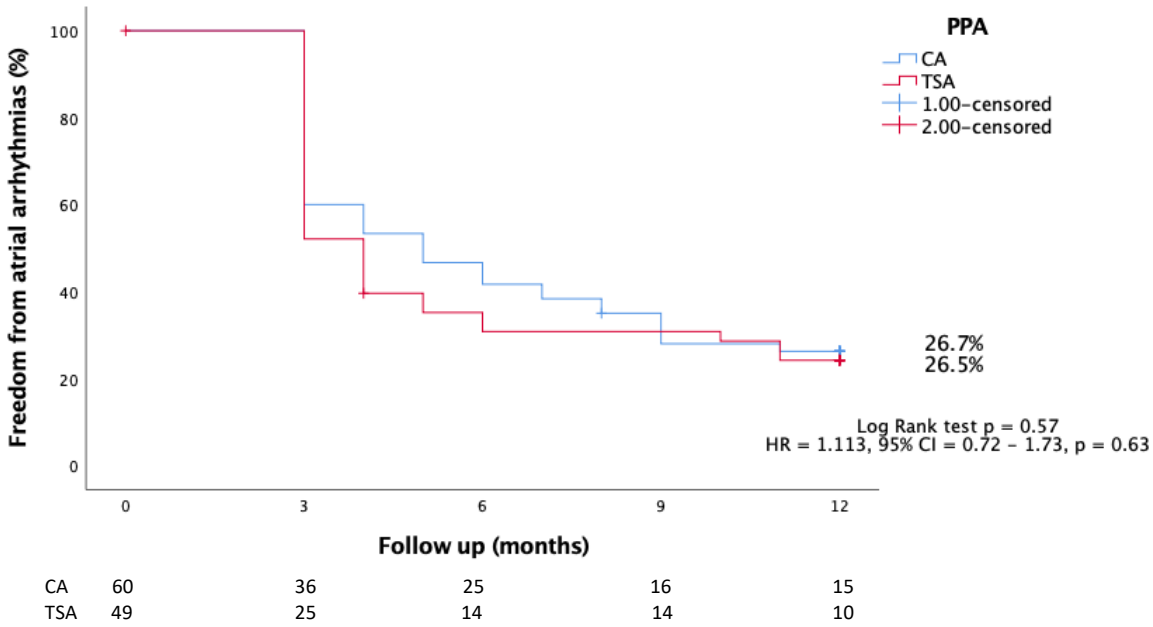


Figure 25: Kaplan-Meier survival analysis between CA and TSA based on per protocol analysis without AADs.

Footnote 14: AADs – antiarrhythmic drugs, CA – catheter ablation, CI – confidence interval, HR – hazard ratio using cox regression analysis, PPA – per protocol analysis, TSA – thoracoscopic surgical ablation

3.6 HOLTER SIMULATION - IMPACT ON RATES OF AF RECURRENCE

In this trial we used highly sensitive ILR and continuously monitored participants' heart rhythm so the results may not be comparable to similar studies using Holter monitors. We have extrapolated ECG data from the ILR records to mimic 7-days Holter monitoring in synchrony with 3, 6, 9 and 12 months follow-up hospital visits. As expected, there was a

reduction in incidence of atrial arrhythmias overall, but there were no differences in freedom from AF between trial arms in ITT analyses (Figure 26). Following ablation and after the blanking period, 43.6% (24/60) of the CA group and 51.7% (31/55) of the TSA group had freedom from atrial arrhythmias using one week recordings from ILR data every three months (Figure 26).

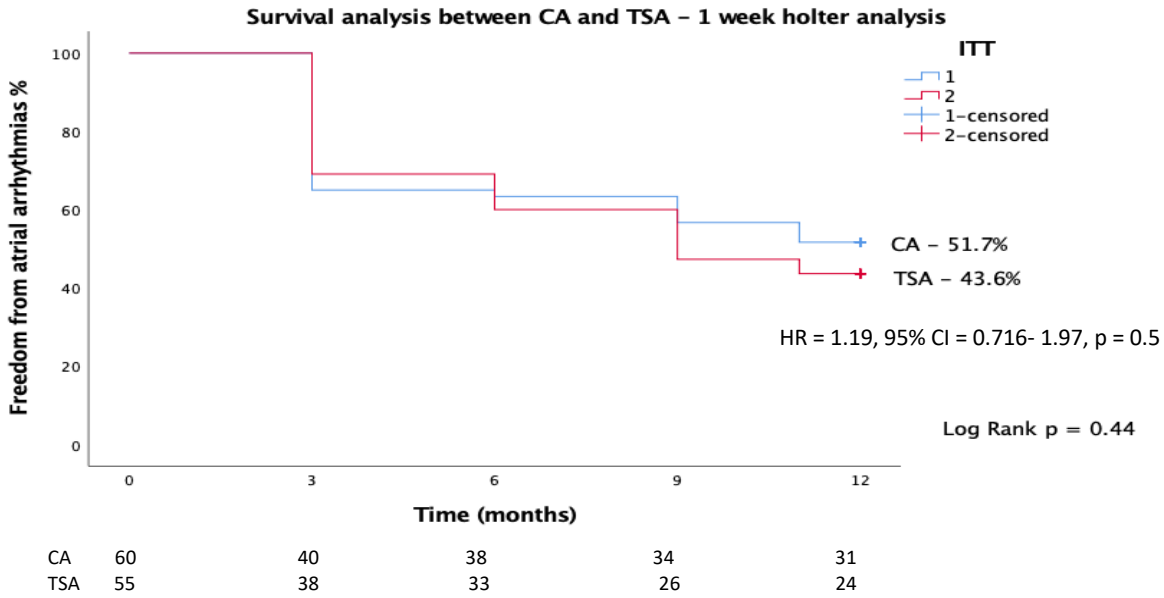


Figure 26: Kaplan-Meier survival analysis of simulated monitoring of 1 week every three months using ILR data for freedom of atrial arrhythmias in patients randomised to CA vs. TSA.

Footnote 15: CA – catheter ablation, CI – confidence interval, HR – hazard ratio using cox regression analysis, ITT – intention to treat analysis, TSA – thoracoscopic surgical ablation

3.7 AF/AT BURDEN REDUCTION OVER 12 MONTHS OF FOLLOW-UP

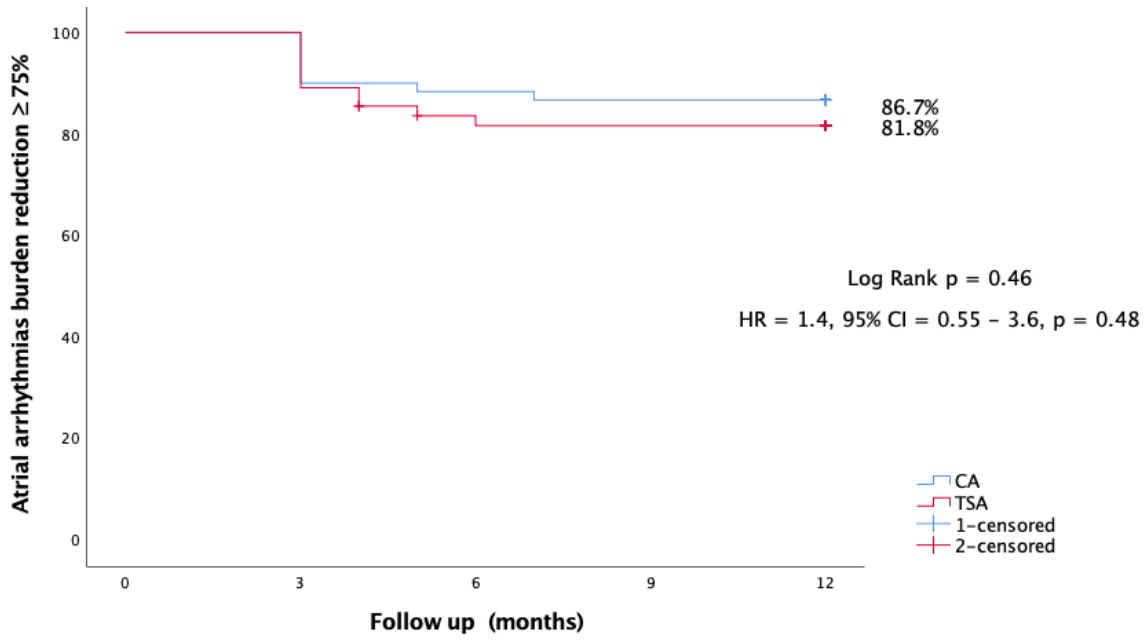


Figure 27: Kaplan-Meier survival analysis for AF/AT burden reduction ≥75%, CA vs. TSA over 12 months in CASA-AF trial.

Footnote 16: Atrial arrhythmias burden reduction is defined as ≥75% reduction of AF and AT each month for all patients, CA – catheter ablation, CI – confidence interval, HR – hazard ratio using cox regression analysis, TSA – thoracoscopic surgical ablation

AF burden reduction of ≥75% after a single procedure without AADs was seen in 52/60 (86.7%) of patients in the CA arm and 45/55 patients in the TSA (81.8%) arm, Log Rank statistics p = 0.46 (Hazard ratio (HR) = 1.4, 95% CI = 0.55 – 3.6, p = 0.48) as shown in Figure 27. There was a significant burden reduction with both groups of patients despite having LSPAF before ablation.

Similar proportions of patients in both treatment arms underwent additional CA ablation for AT/AF recurrence during follow up: 9/60 (15%) in CA arm and 10/55 (18%) n SA arm, odds ratio (OR) 1.2593 (95% CI 0.470-3.375), p = 0.65.

Similarly, DCCV was performed in follow up in similar proportions in both groups: 11/60 (18%) in CA arm and 10/55 (18.2%) in SA group, OR 0.989899 (95% CI 0.384 -2.552), p = 0.98.

3.8 SAFETY OUTCOMES: SERIOUS ADVERSE EVENTS AND COMPLICATIONS

There was no difference in the rate of serious adverse events (SAEs) occurring within 30 days of the ablation: 6/60 (10%) people in CA arm and 7/55 (13%) patients in SA arm experienced serious adverse events related to the study procedure (p = 0.21). Over the entire duration of the follow up period, 31 patients had total of 45 serious adverse events or complications, as outlined in the table below (Table 10). In ITT analysis, 22 patients (40%) from the TSA group had 33 procedure-related adverse events, and nine patients (15%) from the CA group had 12 procedure-related adverse events or serious complications (p = 0.0025).

One patient in the TSA group died 2 weeks after the procedure due to multiorgan failure as a result of shock due to upper GI bleed and recurrence of AT leading to congestive heart failure. Phrenic nerve damage occurred in 3 patients (5.5%) in the TSA group, with 2 patients having partial recovery of hemi-diaphragm function. The phrenic nerve is likely damaged due to suture traction and not a direct injury caused by an incision in the

pericardium. In one case, emergency thoracotomy needed to be performed to control bleeding, and during this, the pericardium was over retracted to visualise the source of bleeding and avoided sternotomy.

TIA was seen in two patients (1 from each arm) with no permanent neurological deficits at the end of the follow up period and no neurorehabilitation was required.

Pneumonia and general respiratory infections were more often in the TSA group while pleural effusion was reported in the TSA group. The likely reason for predisposition to infection and lung congestion is the need for CA to have irrigation system during ablation, to allow for catheters to deliver higher amount of radiofrequency energy termed irrigated cooling of the catheter tip. While in TSA, pleural effusions and chest infections were a consequence of lungs deflation required to visualise the heart resulting in infection of the lungs. In both groups, risk of chest infection is higher as a consequence of intubation for GA.

Acute kidney injury occurred in two patients in the TSA arm due to over diuresis and reduced fluid intake during the day of the procedure and following day of the procedure. It resolved quickly with hydration and cessation of the diuretic treatment.

Table 10: Serious adverse events and significant complications following CA and TSA during the follow-up period

	Procedure-related adverse events	
SAE / Complications	CA (n=9/60)	TSA (n=22/55)
Acute kidney injury*		2
Anaphylaxis to anaesthesia*		1
Chest infection*	4	11
Congestive heart failure*	1	1
Conversion to Thoracotomy*		1
CNS vasculitis		
Colon cancer		
Death		1
Epistaxis		
Gastroparesis*	1	
Gout		
Pain at wound site*		1
Pericardial thrombus / pericarditis*	1	1
Phrenic nerve palsy*		1
Phrenic nerve damage leading to diaphragm paresis*		2
Pleural effusion*		1
Pseudoaneurysm of femoral artery*	1	
PV stenosis*		1

Pyrexia/septicaemia	1	6
Sinus node dysfunction – PPM insertion*	2	1
Surgical emphysema		1
TIA / Stroke*	1	1
Total	12	33

*Footnote 17: * Adverse event related to the procedure. Abbreviations: CA – catheter ablation, CNS – central nervous system, SAE – serious adverse event, TIA – transient ischemic attack, PV – pulmonary vein, TSA – thoracoscopic surgical ablation*

3.9 IDENTIFICATION OF BREAKS IN LESION SETS

In seventeen patients randomised to CA(n=8) and to TSA (n=8) testing of the lesion set was performed prior to isolating any gaps in the lesion sets (Figure 28).

In the CA group, reconnections were found in the inferior line (n=3), roof line (n=5), mitral isthmus line (n=6), and CTI (n=3). Reconnection in the pulmonary veins were found in 5 patients with 12 veins reconnected out of 32 veins. Out of the six patients with connected mitral line, four patients failed to have bidirectional block during the index procedure. The reasons for reconnections across the lesion set are multiple: from differences in contact, time, energy delivered and angulation of the ablation catheter to anatomical variations in individual patients. Local practices such as having oesophageal temperature probes in situ can result in reconnections in regions where a rise in oesophageal temperature impeded adequate lesion delivery.

In the TSA group, reconnections were found in the inferior line (n=2), roof line (n=5), and PV (n=9 / 32 veins).

In three patients of all the redo CA (CA=1, TSA=2), all lines and PV were isolated, thereby suggesting that other substrates could attribute to AF recurrence.

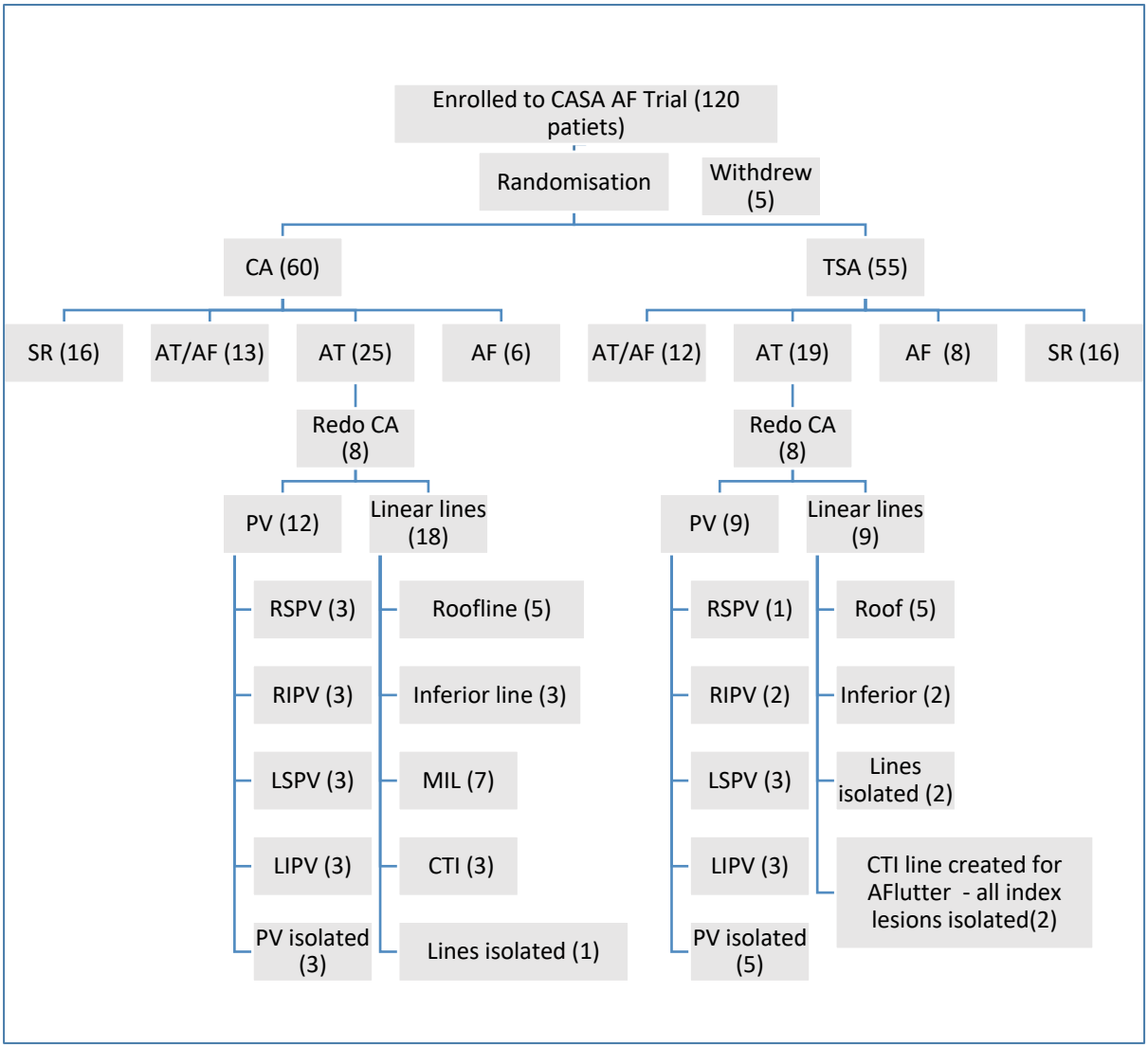


Figure 28: Details of gaps in PV and linear lesion sets resulting in AF recurrence

Footnote 18: AF – atrial fibrillation, AT – atrial tachycardia, CA- catheter ablation, CTI – cavotricuspid isthmus line, LIPV – left inferior pulmonary vein, LSPV – left superior pulmonary vein, MIL – mitral isthmus line, PV – pulmonary vein, RIPV – right inferior pulmonary vein, RSPV – right superior pulmonary vein, TSA – thoracoscopic surgical ablation

3.10 QUALITY OF LIFE MEASURES

Table 11: Quality of life analysis using AFEQT and EQ5D-5L to evaluate the effect of CA and TSA and the effect of rhythm

Variable	**Time**	**n**	**CA**	**n**	**TSA**	**P value**	**n**	**SR**	**n**	**AF**	**P value**
AFEQT	0M	60	53.6 ± 13.5	60	54.6 ± 18.4	0.75	39	55.3 ± 17	81	53.5 ± 15.7	0.57
	3M	58	78.2 ± 17	52	74.6 ± 20.9	0.32	33	81.2 ± 15.7	77	74.5 ± 19.9	0.06
	6M	58	81.9 ± 19	51	79 ± 18.7	0.43	31	87.7 ± 9.6	78	77.7 ± 20.8	0.001
	9M	54	82.1 ± 16.7	50	81.1 ± 20.3	0.79	27	86.2 ± 9.8	73	80 ± 20.5	0.05
	12M	59	85.2 ± 14.5	54	80.7 ± 21.2	0.21	29	87.5 ± 9.1	73	81.4 ± 20.3	0.04
EQ5D-5L	0M	50	64.4 ± 18.7	60	64.2 ± 16.4	0.96	39	65.4 ± 17.2	81	63.8 ± 17.7	0.64
	3M	58	76.9 ± 17.4	52	76.1 ± 16.4	0.81	33	79.4 ± 13.8	77	75.3 ± 17.9	0.19
	6M	57	78.7 ± 18.5	51	78 ± 16.1	0.82	30	82.5 ± 12.2	74	76.7 ± 18.9	0.07
	9M	54	82.3 ± 15.7	50	81.9 ± 14.4	0.90	27	80 ± 17.3	65	82.9 ± 14	0.45
	12M	59	83.9 ± 14.6	54	81.7 ± 20.3	0.54	29	83.4 ± 14.6	63	82.8 ± 18.3	0.86

Footnote 19: 0M -baseline, 3M – 3 months follow-up, 6M – 6 months follow-up, 9M – 9 months follow-up, 12M – 12 months follow-up, AF – atrial fibrillation recurrence, AFEQT - atrial fibrillation effect on quality of life score, CA-catheter ablation, EQ5D-5L - European Quality Five Dimensional- Five-Level score, n – number of patient responses, SR – sinus rhythm

Table 12: EHRA score comparison between CA and TSA and the effect of rhythm during the baseline and followup of 12 months

Score	Time	n	CA Mean (95% CI)	n	TSA Mean (95% CI)	P value	n	SR Mean (95% CI)	n	AF Mean (95% CI)	P value
EHRA	0M	60	3	60	3.02 (2.98 – 3.05)	1	37	3	83	3	1
	3M	60	1.63 (1.45 – 1.82)	53	1.70 (1.48 – 1.92)	0.65	31	1.45 (1.22 – 1.68)	82	1.74 (1.57 – 1.92)	0.04
	6M	56	1.63 (1.43 – 1.82)	46	1.46 (1.27 – 1.64)	0.21	27	1.22 (1.05 – 1.39)	75	1.67 (1.5 – 1.83)	<0.001
	9M	50	1.38 (1.18 – 1.58)	45	1.56 (1.32 to 1.79)	0.25	26	1.38 (1.15 – 1.62)	68	1.49 (1.3 – 1.68)	0.47
	12M	46	1.37 (1.2 – 1.54)	40	1.6 (1.34 to 1.86)	0.14	25	1.32 (1.12 – 1.52)	61	1.54 (1.34 – 1.74)	0.11

Footnote 20: 0M – Baseline visit, 3M – 3 month follow-up visit, 6M -6 month follow-up visit, 9M – 9 month follow-up visit, 12M – 12 month follow-up visit, AF – atrial fibrillation, CA -catheter ablation, CI – confidence interval, EHRA – European heart rhythm association score, SR – sinus rhythm.

3.10.1 AFEQT

Completed AF Effect on QualiTy-of-life (AFEQT) forms were used to calculate the scores in all patients enrolled in the study at every 3 monthly visits till the end of 12 months follow up. The results were compiled at the end of the study, and repeated measures analysis was performed to see if there was an improvement of AFEQT over the 12 months. All patients noted a marked improvement in the quality of life (QOL) following ablation (57.6 ± 7.4 vs. 78.2 ± 6.7, p <0.001) and had sustained improvement throughout the follow-up. There was

no significant difference in the quality of life between patients with maintained SR and those with AF recurrence overall during the follow-up period (Figure 29, Figure 30). However, a higher QOL was reported by patients maintaining SR compared to those with AF recurrence at individual time points (Table 11); 6 months (87.7 ± 9.6 vs. 77.7 ± 20.8, p<0.01); 9 months (86.2 ± 9.8 vs. 80 ± 20.5, p=0.05); 12 months (87.5 ± 9.1 vs. 81.4 ± 20.3, p=0.04).

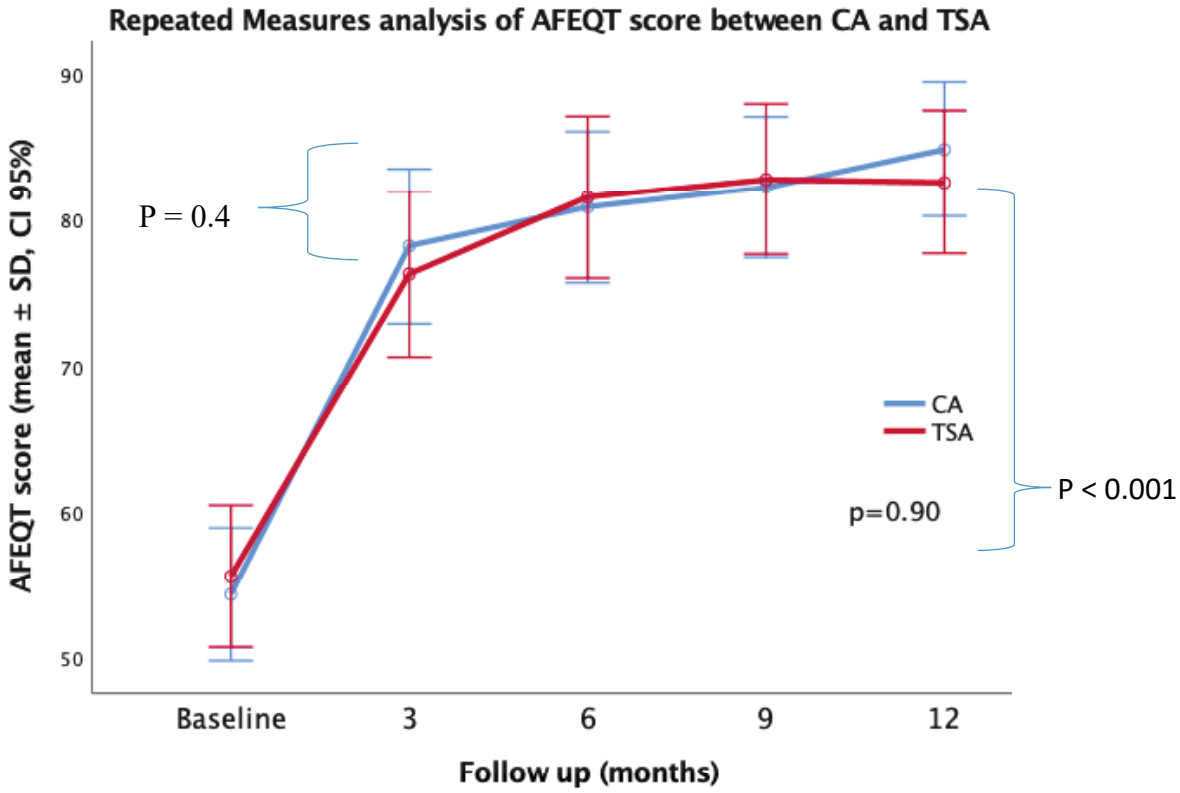


Figure 29: AFEQT scores between CA and TSA using repeated measures over the one-year follow-up

Footnote 21: AFEQT - AF Effect on QualiTy-of-life, CA – catheter ablation, CI – confidence interval, SD -standard deviation, TSA – thoracoscopic surgical ablation.

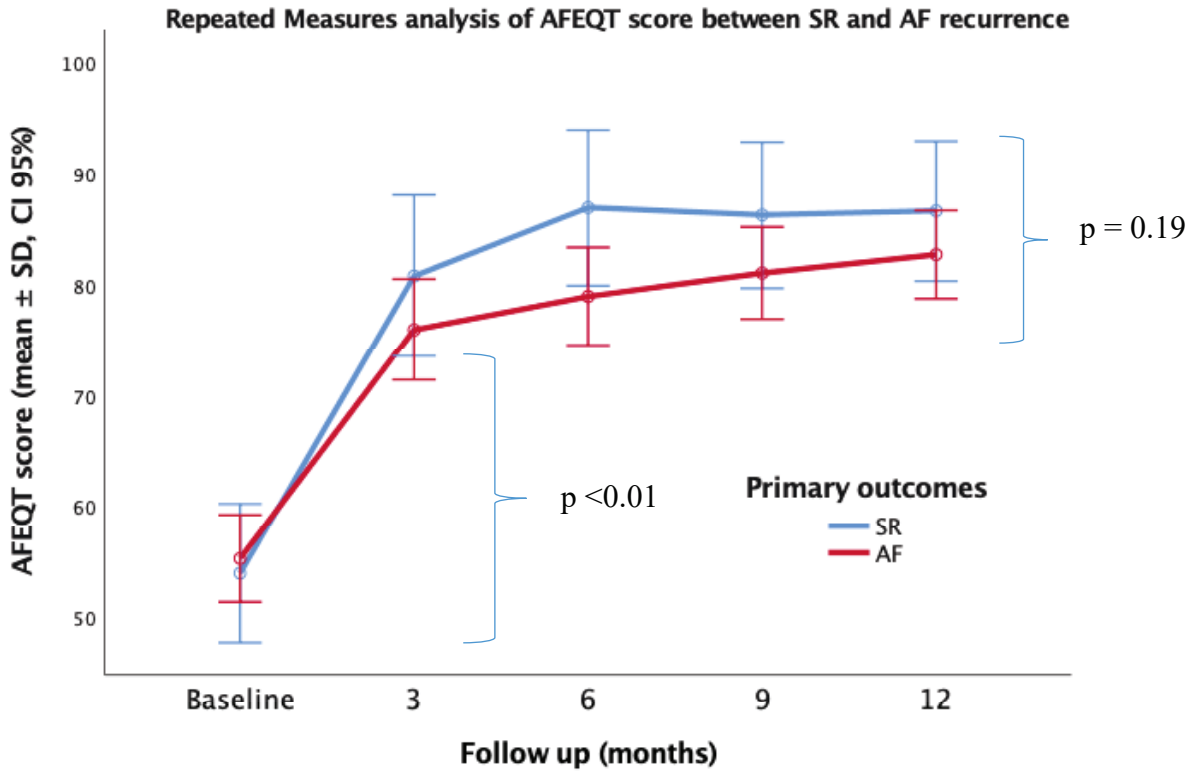


Figure 30: AFEQT scores between SR and AF using repeated measures over one year

Footnote 22: AFEQT - AF Effect on QualiTy-of-life, CA – catheter ablation, CI – confidence interval, SD -standard deviation, TSA – thoracoscopic surgical ablation.

3.10.2 EUROPEAN QUALITY FIVE DIMENSIONAL – FIVEL LEVEL (EQ5D-5L) EVALUATION

European Quality Five Dimensional- Five-Level (EQ5D-5L) questionnaire was used at baseline and follow-up to assess the patient's direct reflection of health at the time questionnaire completion. The overall health of patients based on EQ5D-5L score improved dramatically from baseline to 3 months and maintained till 12 months ($p<0.001$) irrespective of AF recurrence as shown in Figure 31 , Figure 32 and Table 11.

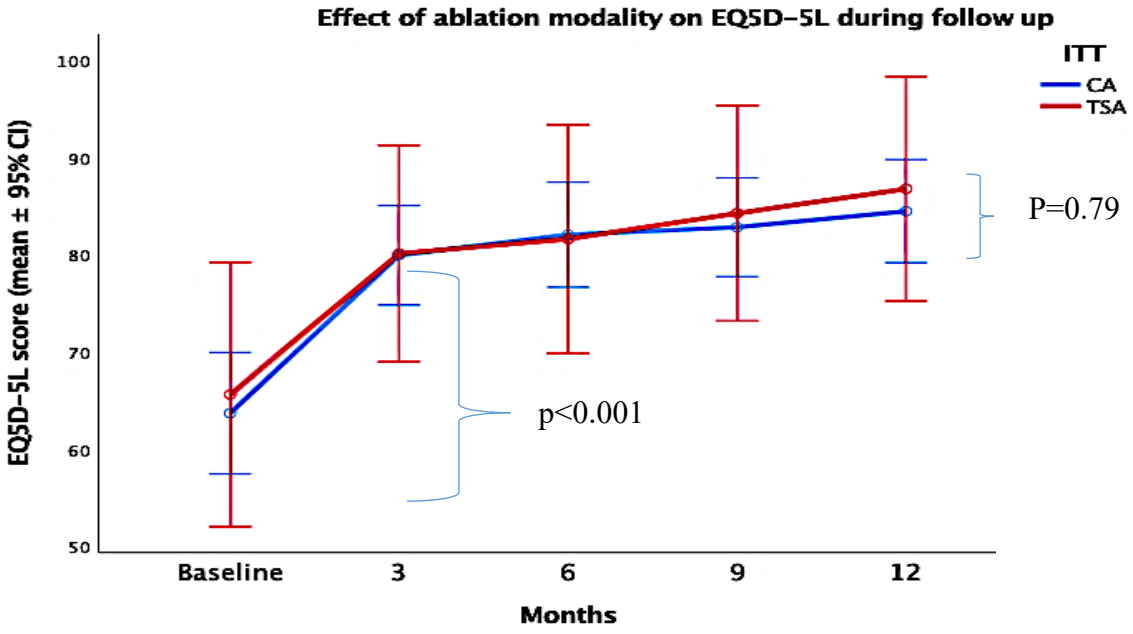


Figure 31: EQ5D-5L scores between CA and TSA using repeated measures for one-year follow-up.

Footnote 23: EQ5D – 5L - European Quality Five Dimensional- Five-Level, CA – catheter ablation, CI – confidence interval, ITT -intention to treat analysis, SD -standard deviation, TSA – thoracoscopic surgical ablation.

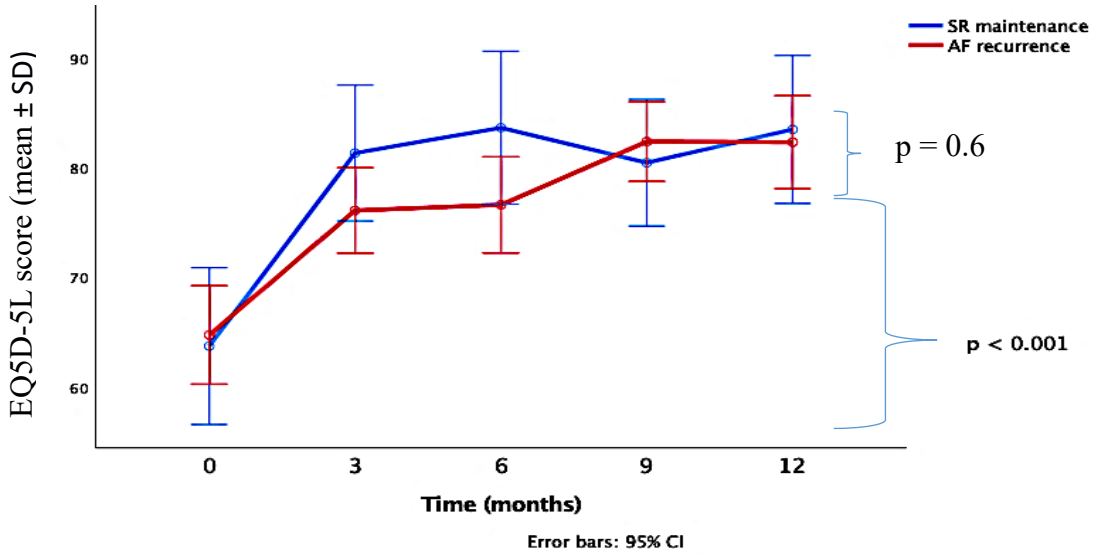


Figure 32: EQ5D-5L scores between SR and AF recurrence using repeated measures analysis for one year follow-up

Footnote 24: EQ5D – 5L - European Quality Five Dimensional- Five-Level, CA – catheter ablation, CI – confidence interval, ITT -intention to treat analysis, SD -standard deviation, TSA – thoracoscopic surgical ablation.

3.10.3 EUROPEAN HEART RHYTHM ASSOCIATION AF SYMPTOM SCORE

The European Heart Rhythm Association (EHRA) AF symptom score was used as part of recruitment to include only those patients who had a score of ≥ 3 (severe symptoms affecting activities daily). EHRA score was used to assess symptoms during each 3 monthly visits. There was a significant reduction in the symptom score from baseline to 3 months that was maintained till 12 months following both CA and TSA (

Table 12, Figure 33). There was no difference between CA and TSA at the follow up visits. However, there was a higher degree of symptom reduction in patients who maintained SR at 3 months and 6 months following ablation compared to patients with AF recurrence (

Table 12, Figure 34).

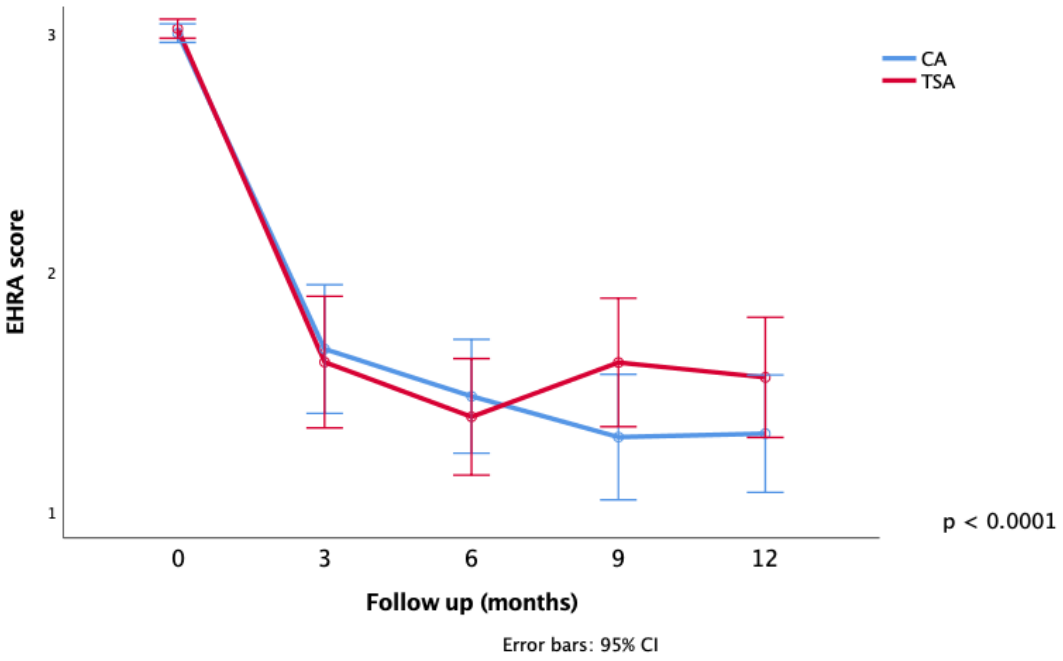


Figure 33: EHRA AF symptom scores between CA and TSA using repeated measures analysis for one year follow-up

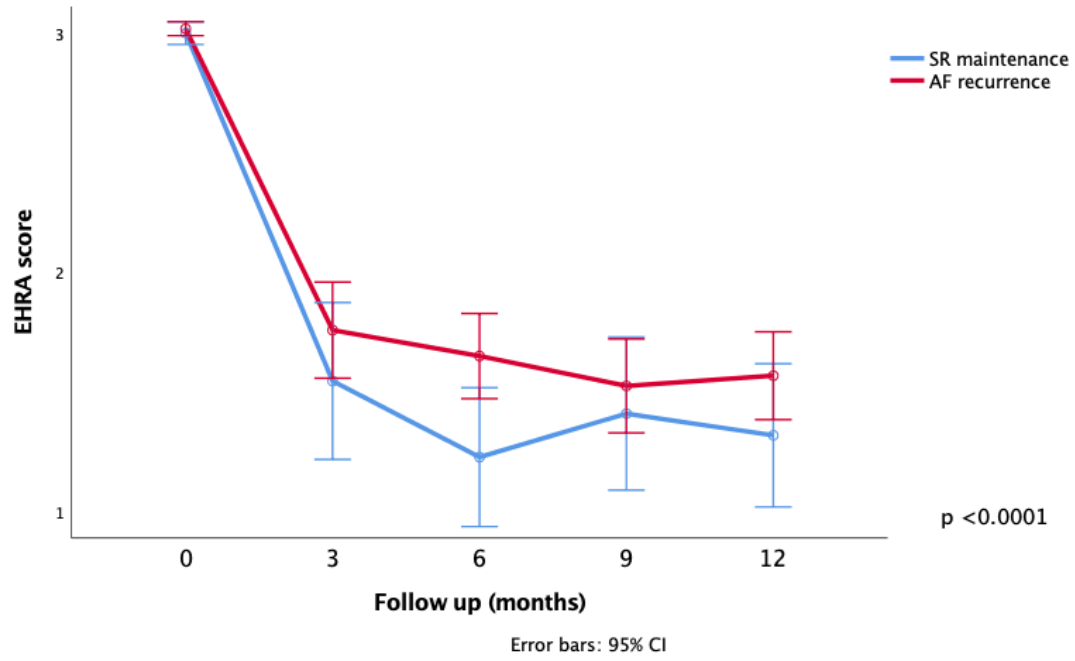


Figure 34: EHRA AF symptom scores between SR and AF recurrence using repeated measures analysis for one year follow-up

3.11 DISCUSSION

CASA AF RCT is the first randomised control study comparing the efficacy of CA and TSA in treating patients with LSPAF while using continuous heart rhythm monitoring. The AF/AT recurrence (≥30 sec) was identified using continuous heart rhythm monitoring.

Our findings are:

1) Similar proportion of patients are free from AT/AF after a single procedure and without AADs in both treatment arms at the end of the study follow up.

2) Similar proportion of patients in both treatment arms experience ≥75% burden of AT/AF reduction during follow-up.

3) All patients report improvements in their quality of life following ablation

4) SAE rates are similar in both treatment arms although significantly more adverse events are associated with TSA arm.

5) Length of stay is significantly longer in those patients undergoing TSA.

Despite two decades of CA use in the treatment of AF, outcomes in persistent and LSPAF remain suboptimal [707].LSPAF is the most difficult to treat AF with suspected advanced substrate remodelling[708-711] and a high rate of recurrence following ablation[712-714]. At

present, the European Society of Cardiology guidelines recommend consideration of thoracoscopic SA for symptomatic AF when catheter ablation has failed (IIa B) or for symptomatic drug refractory persistent or LSPAF (IIa C).[707]

LSPAF is also the least studied type of AF, and in most cases, patients with LSPAF are managed with rate control strategies despite having significant symptoms[715]. The lesion sets applied in CA and TSA were carefully chosen based on the results from earlier studies and in particular the pilot phase of the CASA AF study [191].

AF recurrence

Our results, in terms of the primary outcome, show that some 30% of patients in each treatment arm are free from AT/AF after single procedure without AADs in the 12 months follow up and that TSA is not better than CA.

In comparison to similar studies [290,716-718] as well as our pilot study [191] this proportion may appear low but there are significant differences in methodology between our trial and these studies. Most of the studies have focused on individual ablation techniques or used a hybrid approach to manage a spectrum of AF, including LSPAF [184]. Promising results with reports of up to 80% success rate with PAF, for example, have not been repeated in patients who have persistent AF and LSPAF. Moreover, surgical ablation using RF technology in cases with combined valvular repair or CABG have also shown promising results. In these cases, the surgical procedure to correct valvular heart disease or CABG is required and additional AF ablation does not increase risk significantly compared to index surgical procedure. As

experiences in tertiary surgical ablation centres increase and TSA is more commonly performed, it shows more promise in combination with minimally invasive CABG and valvular repair. Chen et al. reported a retrospective study of 155 patients who required mitral valve surgery in addition to either CA (n=98) or SA(n=57) reported higher success in SA (64.2% vs. 38.3%, p=0.002) compared to CA.[719] Similarly, Osmancik et al. reported 5 year results on the PRAGUE-12 randomised control trial comparing cardiac surgery (CABG or valvular surgery) to cardiac surgery and AF ablation.[720] The rate of major events was similar between two groups, although the AF recurrence rate was significantly lower (subhazard ratio=0.44, 95% CI = 0.31-0.62, p <0.001) in the cardiac surgery with AF ablation group.

Early thoracoscopic SA investigations showed promise in terms of arrhythmia free outcomes [285,721]and this was subsequently borne out by two out of three randomised control trials. In the first of these trials, the FAST study, 124 patients had either SA or CA.[716] The SA group had significantly greater AF-free survival at 12 months without AADs (65.6% vs 36.5%; p=0.0022), although the adverse event rate was considerably higher (34% vs 16%). Two-thirds of patients had an unsuccessful CA before participating in the trial and 67% had paroxysmal AF. Castella et al. (2019) reported the seven-year to follow up on the FAST randomised control study comparing CA and TSA with recurrence of AF in 87% vs 56% respectively[290]

Limitations of the trial included significant heterogeneity in lesion sets with inconsistent verification of conduction block and the use of intermittent 7-day ambulatory ECG monitoring used to identify AF recurrence. The second randomised control trial by

Pokushalov et al. enrolled 64 patients, again with a mixed caseload of paroxysmal and persistent AF and failed initial CA.[717] At 12 months, SA was superior in terms of AF-free survival (81% vs. 47%; p=0.004) compared to CA. AF recurrence in this study was identified by continuous cardiac monitoring via an ILR. The third randomised study by Adiyaman et al. was a smaller non-inferiority trial with 52 predominantly paroxysmal (74%) patients again using continuous cardiac monitoring over 2 years follow up.[722] CA was not inferior to SA in terms of freedom from arrhythmia at 2 years (56% vs. 29%; log rank p = 0.059) and was not associated with major complications contrary to SA which had a 20% major complication rate.

In keeping with the majority of these trials, in our own pilot non-randomised study, 73% of participants with LSPAF were free from AF/AT 12 months after SA compared to 32% after CA (p=0.003) using intermittent 7-day ambulatory ECG monitoring in follow-up. This current study was subsequently designed to try and definitively determine which of the two techniques was better in restoring normal heart rhythm and to further evaluate their effects on patients' quality of life and health economic outcomes in a multicentre, randomised controlled trial. All our patients were diagnosed with de-novo LSPAF and had their first invasive treatment in high-volume centres using continuous cardiac monitoring to measure rhythm outcomes. We found no difference in the proportion of patients being arrhythmia free at the end of the follow up between the two treatments. There are a few possible explanations for this finding which contradicts the results of our own pilot study.

Firstly, the use of continuous cardiac monitoring is far more sensitive for detecting AF recurrence than intermittent monitoring methods especially in patients without any symptoms. [723] Thus, intermittent monitoring significantly overestimates the success rate of

ablation procedures [703,724,725] and this is likely to be the main reason for the difference in our outcomes compared to other studies.

Secondly, in our trial the recruited patients all had true de-novo LSPAF with a mean time from persistent AF diagnosis to ablation of just under 2 years and an overall AF history of about 3 years. It is well known that LSPAF is resistant to different treatment approaches and our results are in line with those experiences. In keeping with previous reports, in this population a single CA procedure achieves AF/AT-free status without AADs, in about 30% of cases[418,714,726,727]. However, the TSA results we report are in contrast to previous studies, except that of Adiyaman et al., which may be due to the different characteristics of the study populations [722]. The key difference is that previous studies included a high proportion of patients who failed prior CA procedures, and hence the TSA procedure was in essence a reverse staged hybrid case (CA then TSA) which was extended lesion set on previous lesion sets. Therefore, the efficacy of TSA in these studies is in fact the efficacy of two ablative procedures done in succession.

Third, although the TSA operators in our study were expert cardiothoracic surgeons skilled in thoracoscopic techniques, their experience in treating AF thoracoscopically was still relatively limited in comparison to the greater volume of experience of the electrophysiologists delivering CA treatment. It is therefore likely that specific procedural expertise may have played a role in the final outcomes.

Finally, the evolution of CA techniques, including the use of contact force catheters, high density multielectrode mapping and lesion predication algorithms, lead to incremental

benefits in durability of lesion sets and reducing the potential benefit of direct application of the RF to the myocardial tissues as performed in TSA.[728-730]

The high AF recurrence rate we report in this trial is likely due to more accurate recording of the recurrence of atrial arrhythmias by using an ILR instead of interrupted ambulatory monitoring for a week as shown in other studies. Based on using the same data but simulating 7-days Holter monitoring, the rates of atrial arrhythmia recurrence drop significantly in both CA and TSA groups. With 7-days Holter monitoring simulation, 51.7% of patients in CA and 43.6% in TSA group would be classed as free from AT/AF, p=0.44. Still, there was no differences in atrial arrhythmia recurrence between the ablation techniques in our study.

Symptom correlation of AF is likely one of the important markers of success following AF ablation. However, majority of the symptoms in LSPAF are dyspnea or fatigue and difficult to evaluate objectively post ablation as most patients still felt these symptoms due to medication or other medical comorbidities, post procedural pneumonia, atelectasis or phrenic nerve palsy. The overall symptoms and quality of life addressed using AFEQT and EQ5D-5L scores showed a higher score for patients at individual timepoints who maintained sinus rhythm compared to patients with AF recurrence without differences between the ablation modalities.

Our results are based on the outcomes following a single procedure in ablation naïve patients with LSPAF so cannot be compared to the results from studies using hybrid ablation methodology [185,700,718]. In addition, there was not a control group or sham to compare the

true effect of individual ablation modality on AF recurrence in LSPAF. Sham procedure would allow to evaluate psychological effects on QOL indices. Moreover, with the higher incidence of complications from TSA, it can be proposed that it might have a greater role in subjects who need concomitant thoracoscopic valvular or coronary bypass graft surgery.

AT/AF burden reduction

We report here that patients in both treatment arms experience 75% burden reduction of AT/AF in similar proportions, 86.7% in CA and 81.8% in TSA, p = 0.48. This success is reflected in improvement in patient reported health measures in both treatment arms and is important to consider when deciding on the most appropriate treatment strategy.

Safety

The reported success of TSA in achieving freedom from AT/AF is usually offset by a greater rate of complications which include conversion to thoracotomy and sternotomy [716]. However, recent meta analyses reported that adverse events are comparable between the two treatments [185] and our results are in line with this study. When serious adverse events are considered within 30 days of the procedure and over the whole follow-up period there is no difference in safety outcomes between the two treatments. However, when all adverse events in follow up are considered, then TSA is associated with considerably more of them.

Mechanisms for AF recurrence

In most cases the recurrence of AF is paroxysmal in nature. There was a higher incidence of gaps and reconnections in the CA group predominantly was related to mitral isthmus lines. Mitral isthmus line block is difficult to achieve due to thickness of the myocardium, an independent factor for AF recurrence, and shown in studies to have varying acute procedural success between 30-40% [731-734]. Failure to isolate the mitral line via endocardial or epicardial route via the coronary sinus due to thickness, length of the lesion, coronary sinus flow and myocardial sleeve around the coronary sinus can lead to peri mitral flutters that are sometimes roof, PV ridge dependent and difficult to treat[735-737]. The anatomical variations have been seen using intracardiac ultrasound and CT, which can be used to predict mitral isthmus line block [734,738].

Recurrence of AF following TSA may be due to scar associated with gaps in the edges due to clamp design resulting in macro re-entrant AT [272]. Electrophysiological testing during procedures showed promise when performing TSA to ensure bidirectional blocks across PVI and linear lesions [285,739,740]. In our trial, we analysed this on first twenty patients with electrophysiology catheters wrapped around the PVs and in the posterior wall to check the roof and inferior line isolations. There was no difference in testing isolation across PVI and linear lines using electrophysiology catheter compared to the surgical bipolar Isolator® pen [741].

Linear lines to isolate the posterior wall when successful is associated with higher maintenance of SR in patients with persistent AF [742-744]. Attempting to isolate gaps with larger or increased lesions on the posterior wall do not improve chances of SR restoration [186], but instead increase the risk of atrio-oesophageal fistula and instances of peri-mitral

flutters[745-747]. In our study, we did not have complications of atrio-oesophageal fistula despite prolonged ablation times and the number of lesions at this site. Sugumar et al. (2018) described techniques that can be employed to achieve PWI, although currently, it is not known whether PWI plays a role in the long-term SR restoration[748]. A more recent metanalysis by Thiyagarajah et al. (2019) suggests that PWI might be supportive of SR maintenance when completed in conjunction with PVI without benefit when PWI performed on its own compared to PVI in maintaining SR [746].

Haissaguerre et al. (2005) have shown CA to be acutely successful in the management of LSPAF in the majority of cases, although there is recurrence through AT in nearly half of the treated patients. Their ablation strategy involved the use of PVI, roof line and mitral isthmus lines[749]. Other studies have also shown similar unfavourable results with circumferential PVI, complex fractionated atrial electrograms (CFAE) and linear lines[22,418,711,750-753]. Metanalysis of varying lesions yields different medium and long term results resulting in more complex lesions achieving a range of 20 – 65% longer-term success [754].

Yilmaz et al. (2008) first described the first series of nine patients with PAF receiving thoracoscopic bilateral PVI with GP ablation and LAA ligation as part of one procedure[280]. The reported complications of the procedure were related to phrenic nerve damage in two patients with a success rate of 78% on 24 hour Holter monitor performed at the end of follow-up with or without AADs. Yilmaz et al. (2010) repeated the study with 30 patients, with different types of AF capturing heart rhythm by 24-hour Holter monitoring performed 3-monthly for one year[281]. Freedom from AF was reported in 77% of patients. Complications occurring during the early phase of the study were suggested to be due to the learning

curve of the operators performing TSA. Failures in TSA were suggested to be caused by clamp associated scar development resulting in macro re-entrant substrates responsible for AT[272]. Electrophysiological testing during procedures showed promise when performing TSA to ensure PVI and bidirectional blocks across linear lesions[285,739,740]. PWI, along with PVI, showed improvement in the maintenance of SR in greater than 80% of not-LSPAF subjects at nine-month follow up [293]. TSA with PWI, GP ablation and LAA exclusion not yet been evaluated for long term maintenance of SR following ablation for persistent or LSPAF.

Comparison between CA and TSA have been made and mostly report similar results over short and medium-term follow-ups. Wang et al. in 2001, firstly reported a retrospective analysis comparing CA and TSA with 166 LSPAF subjects. They showed freedom from AF in 59% of CA and 74.7% of TSA when using 24-48 hour Holter monitor data at 1,3,6 and 12 months follow up.

QOL

QOL outcomes are useful in appreciating the effect of an intervention on patient's well-being. Most of the studies used SF36 or AF-QoL questionnaires to compare health outcome measures in patients undergoing ablation and those treated with AADs [265,435,755,756]. Significant difference in QOL outcomes measured by EQ5D was reported for patients with PAF and LSPAF following AAD or ablation therapy [189,757-759].

In our study, there was a significant improvement in QoL following ablation in both modalities with no significant difference during follow-up between CA and TSA groups. There was also no significant difference overall between QOL in patients who maintained SR and those experiencing AF recurrence.

3.12 LIMITATIONS

The study was conducted in four highly specialised centres in England with significant expertise in both treatment modalities so the results may not be widely generalisable. TSA delivering teams were not as experienced in AF treatment as CA delivering teams so this may have impacted on the apparent efficacy of the TSA. There were no comparisons made with a control group or a sham procedure to measure a true effect of individual ablation modalities.

The length of follow-up was restricted to the first 12 months after ablation and further follow up may be required to detect any nuances in AF recurrence between the treatment groups.

Lastly, there was a loss of ILR data due to over-writing feature once the device was full despite the research teams' efforts to notify patients promptly to transmit transmissions. The Reveal LINQ™ can only store 15 episodes triggered by the program or four symptomatic episodes before over-writing commences and proportion of data that is lost by the new

episodes. The overwriting feature might have resulted in a degree of underestimation of the burden of arrhythmias and AF/AT recurrences.

3.13 CONCLUSION

CASA AF trial is the first randomised control trial to compare the effectiveness of TSA and CA in patients with symptomatic LSPAF. Based on the detection of AT/AF episodes ≥30 seconds using continuous monitoring by ILR, similar proportion of patients in each treatment arm is free from AT/AF at the 12-months' follow up. This was also true for the proportion of patients with >75% reduction in AT/AF burden in each treatment arm.

More adverse events, including one death, were associated with TSA. Improvement in QoL measures were seen in both treatment groups and based on the overall results LSPAF patients should be considered for ablative treatments.

CHAPTER 4

LEFT ATRIAL STRUCTURE AND FUNCTION ASSESSED BY ADVANCED ECHOCARDIOGRAPHY IN PATIENTS ENROLLED IN THE CASA-AF TRIAL

4.1 BACKGROUND

The left atrium modulates ventricular filling and contributes to cardiac output through its reservoir, conduit and contractile function. LA reservoir function is the elastic ability of the walls of the atrium to stretch during LA filling. LA conduit function is the passive recoil of the LA during early emptying of blood from the left atrium into the left ventricle. LA contractile function (booster) is the active emptying of blood from LA to LV achieved by contraction of the LA. These functions can be impaired due to advancing age and health issues like obesity, diabetes, cardiovascular diseases, renal, respiratory and endocrine disorders [5,18,49-52,76,615,617,760-766]. Atrial fibrillation is another factor associated with poor LA function or LA remodelling manifested by the LA enlargement[598,767-769]. Duration of AF is positively correlated with worsening of LA function [615,770-773], so early assessment and intervention may arrest progression of LA remodelling.

SR restoration therapy leads to reduction in size of the LA and improvements in its function, the process known as reverse remodelling. It is thought that, in LSPAF patients, the advanced electro-anatomical remodelling along with metabolic and neurohormonal alterations cause irreversible changes in the LA through fibrosis and post-ablation stunning, which often accompanies early recurrences of AF following ablation [18,76,91,503]. Timely

assessment of the LA function helps determine the best treatment strategy as well as the success of ablation [616,774-777] or cardioversion [600,638,778-780]. Evaluating LA reservoir, conduit and contractile function can also be helpful in predicting LA electromechanical stunning which can lead to thromboembolic events [781-783].

LA function can be evaluated by measuring changes in LA volumes (maximum, minimum and volume at P wave) or atrial tissue displacement and deformation at the different ECG-derived stages of the cardiac cycle linked with mechanical motion related to LA relaxation and contraction [600]. Transthoracic echocardiography supports a comprehensive assessment of LA function by: (i) deriving LA volumes by 2D imaging, (ii) measuring LA myocardial velocities by Tissue Doppler imaging and (iii) assessing LA myocardial strain and strain rate by 2D speckle tracking echocardiography [600,616,766,784-787].

Tissue Doppler imaging (TDI) measures myocardial wall tissue velocities as opposed to blood flow velocities. Using pulsed-wave TDI at different regions of interest it is possible to assess both regional and global changes in LA function. During LA filling, the peak atrial myocardial velocity at a given region of interest in the LA wall is called the expansion index and is a measure of reservoir function. The peak LA myocardial velocity during the passive emptying phase is a measure of conduit function, and the peak LA tissue velocity during contraction is termed the booster function, a measure of contractile function [600,788-790].

In addition, pulsed wave TDI velocities measured at two different regions of interest can be used to assess myocardial deformation quantified as strain and strain rate. Strain refers to

the change in myocardial length during a given time period in the cardiac cycle, whereas strain rate refers to the rate of change in myocardial length.

Measurement of LA myocardial tissue velocities has shown reduced function of the atria in atrial myopathies, diastolic impairment, atrioventricular valvular heart disease, atrial pressure overload, and heart failure [791] [792,793]. Myocardial tissue velocities of the LA have been shown to predict new-onset AF and AF recurrences following cardioversion and ablation [794-797]. In addition, TDI has been validated to calculate total atrial conduction time (TACT) which is related to the incidence of new-onset AF in post-surgical ablation and recurrence in patients known to have PAF[798,799]. TACT is defined as the duration from the onset of P wave to the peak atrial contraction velocity at the lateral LA wall [614,800]. Atrial asynchrony assessed by comparing regional differences in TACT, has been shown to be associated with low atrial voltages during catheter ablation and higher rates of AF recurrence [795].

A major limitation of TDI is that it is angle-dependent such that the sample tissue has to be parallel to the probe for accurate measurement of tissue velocities and strain assessment [801]. Two-dimensional speckle tracking echocardiography has overcome these limitations by being independent of the direction of movement and is not affected by volume changes and preload conditions [802,803]. Speckle tracking has allowed for strain and strain rate measurements of myocardial tissue to be analysed more accurately among the general population [802,803]. Speckle points of the heart are tagged, and the anatomical change in movement is measured as a difference between two points on the myocardium [802,803]. Speckle tracking has limitations due to factors such as the width of interest, frame rates of

2D acquisition (need to be >55/s) and gating either the onset of P wave or R wave of the cardiac cycle[804,805]. These limitations can be improved with increased averaging of cardiac cycles and reducing the width of interest which improves resolution of the myocardium. A recent meta-analysis by Pathan et al. (2017) did not show any variations between P-P wave or R-R wave measurements of LA strain [805]. Moreover, components of LA function are more reproducible with 2D strain with fewer confounding factors than in LA volume or TDI measurements. Strain values may also predict new-onset AF and AF recurrence before and after ablation [625,638,771,806-810].

A number of studies used LA volume, TDI and strain assessments to investigate changes in LA anatomy and function but they were mostly done in patients with earlier stages of atrial fibrillation, paroxysmal and persistent. [615,771,776,807,811,812]. These studies also reported changes following specific treatments, cardioversion or ablation.

In this sub-study of the CASA-AF trial, we show the results of LA function assessments pre- and post-ablation in patients with LSPAF. We also investigate if catheter and surgical ablation affect the LA function in different ways and report on the outcomes related to the treatments and to the recurrence of atrial fibrillation.

The two ablative techniques used in the Trial did not deliver identical lesion sets. Specifically, CA lesion set included mitral isthmus and cavotricuspid line lesions which were not done in the TSA arm. Ganglionic plexi ablation and mechanical isolation of the LA appendage were only performed in the TSA arm. These lesions may affect LA reverse

remodelling in different ways by acting on specific regional LA wall functions (septal, lateral, anterior and inferior LA segment) which can be assessed using echocardiography.
Our comprehensive assessments of LA function therefore include 2D volume measurements, TDI velocities and 2D speckle tracking strain and strain rate.

The main objectives in these analyses are:

(i) To assess the effects of CA and TSA on LA structure and function using TTE derived 2D volumes, tissue Doppler velocities and speckle tracking strain and strain rate imaging.

(ii) To compare LA structure and function in study participants who sustained sinus rhythm compared to those with recurrent paroxysms of atrial fibrillation.

(iii) To determine the independent predictors of atrial fibrillation recurrence within 12 months follow up.

(iv) To assess the effects of ablation of mitral isthmus line in CA and mechanical LAA occlusion in TSA on regional LA function using tissue Doppler imaging.

4.2 METHODS

4.2.1 POPULATION

Patients with LSPAF enrolled into CASA AF RCT who underwent TSA or CA (n = 115) and were followed up for 12 months. As part of the study assessments echocardiographic measurements of the LA parameters were completed at baseline, 3 months and 12 months after the ablation. Continuous heart rhythm monitoring was enabled by implanted loop recorded as described earlier (Reveal LINQ™, Medtronic, Minnesota, USA).

4.2.2 ECHOCARDIOGRAPHY

Transthoracic echocardiography was performed at baseline, on average 48 days (34-68.5) prior to ablation, and then at 3 and 12 months following ablation using Philips IE33 (Andover, MA, USA) and GE Vivid E9 and E95 machines (Chicago, Illinois, USA). All images were acquired using the standard minimum dataset recommended by the British Society of Echocardiography[813]. In addition to the minimum dataset, images of the LA were acquired to enable regional TDI measurements. The LAA is not clearly seen on TTE and therefore, its volumes were not calculated.

All measurements in follow up were completed in patients who were in sinus rhythm at that time point so that all aspects of LA function, in particular LA contractile function, could be evaluated. Images were obtained with loops of at least three cardiac cycles to ensure averaging of measurements which was particularly important for pre-ablation scans when

patients were in AF. LA function was assessed by calculating reservoir, conduit and contractile function using echo modalities of LA volume, TDI and strain imaging as described below.

4.2.2.1 LEFT ATRIAL VOLUMES

Images were acquired over three cardiac cycles with minimum frame rate of 55 Hz. The width and depth of the acoustic window was set to allow visualisation of the whole LA to its base. The gain was adjusted to allow clear distinction between blood pool and myocardial tissues.

Left atrial volumes were calculated based on the biplane area length method and measurements were performed manually (Figure 35). LA volume measurements included the maximum volume (LAmax), minimum volume (LAmin), and volume at the onset of the P-wave (LAp-wave). LAmax was defined as the volume of the LA just before mitral valve opening. LAmin was the volume at the beginning of mitral valve closure and electrically defined as the beginning of the QRS on ECG. LAp-wave was the volume at the onset of the p wave on ECG. In patients with AF, only LAmax and LAmin were measured because of the absence of a P wave; in sinus rhythm it was possible to measure all three components. Patients with inadequate views to allow all 3 LA volume measurements (LAmax, LAmin, LAp-wave) where the LA endocardial outline could not be reliably be determined, were excluded from the study.

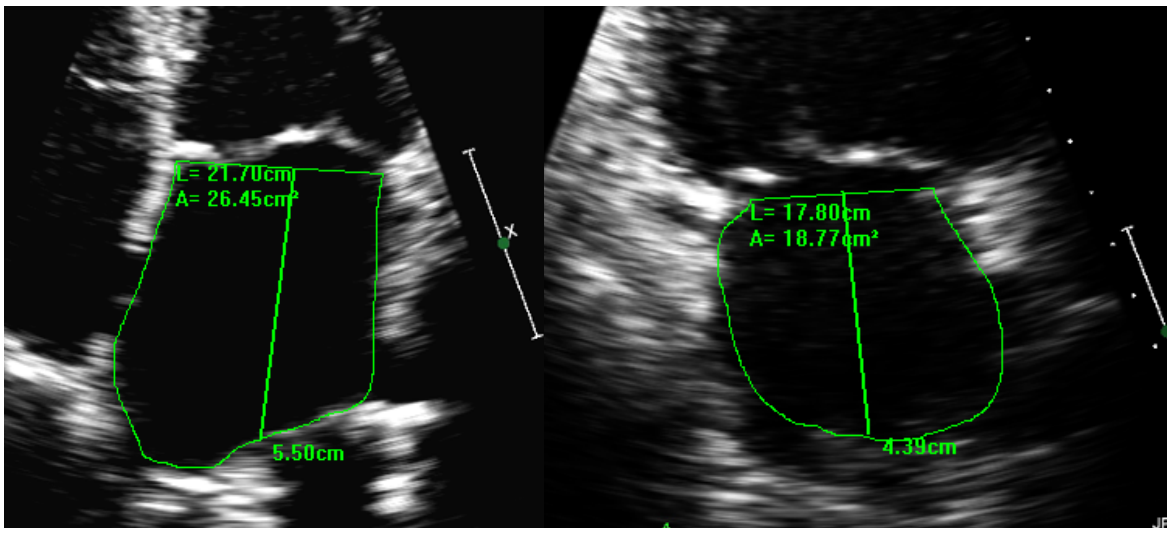


Figure 35: LA volume calculation using biplane area length method in 4 chamber view (left panel) and 2 chamber view (right panel)

The echocardiographic measurements for each LA volume dataset were as follows:

LA volume max (LA_{max}) =0.85 x $\frac{(LA\ 4ch\ \max area\ cm2\ x\ LA2ch\ \max area\ cm2)}{LA4ch\ \max LA\ AP\ length\ cm}$

LA volume min (LA_{min}) = 0.85 x $\frac{(LA\ 4ch\ \min area\ cm2\ x\ LA2ch\ \min area\ cm2)}{LA4ch\ \min LA\ AP\ length\ cm}$

LA volume at p wave ($LA_{P\ wave}$) =0.85 x $\frac{(LA\ 4ch\ \text{p wave}\ area\ cm2\ x\ LA2ch\ \text{p wave}\ area\ cm2)}{LA4ch\ \text{p wave}\ LA\ AP\ length\ cm}$

LA emptying fraction (LAEF%) = $\left[\frac{(\text{LA volume max} - \text{LA volume min})}{LA\ volume\ max}\right] \text{x}100$

These volumetric measurements were then used to derive LA reservoir, conduit and contractile function using the equations below:

LA reservoir function = $\left[\frac{(\text{LA volume max} - \text{LA volume min})}{LA\ volume\ min}\right] \text{x}100$

LA conduit function = $\left[\frac{(\text{LA volume max} - \text{LA volume P wave})}{LA\ volume\ max}\right] \text{x}100$

LA contractile function = $\left[\frac{(\text{LA volume P wave} - \text{LA volume min})}{LA\ volume\ P\ wave}\right] \text{x}100$

An illustration of the 3 components of LA function is given in Figure 36.

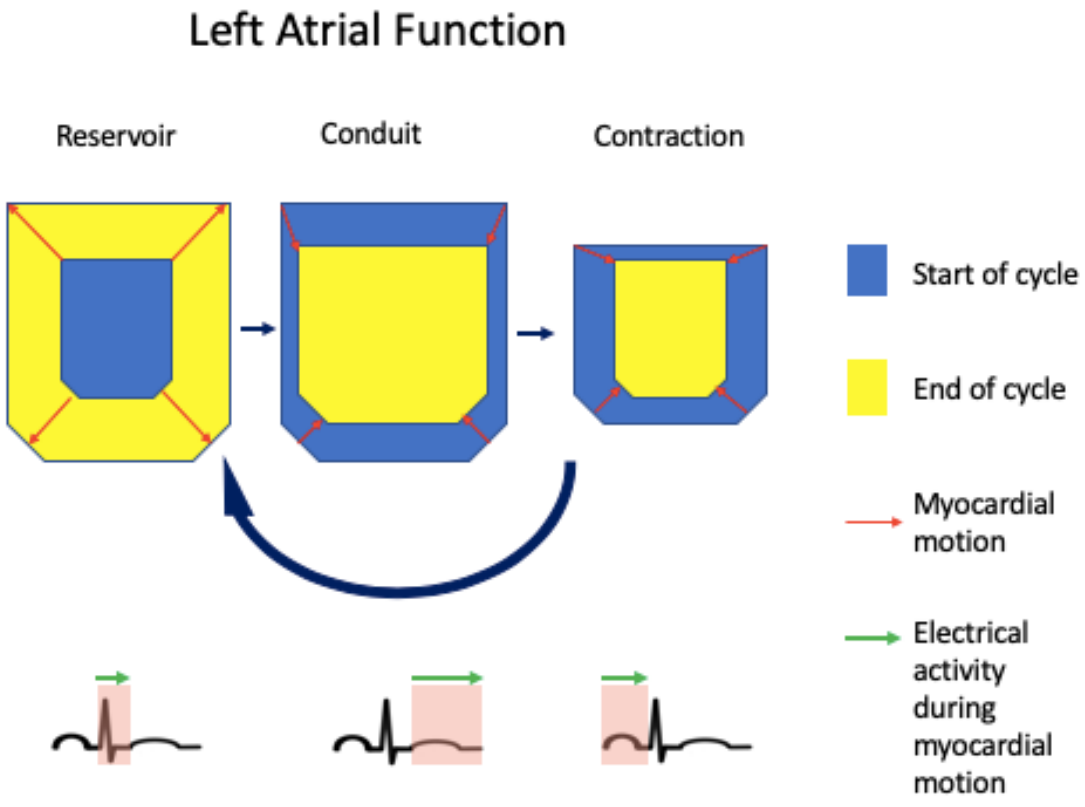


Figure 36: Three components of the LA function using volume indices during sinus rhythm through one cardiac cycle.

LA reservoir function represents LA expansion, the % increase in LA volume from its minimum volume to maximum volume. LA conduit function represents passive emptying of the left atrium, the % reduction in LA volume from its maximum volume to the volume just before P wave onset (active atrial contraction). LA contractile function represents active atrial contraction, the % reduction in LA volume from the onset of the P wave to the LA minimum volume (end of contraction).

4.2.2.2 LEFT ATRIAL STRAIN AND STRAIN RATE BY 2D SPECKLE TRACKING ECHOCARDIOGRAPHY

LA strain and strain rate were performed on standard 2D images. The patient had ECG gated images taken with loops of cardiac cycles per acquisition. The images were acquired once the 2D frame rate in 2D was at least 50Hz and sector widths reduced to focus on the area of interest. The images were read offline using TomTec (TomTec imaging systems, Unterschleissheim, Germany) software to measure atrial strain and strain rate. The image analysis in TomTec was conducted by one experienced operator to minimize variability. TomTec has a semiautomatic process of analysing strain and it was important to ensure that the resolution and grey scale were of adequate quality to delineate the LA endocardial border. The semiautomatic process was manually adjusted where needed to ensure that all cardiac cycles were tracked appropriately along with the correct demarcation of end-systolic and end-diastolic periods. Once accepted, the strain and strain rate measurements were derived automatically from the software.

LA strain and strain rate were assessed during the reservoir, conduit and contractile phases of LA function (Figure 37A and B, respectively). Strain measurements reflected the peak % change in length of the LA myocardium during the 3 phases of the cardiac cycle (SSR – reservoir strain; ESR - conduit strain; ASR – contractile strain), whereas strain rate was the peak change in length per second (SSR' – reservoir strain rate; ESR' – conduit strain rate; ASR' – atrial contractile strain rate).

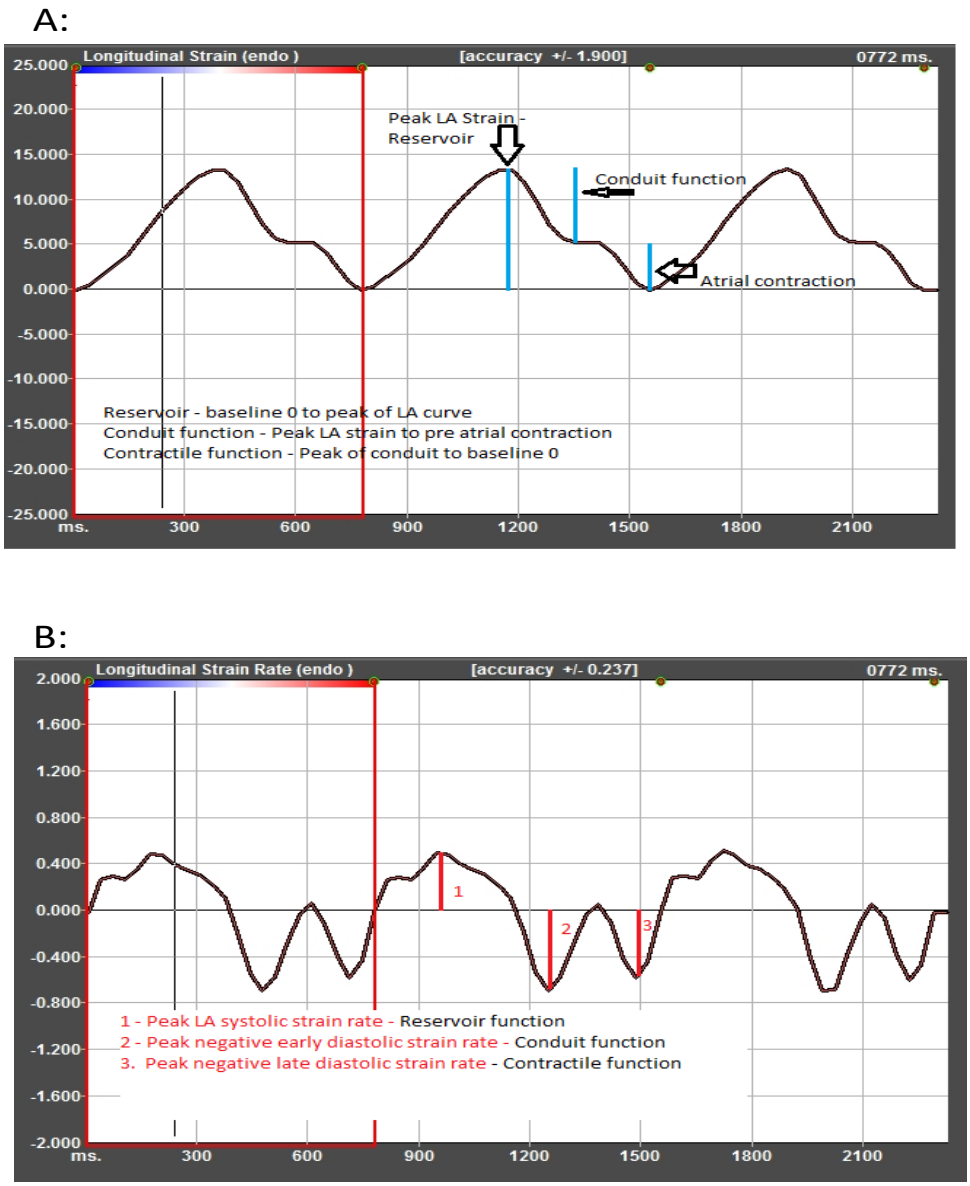


Figure 37: Left atrial strain (panel A) and strain rate (panel B) showing reservoir, conduit and contractile functions in a patient in SR.

4.2.2.3 LEFT ATRIAL TISSUE DOPPLER IMAGING

Tissue Doppler images were acquired in the apical 4 chamber and 2 chamber views using 3.5 – 5.5MHz frequency probe with Nyquist limits of 10- 20cm/s velocities. The frame rate of the acquisition was maintained above 100 frames/sec. The LA wall under interrogation was centred in the images to ensure that the wall was parallel to the probe (Figure 38, Figure 39). Once the images were of adequate quality, pulsed-wave TDI was obtained for at least 2 cardiac cycles to minimise variability in measurements. The sampling was taken from the atrial tissue just below the level of the mitral valve annulus so annular velocities were not captured. The septal, lateral, anterior and inferior LA walls were examined and TDI velocities from each of these walls were then averaged to provide a global score for each parameter.

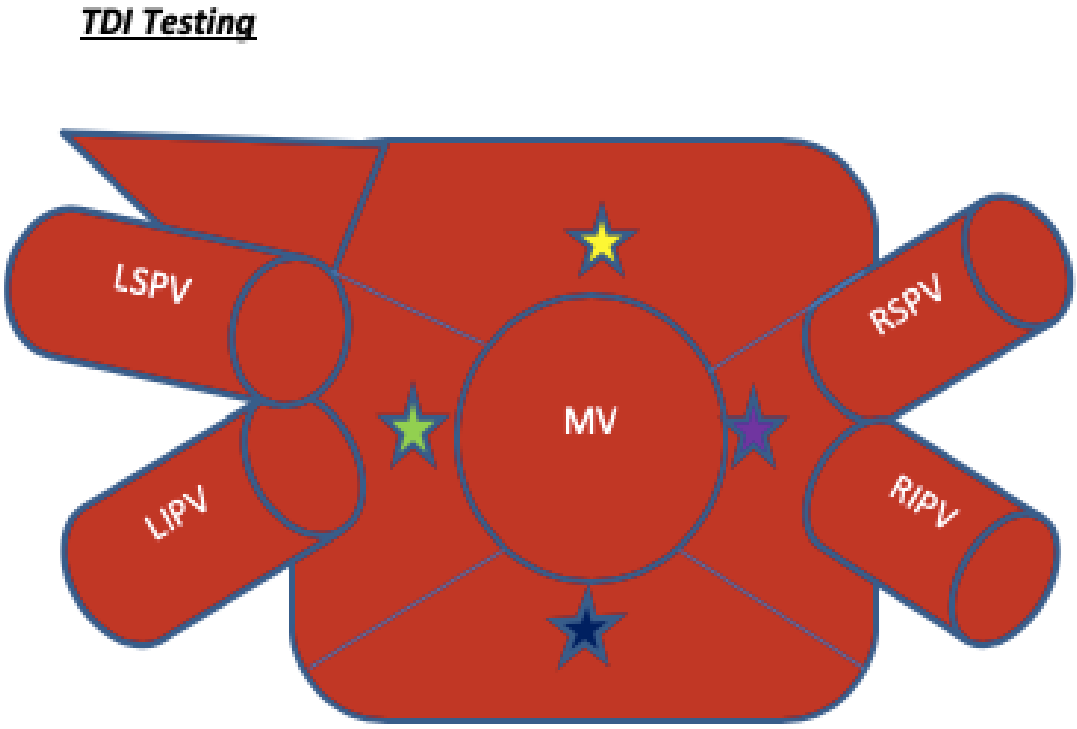


Figure 38: TDI sampling obtained at four locations: anterior LA wall, lateral LA wall, inferior LA wall, and septal LA wall.

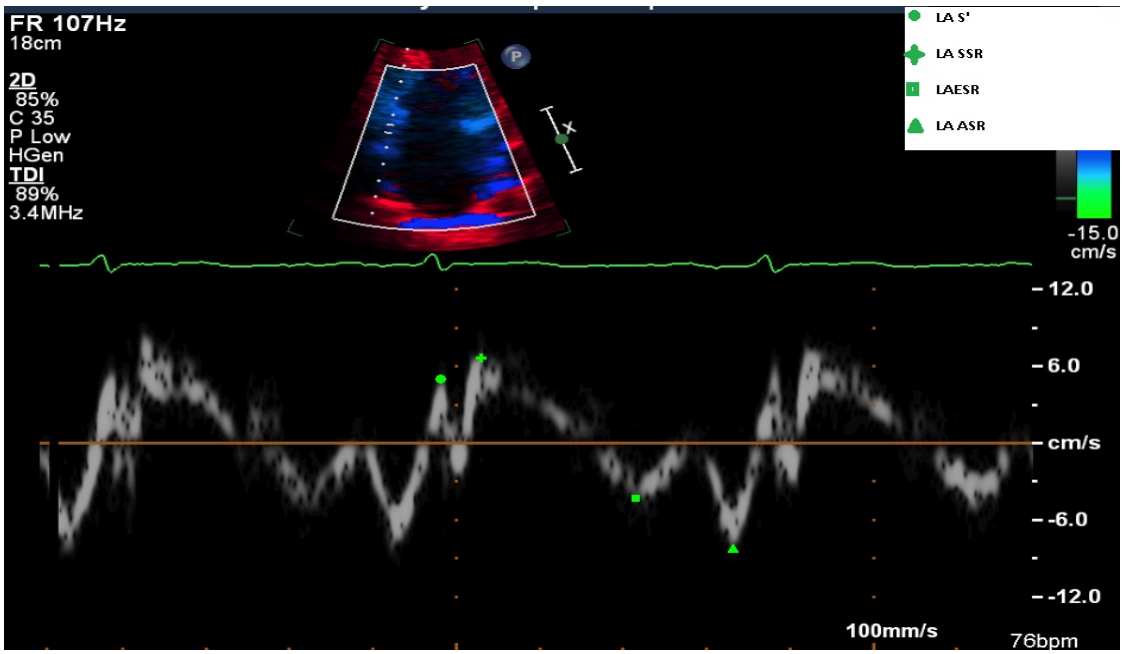


Figure 39: Pulsed wave tissue doppler of the inferior atrial wall below the mitral valve annulus. Mitral annular velocity during onset of ventricular systole (S'), LA reservoir (LA SSR), LA conduit (LA ESR) and LA contractile function (LA ASR).

LA SSR is the peak LA velocity during LA filling and therefore represents LA reservoir function; LA ESR is the peak LA velocity during passive filling and represents conduit function; LA ASR is the peak LA velocity during atrial contraction. Finally, we included S' velocity as a measure of the effect of mitral valve closure at the isovolumic LA contraction period just before LA diastole. The hypothesis is that if LA pressures are low, this may be reflected in a higher S' velocity created by MV closure. Similarly, in instances of increased LA pressure the S' velocity should be reduced.

Finally, total atrial contraction time (TACT) was measured from the onset of the P wave on ECG to the peak A wave (LA ASR) in the lateral wall of the LA.

The effect of LAA ligation on LA function, in patients who had TSA, was measured by comparing anterior wall function to other walls considering that the clip might have a greater impact on LA anterior wall function.

Similarly, we evaluated the effect of LA mitral isthmus line ablation in patients who had CA by comparing the LA inferior and lateral wall functions.

Statistical analysis

Statistical analysis was performed using SPSS version 25. Continuous variables that followed a parametric distribution are shown as mean with standard deviation. Comparison of demographic and echocardiographic data between treatment groups was performed using Student's t-Test. Within group analyses of demographic and echocardiographic data between time points (baseline versus 3 months, baseline versus 12 months, and 3 months versus 12 months) were performed by paired Student's t-test. Non-parametric continuous variables are shown as median and inter-quartile ranges and significance testing was performed using the Mann-Whitney test. Categorical values are expressed as percentages and analysed using Chi-square test. A comparative analysis of patients who remained in sinus rhythm throughout the study versus those who developed recurrences of AF was also performed in a similar fashion. Univariable logistic regression analysis for the prediction of recurrent AF was then performed for all variables. Variables with p value <0.2 were included in multivariable logistic regression analysis. Receiver operating characteristics (ROC) curves were then constructed for each of the independent predictors to identify the optimal cut-off

values to identify patients with higher risk of AF recurrence. A p-value ≤ 0.05 was considered statistically significant.

4.3 RESULTS

4.3.1 LA VOLUMES

4.3.1.1 LA VOLUMES AND VOLUME-DERIVED FUNCTION IN CA AND TSA GROUPS

The analyses in this section are based on TTE data from 59 patients, representing 51% of the participants in CASA AF Trial who underwent CA (n = 60) or TSA (n = 55) as part of the study. The main reason for reduced sample size in these analyses is the requirement for the patients to have good quality TTE scans from all three study time points.

Of 59 patients in these analyses, 33 had CA and 26 had TSA. Demographics and clinical characteristics at baseline were similar in both treatment arms (Table 13) although three participants in TSA group (12%) had a history of TIA, compared to none in CA group (p= 0.05). Baseline characteristics of this subgroup did not differ from the remainder of the trial population.

Table 13: Comparison of baseline demographic characteristics and clinical data in the catheter ablation versus surgical ablation group.

DEMOGRAPHIC DATA	CA	TSA	P value

	(n=33)	**(n=26)**	
Age, years (±SD)	61 ± 11	65.2 ± 8.4	0.11
Sex, n = male (%)	25 (76)	20 (77)	0.99
AF duration, days; mean (95%CI)	575 (417.5 – 858.5)	754.5 (416.5 – 905)	0.53
Body mass index, kg/m^2; mean (±SD)	31.4 ± 5.8	29.7 ± 4.1	0.19
LVEF (%)	55.8 ± 7.2	57 ± 7.7	0.53
Smoking, n (%)	3 (9)	1 (4)	0.65
Hypertension, n (%)	17 (52)	14 (54)	0.99
Diabetes, n (%)	3 (9)	1 (4)	0.43
Alcohol, n (%)	19 (58)	12 (46)	0.67
Stroke/TIA, n (%)	0	3 (12)	0.05
Thyroid disorders, n (%)	2 (6)	2 (8)	0.8
Coronary artery disease, n (%)	4 (12)	3 (11.5)	0.95
Renal disease, n (%)	4 (12)	1 (4)	0.26
Respiratory disease, n (%)	3 (9)	6 (23)	0.14
DRUG THERAPY			
Betablocker, n (%)	29 (88)	22 (85)	0.72
Digoxin, n (%)	10 (30)	3 (12)	0.08
Ca channel blocker, n (%)	4 (12)	4 (15)	0.72
ACE/ARB, n (%)	16 (49)	11 (42)	0.79
Diuretic, n (%)	8 (24)	9 (35)	0.4
AADs, n (%)	4 (12)	3 (12)	0.95
Statin, n (%)	13 (39)	14 (54)	0.3

4.3.1.2 COMPARISONS OF LA VOLUMES AND FUNCTION IN THE TWO TREATMENT ARMS

Within group analysis of the CA group showed significant reductions in LAmax and LAmin at 3 months compared to baseline and a plateau effect at 12 months (Table 14). LA reservoir function and LAEF increased significantly at 3 months and were also maintained at 12 months. There were no significant differences in LA conduit function, P wave volume, and contractile function from 3 months to 12 months. Compared to baseline values, there was a graded increase in LA sphericity index during follow-up which became significant at 12 months.

In TSA group there were significant reductions in LAmax and LAmin at 3 months compared to baseline (Table 14). However, at 12 months there was an increase in LAmax, towards baseline values. Consequently, there was a non-significant trend toward less reverse remodelling at 12 months compared to 3 months. LA reservoir function and LAEF increased significantly at 3 months and showed a plateau at 12 months. LA conduit function, p-wave volume and contractile function measured at 3 months remained unchanged at 12 months. LA sphericity index increased at 12 months, possibly reflecting a reduction in AP diameter.

Table 14: Changes in LA volumes and volume derived LA function in CA and TSA groups

CA (n = 33)						
Parameter	**a. baseline**	**b. 3 months**	**c. 12 months**	**P value (a vs. b)**	**P value (b vs. c)**	**P value (a vs. c)**

LA sphericity index	0.678 ± 0.094	0.714 ± 0.093	0.752 ± 0.102	0.092	0.09	**0.001**
LAmax, (ml/m2)	51.4 ± 16.4	44.3 ± 14.8	44.6 ± 17.9	**0.002**	0.87	**0.001**
LAmin, (ml/m^2)	41.2 ± 15.6	30.9 ± 13.1	31.8 ± 16.6	**<0.001**	0.58	**<0.001**
LA p-wave (ml/m^2)		36.9 ± 13.1	37.1 ± 17.5		0.9	
LA reservoir (%)	27.2 ± 14.7	48.8 ± 25.2	49.5 ± 28.9	**<0.001**	0.91	**<0.001**
LAEF (%)	20.4 ± 9.1	31.1 ± 10.5	30.8 ± 12.2	**<0.001**	0.9	**<0.001**
LA conduit (%)		16.5 ± 8	18.4 ± 12.3		0.52	
LA contraction (%)		17.3 ± 11	15.1 ± 10.1		0.32	
LA RRM (%)		-14.1 (-24.2 – (-6.4)	-14.1 (-25.6 – 0.65)		0.7	
TSA (n = 26)						
Parameter	**a. baseline**	**b. 3 months**	**c. 12 months**	**P value (a vs. b)**	**P value (b vs. c)**	**P value (a vs. c)**
LA sphericity index	0.696 ± 0.081	0.716 ± 0.075	0.733 ± 0.065	0.27	0.3	**0.032**
LAmax, (ml/m^2)	49.6 ± 13.1	44.9 ± 10.8	47.2 ± 10	**0.038**	0.26	0.33
LAmin, (ml/m^2)	39.8 ± 13	31.7 ± 10.8	33.7 ± 9.9	**< 0.001**	0.24	**0.005**
LA p-wave, (ml/m^2)		37.7 ± 9.9	39.7 ± 9.8		0.26	
LA reservoir (%)	27.5 ± 16.1	46.9 ± 22.3	44.2 ± 21.2	**<0.001**	0.55	**0.002**
LAEF (%)	20.4 ± 9.3	30.4 ± 10.5	29.1 ± 11	**<0.001**	0.56	**0.002**
LA conduit (%)		16.3 ± 7.6	16.2 ± 10		0.96	

LA contraction (%)		17 ± 9.2	15.5 ± 7.8		0.47	
LA RRM (%)		-11.4 (-21.3 – 2.5)	-4.5 (-15 – 6.6)		0.16	

Footnote 25: CA – catheter ablation, EF – emptying fraction, LA – left atrium, max – maximum volume, min – minimum volume, TSA -thoracoscopic surgical ablation.

Between group comparisons of LA volumes and function among the 2 treatment groups showed that there were no significant differences between LA parameters at equivalent time points (Table 15). A non-significant trend towards less reverse remodelling in the TSA group at 12 months was noted.

Table 15: Comparison of LA volumes and function between the CA and TSA groups

Parameter	**Time point**	**CA (n = 33)**	**TSA (n = 26)**	**P Value**
LA sphericity index	Baseline	0.678 ± 0.094	0.696 ± 0.081	0.43
	3 months	0.714 ± 0.093	0.716 ± 0.075	0.9
	12 months	0.752 ± 0.102	0.733 ± 0.065	0.4
LAmax (ml/m^2)	Baseline	51.4 ± 16.4	49.6 ± 13.1	0.64
	3 months	44.3 ± 14.8	44.9 ± 10.8	0.86
	12 months	44.6 ± 17.9	47.2 ± 10	0.47
LAmin (ml/m^2)	Baseline	41.2 ± 15.6	39.8 ± 13	0.69
	3 months	30.9 ± 13.1	31.7 ± 10.8	0.8
	12 months	31.8 ± 16.6	33.7 ± 9.9	0.59

LA p wave (ml/m^2)	3 months	36.9 ± 13.1	37.7 ± 9.9	0.79
	12 months	37.1 ± 17.5	39.7 ± 9.8	0.48
LA reservoir (%)	Baseline	27.2 ± 14.7	27.5 ± 16.1	0.95
	3 months	48.8 ± 25.2	46.9 ± 22.3	0.76
	12 months	49.5 ± 28.9	44.2 ± 21.2	0.43
LA EF (%)	Baseline	20.4 ± 9.1	20.4 ± 9.3	0.99
	3 months	31.1 ± 10.5	30.4 ± 10.5	0.81
	12 months	30.8 ± 12.2	29.1 ± 11	0.58
LA conduit (%)	3 months	16.5 ± 8	16.3 ± 7.6	0.91
	12 months	18.4 ± 12.3	16.2 ± 10	0.45
LA contraction (%)	3 months	17.3 ± 11	17 ± 9.2	0.89
	12 months	15.1 ± 10.1	15.5 ± 7.8	0.87
LA RRM (%)	3 months	-14.1 (-24 – -6)	-11.4 (-21.3 – 2.5)	0.38
	12 months	-14.1 (-26 – 0.7)	-4.5 (-15 – 6.6)	0.11

Footnote 26: CA – catheter ablation, EF – emptying fraction, LA – left atrium, max – maximum volume, min – minimum volume, RRM -reverse remodelling, TSA -thoracoscopic surgical ablation.

4.3.1.3 COMPARISON OF LA VOLUMES AND FUNCTION BETWEEN SINUS RHYTHM AND AF RECURRENCE GROUPS

Patients were followed up for 12 months after ablation and their heart rhythm was assessed from continuous monitoring by ILR from baseline onwards. Among the 59 patients, SR was maintained throughout follow up in 32 (54%) patients, whereas AF recurrence was recorded

in 27 (46%) patients. Similar proportions of patients in each of the CA and TSA groups had AF recurrence during follow up. All patients were in sinus rhythm at the time of the TTE scans.

In the group that maintained SR throughout the follow up period, there were significant reductions in LAmax and LAmin and increases in LA reservoir function and LAEF at 3 months which were maintained at 12 months (Table 16). The degree of reverse remodelling was similar at 3 months and 12 months. LA conduit function and contractile function were similar at 3 months and 12 months. There was a trend towards an increase in LA sphericity at 3 months which became significant at 12 months.

While in the group with any duration of atrial arrhythmia recurrence at any timepoint during follow up, there were significant reductions in LAmax and LAmin and increases in LA reservoir function and LAEF at 3 months which were maintained at 12 months despite being in sinus rhythm at the time of the echocardiograms. LA conduit function and contractile function were similar at 3 months and 12 months. There was a trend towards an increase in LA sphericity at 3 months and 12 months. The degree of reverse remodelling was similar at 3 months and 12 months.

Table 16: Comparison of LA volumes and volume-derived function in groups based on heart rhythm in follow up

SR (n =32)		
Parameter	**Time points**	**P values**

	a. baseline	b. 3 months	c. 12 months	a vs. b	b vs. c	a vs. c
LA sphericity	0.67 ± 0.092	0.7 ± 0.092	0.748 ± 0.103	0.118	0.046	<0.001
LAmax, ml/m2	47.1 ± 15.6	42 ± 13.8	42.8 ± 14.5	0.017	0.65	0.071
LAmin, ml/m2	38.1 ± 15.3	28.5 ± 12.9	29.4 ± 13.5	<0.001	0.47	<0.001
LA p-wave, ml/m2		34.3 ± 12.2	34.7 ± 14.2		0.81	
LA reservoir %	26.5 ± 12.6	53.2 ± 25	52.5 ± 24.9	<0.001	0.90	<0.001
LAEF, %	20.2 ± 7.8	33 ± 10.8	32.6 ± 11.8	<0.001	0.83	<0.001
LA conduit, %		18 ± 8.9	20.1 ± 10.8		0.38	
LA contraction, %		18.3 ± 10.1	15.8 ± 7.6		0.20	
LA RRM (%)		-6.6 ± 30.1	-4.2 ± 33.9		0.59	
AF (n =27)						
Parameter	**Time points**			**P values**		
	a. baseline	**b. 3 months**	**c. 12 months**	**a vs. b**	**b vs. c**	**a vs. c**
LA sphericity	0.704 ± 0.082	0.732 ± 0.74	0.739 ± 0.066	0.21	0.62	0.096
LAmax, ml/m^2	54.7 ± 13.3	47.6 ± 11.8	49.3 ± 14.7	0.005	0.47	0.006
LAmin, ml/m^2	43.5 ± 12.9	34.6 ± 10.3	36.5 ± 13.7	<0.001	0.36	<0.001
LA p-wave, ml/m^2		40.7 ± 10.3	42.5 ± 14		0.41	
LA reservoir %	28.3 ± 18.1	41.9 ± 21.1	40.7 ± 25.7	0.009	0.85	0.011
LAEF, %	20.6 ± 10.6	28.2 ± 9.4	27.1 ± 10.9	0.004	0.68	0.007
LA conduit, %		14.6 ± 5.8	14.2 ± 11.4		0.91	
LA contraction, %		15.9 ± 10.3	14.6 ± 10.7		0.61	
LA RRM (%)		-11.2 ± 20.1	-9.5 ± 17.9		0.66	

Footnote 27: CA – catheter ablation, EF – emptying fraction, LA – left atrium, max – maximum volume, min – minimum volume, RRM -reverse remodelling, TSA -thoracoscopic surgical ablation.

Baseline LAmax was significantly higher in the AF group compared to the SR group. In general, there was a trend towards higher LAmax and LA min and lower reservoir function, LAEF and conduit function in the AF group compared to the SR group at 3 months and 12 months (Table 17). Indeed, LAmin and LAp-wave volume were significantly higher in the AF group at 3 months and 12 months. There were no significant differences in contractile function and the extent of reverse remodelling between the two groups.

Table 17: Comparison of LA volumes and volume-derived function between the SR and AF groups

Parameter	**Study time point**	**SR (n = 32)**	**AF (n =27)**	**P value**
LA sphericity index	Baseline	0.67 ± 0.092	0.704 ± 0.082	0.137
	3 months	0.7 ± 0.092	0.732 ± 0.74	0.154
	12 months	0.748 ± 0.103	0.739 ± 0.066	0.68
LAmax, ml/m^2	Baseline	47.1 ± 15.6	54.7 ± 13.3	0.047
	3 months	42 ± 13.8	47.6 ± 11.8	0.094
	12 months	42.8 ± 14.5	49.3 ± 14.7	0.096
LAmin, ml/m^2	Baseline	38.1 ± 15.3	43.5 ± 12.9	0.15
	3 months	28.5 ± 12.9	34.6 ± 10.3	0.048
	12 months	29.4 ± 13.5	36.5 ± 13.7	0.049
LA p-wave, ml/m^2	3 months	34.3 ± 12.2	40.7 ± 10.3	0.036
	12 months	34.7 ± 14.2	42.5 ± 14	0.039
LA reservoir %	Baseline	26.5 ± 12.6	28.3 ± 18.1	0.66
	3 months	53.2 ± 25	41.9 ± 21.1	0.066

	12 months	52.5 ± 24.9	40.7 ± 25.7	0.08
LAEF, %	Baseline	20.2 ± 7.8	20.6 ± 10.6	0.86
	3 months	33 ± 10.8	28.2 ± 9.4	0.072
	12 months	32.6 ± 11.8	27.1 ± 10.9	0.067
LA conduit, %	3 months	18 ± 8.9	14.6 ± 5.8	0.08
	12 months	20.1 ± 10.8	14.2 ± 11.4	0.048
LA contraction, %	3 months	18.3 ± 10.1	15.9 ± 10.3	0.37
	12 months	15.8 ± 7.6	14.6 ± 10.7	0.61
LA RRM (%)	3 months	-6.6 ± 30.1	-11.2 ± 20.1	0.49
	12 months	-4.2 ± 33.8	-9.5 ± 17.9	0.44

Footnote 28: CA – catheter ablation, EF – emptying fraction, LA – left atrium, max – maximum volume, min – minimum volume, RRM -reverse remodelling, TSA -thoracoscopic surgical ablation.

4.3.1.4 LA VOLUMES AND FUNCTION AS PREDICTORS OF AF RECURRENCE

BASELINE DATA

Univariable analysis of the baseline parameters showed that there were no significant predictors of AF recurrence, although there was a trend for age, body mass index and LA max (Table 18). However, multivariable analysis revealed body mass index and LAmax to be independent baseline predictors of AF recurrence.

Table 18: Univariable and multivariable logistic regression analysis of baseline parameters for the prediction of AF recurrence during follow up.

Timeline	Parameter	Univariable			Multivariable		
		OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Baseline	LA sphericity index	1.047	0.99 – 1.11	0.14			
	BMI (kg/m^2)	1.104	0.99 – 1.23	0.07	1.133	1.01 – 1.28	0.042
	AF duration (days)	0.999	0.998 – 1.001	0.5			
	Age (years)	1.05	0.994 – 1.11	0.079			
	Male	1.825	0.54 - 6.13	0.33			
	Hypertension	1.25	0.447 – 3.494	0.67			
	Respiratory disease	3.5	0.661 – 18.5	0.14			
	Diabetes Mellitus	1.095	0.397 – 3.024	0.86			
	CAD	1.681	0.342 – 8.276	0.523			
	Thyroid disorders	1.969	0.616 – 6.295	0.25			
	Stroke/TIA	0.577	0.049 – 6.734	0.661			
	Renal disease	1.875	0.29 – 12.14	0.51			
	Smoker	0.84	0.447 – 1.578	0.59			
	Alcohol	1.067	0.72 -1.582	0.75			
	LA max (ml/m^2)	1.038	0.999 – 1.079	0.059	1.046	1.01 – 1.09	0.032
	LA min (ml/m^2)	1.028	0.99 – 1.068	0.155			
	LAEF (%)	1.006	0.95 – 1.064	0.848			
	LA reservoir (%)	1.008	0.974 – 1.043	0.65			

Footnote 29: AF -atrial fibrillation, BMI – body mass index, CAD – coronary artery disease, CI -confidence interval, EF – emptying fraction, LA – left atrium, max – maximum volume, min – minimum volume, OR – odds ratio

ROC curve analysis of baseline LAmax provided an area under the curve of 0.676 (95% CI = 0.539 – 0.813, p = 0.021). The optimal LAmax cut-off value to predict AF recurrence was 42ml/m^2 conferring a sensitivity of 85% and specificity of 47% (Figure 40A). Using Kaplan Meier survival analysis (Figure 40B) the LAmax <42 ml/m^2 was associated with a 79% freedom from AF recurrence (p=0.025).

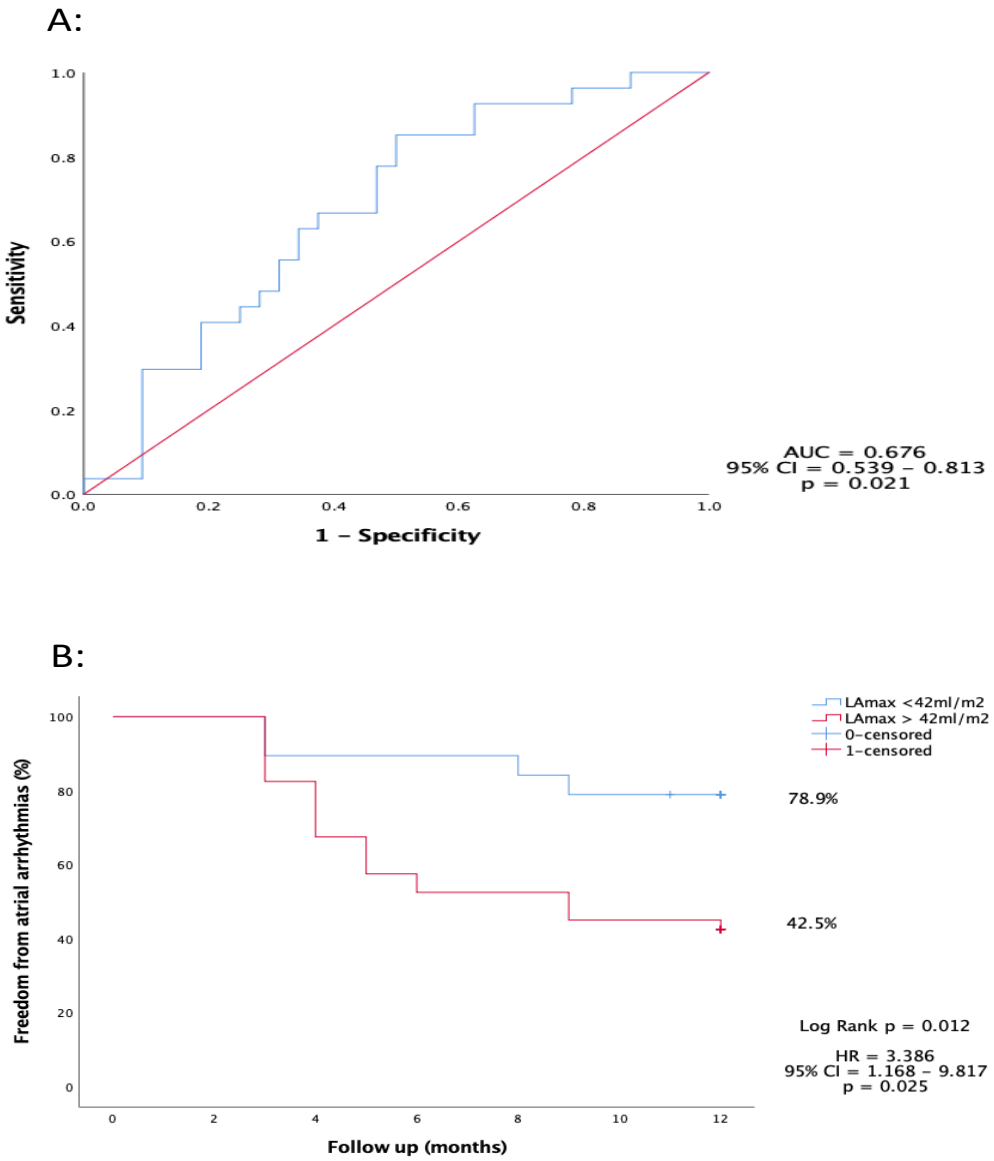


Figure 40: Receiver-operating characteristic curve using baseline LAmax data for the prediction of AF recurrence (A). Kaplan-Meier survival analysis using a baseline LAmax cut-off of 42 ml/m2 (B).

3 MONTHS' FOLLOW-UP DATA

In univariable and multivariable analyses of the variables collected at 3 months' follow up, the LA p-wave volume appeared to be a statistically significant predictor of AF recurrence (

Table 19). BMI became a significant predictor of AF recurrence but only in multivariable analyses.

Table 19: Results of univariable and multivariable logistic regression analysis of the 3 months data for the prediction of AF recurrence during follow up.

Timeline	Parameter	Univariable			Multivariable		
		OR	95% CI	P value	OR	95% CI	P value
3 months	BMI	1.104	0.991 – 1.23	0.07	1.173	1.03 – 1.33	0.015
	Age	1.05	0.994 – 1.11	0.079			
	LA sphericity index	1.048	0.982 – 1.118	0.156			
	LA max	1.037	0.992 - 1.084	0.11			
	LA min	1.049	0.997 – 1.104	0.065			
	LA p-wave	1.055	1.001 – 1.113	0.048	1.08	1.02 – 1.14	0.01
	LAEF	0.953	0.904 – 1.006	0.08			
	LA reservoir	0.978	0.955 – 1.002	0.077			
	LA conduit	0.941	0.877 – 1.011	0.095			
	LA contraction	0.976	0.927 – 1.028	0.366			
	LA RRM	1.008	0.988 – 1.029	0.422			

Footnote 30:BMI – body mass index (kg/m2), EF – emptying fraction (%), max – maximum volume (ml/m^2), min – minimum volume (ml/m^2), OR – odds ratio, RRM – reverse remodelling, LA function - reservoir, conduit and contraction represented in %.

ROC curve analysis of LA p-wave volume at 3 months shows an area under the curve of 0.726 (95% CI = 0.592 – 0.86, p = 0.003). The optimal LAmax cut-off value to predict AF recurrence was 35ml/m^2 conferring a sensitivity of 70.4% and specificity of 71.9%. Kaplan Meier survival analysis showed that a LA p-wave volume at 3 months of <35ml/m^2 was associated with a 74% freedom from AF recurrence (p=0.005), Figure 41.

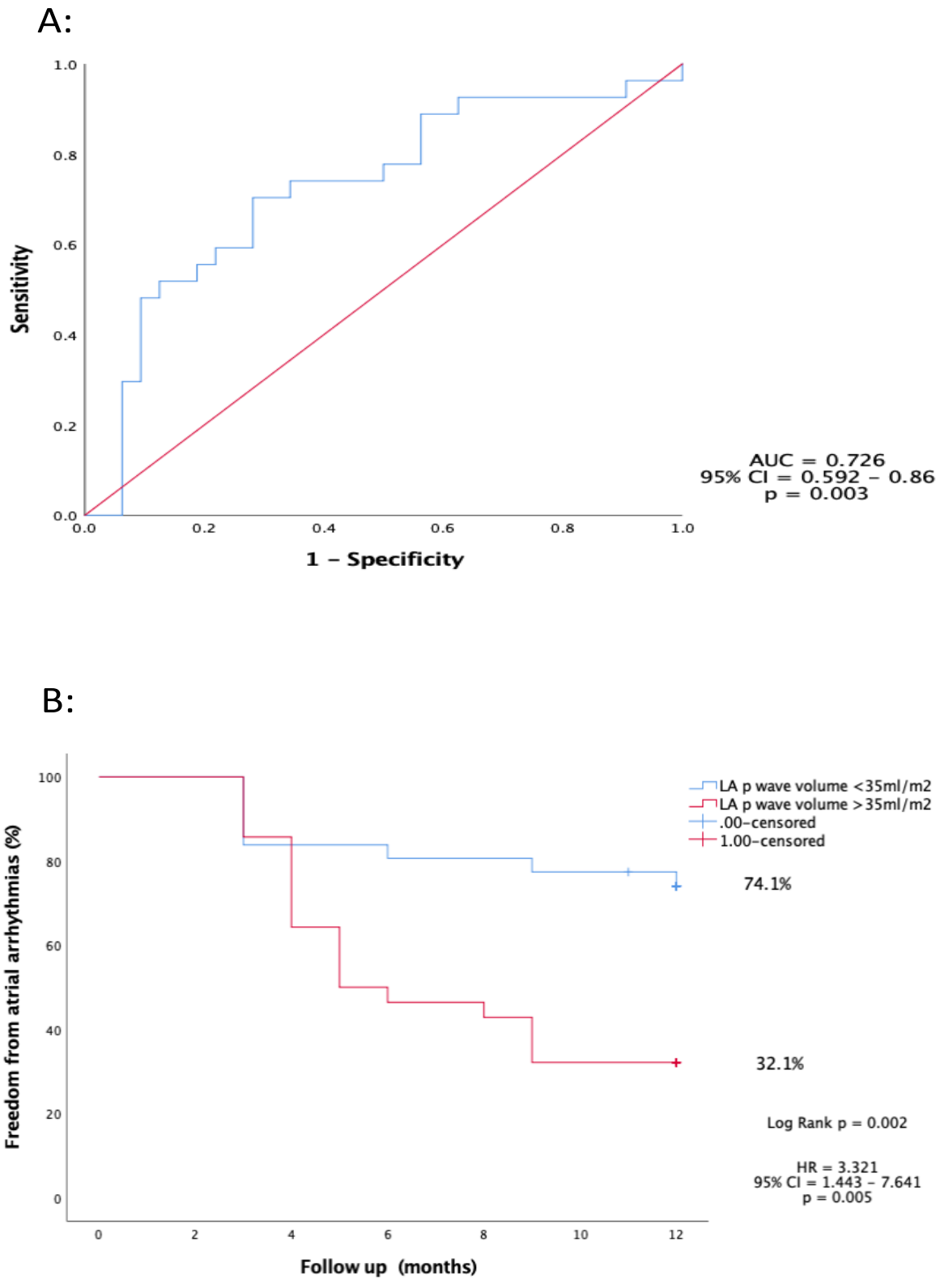


Figure 41: Receiver-operating curve analysis evaluating LA p-wave volume at 3 months and its association with AF recurrence (A). Kaplan-Meier survival analysis showing freedom from AF recurrence using a LA p-wave volume at 3 months cut-off value of 35 ml/m2 (B).

4.3.2 LA FUNCTION USING 2D SPECKLE TRACKING ECHOCARDIOGRAPHY FOR LA STRAIN AND STRAIN RATE

Of the 59 patients who had complete LA volumes data as above, 5 were excluded from the strain analysis, because of inadequate tracking of left atrial myocardium throughout the cardiac cycle. The remaining 54 patients had good quality, analysable TTE images at all 3 time points (baseline, 3 months and 12 months). Four patients had cardioversion in the blanking period, but they were in SR at the time of the 3-months scan. Of the 54 patients, 29 underwent catheter ablation and 25 had surgical ablation.

Their baseline characteristics are shown in Table 20. Within group and between group comparisons of all parameters of LA strain and strain rate-derived function were performed at baseline and at 3 and 12 months following ablation.

Table 20: Baseline characteristics of patients in strain and strain rate analyses in groups based catheter ablation versus thoracoscopic surgical ablation

BASELINE CHARACTERISTICS	CA (n=29)	TSA (n=25)	P value
Age (mean years, ±SD)	60 ± 10.2	65 ± 8.5	0.056
Sex, n = male (%)	24 (82.8)	19 (76)	0.74
Body mass index, kg/m^2 (mean ± SD)	31.6 ± 6	29.6 ± 4.1	0.15
Smoking, n (%)	1 (3.4)	1 (4.2)	0.97
Hypertension, n (%)	16 (55.2)	13 (52)	1
Diabetes, n (%)	3 (10.3)	1 (4.2)	0.38
Stroke, n (%)	0	3 (12)	0.055

Coronary artery disease, n (%)	4 (13.8)	2 (8)	0.5
Renal disease, n (%)	4 (13.8)	1 (4.2)	0.22
Respiratory disease, n (%)	3 (10.3)	6 (24)	0.18
Thyroid disorders, n (%)	2 (6.9)	2 (8)	0.88
Alcohol, n (%)	17 (58.6)	12 (48)	0.58
MEDICATIONS			
Betablocker, n (%)	26 (90)	21 (84)	0.69
Digoxin, n (%)	7 (24.1)	3 (12)	0.25
Calcium channel blocker, n (%)	3 (10.3)	4 (16)	0.54
ACE/ARB, n (%)	15 (51.7)	10 (40)	0.43
Diuretic, n (%)	7 (24.1)	9 (36)	0.24
Antiarrhythmic drugs, n (%)	4 (13.8)	3 (12)	0.85
Statin, n (%)	11 (37.9)	13 (52)	0.41

Footnote 31: ACE – angiotensin converting enzyme, ARB – angiotensin receptor blocker, CA – catheter ablation, TSA – thoracoscopic surgical ablation.

4.3.2.1 COMPARISONS OF LA STRAIN AND STRAIN RATE IN THE TWO TREATMENT ARMS

In the CA group, there was an increase in LA SSR and LA SSR' from baseline to 3 months which was maintained at 12 months (Table 21). This indicates an increase in the magnitude and rate of LA myocardial lengthening during LA filling. LA ESR also increased from baseline to 3 months with no further change at 12 months. This represents significant LA myocardial shortening during passive emptying. However, there was no change in LA ESR' indicating that the rate of shortening did not change. LA ASR and LA ASR' were similar at 3 months and

12 months. An increase in time to peak LA SSR was noted from baseline to follow-up; this may reflect a reduction in heart rate on return to sinus rhythm.

Similar findings were true in the TSA group apart from the LA ASR' which was lower at 12 months compared to 3 months.

Table 21: Strain and strain rate measurements in CA and TSA treatment arm. The values are means ±SD.

CA, n = 29						
LA parameter	**a. baseline**	**b. 3 months**	**c. 12 months**	**p value a vs. b**	**p value b vs. c**	**p value a vs. c**
LA strain time to peak (ms)	347 ± 58	402 ± 50	380 ± 60	<0.001	0.810	0.001
LA SSR; %	10.6 ± 4.5	20.6 ± 8	20.3 ± 7.4	<0.0001	0.821	<0.0001
LA ESR; %	5.7 ± 2.9	13.8 ± 5.8	12.5 ± 5.6	<0.0001	0.248	<0.0001
LA SSR'; 1/s	0.50 ± 0.21	0.83 ± 0.26	0.80 ± 0.31	<0.0001	0.478	<0.001
LA ESR'; 1/s	0.82 ± 0.48	0.96 ± 0.58	0.75 ± 0.38	0.30	0.093	0.35
LA ASR; %		6.8 ± 3.3	7.8 ± 3.5		0.18	
LA ASR'; 1/s		0.64 ± 0.33	0.61 ± 0.39		0.71	
TSA, n = 25						
LA parameter	**a. baseline**	**b. 3 months**	**c. 12 months**	**p value a vs. b**	**p value b vs. c**	**p value a vs. c**
LA strain time to peak (ms)	350 ± 57	388 ± 42	377 ± 59	0.004	0.52	0.035

LA SSR; %	11.9 ± 3.9	18.5 ± 6.6	16.5 ± 4.9	<0.001	0.138	<0.001
LA ESR; %	6 ± 2.1	11 ± 4.7	9.5 ± 3.9	<0.001	0.161	<0.001
LA SSR'; 1/s	0.59 ± 0.2	0.78 ± 0.28	0.65 ± 0.27	0.001	0.021	0.24
LA ESR'; 1/s	0.82 ± 0.38	0.78 ± 0.34	0.94 ± 1.8	0.48	0.66	0.74
LA ASR; %		7.5 ± 3	7 ± 2.6		0.47	
LA ASR'; 1/s		0.64 ± 0.26	0.51 ± 0.27		0.001	

Footnote 32: % - represents strain imaging, 1/s – represents strain rate, ASR -contraction, CA – catheter ablation, ESR -conduit, ms- milliseconds, SSR – reservoir, TSA – thoracoscopic surgical ablation

Between group comparisons showed significantly higher LA SSR and LA ESR at 12 months in the CA group compared to the TSA group (Table 22). All other LA parameters at equivalent time points were similar between the two groups.

Table 22: Comparison of LA strain and strain rate parameters between the CA and TSA groups. The values are means ± SD.

LA parameter	Study time point	CA (n=29)	SA (n=25)	P value
LA strain time to peak (ms)	Baseline	347 ± 58	350 ± 57	0.81
	3 months	402 ± 50	388 ± 42	0.24
	12 months	380 ± 60	377 ± 59	0.85
LA SSR; %	Baseline	10.6 ± 4.5	11.9 ± 3.9	0.28
	3 months	20.6 ± 8	18.5 ± 6.6	0.29
	12 months	20.3 ± 7.4	16.5 ± 4.9	0.03
LA ESR; %	Baseline	5.7 ± 2.9	6 ± 2.1	0.7

	3 months	13.8 ± 5.8	11 ± 4.7	0.052
	12 months	12.5 ± 5.6	9.5 ± 3.9	0.02
LA SSR'; 1/s	Baseline	0.5 ± 0.2	0.59 ± 0.2	0.13
	3 months	0.83 ± 0.29	0.78 ± 0.28	0.51
	12 months	0.8 ± 0.31	0.65 ± 0.27	0.062
LA ESR'; 1/s	Baseline	0.82 ± 0.48	0.82 ± 0.38	0.99
	3 months	0.96 ± 0.58	0.78 ± 0.34	0.16
	12 months	0.75 ± 0.38	0.94 ± 1.8	0.63
LA ASR; %	3 months	6.8 ± 3.3	7.5 ± 3	0.42
	12 months	7.8 ± 3.5	7 ± 2.6	0.36
LA ASR'; 1/s	3 months	0.64 ± 0.33	0.64 ± 0.26	0.13
	12 months	0.61 ± 0.39	0.51 ± 0.27	0.38

Footnote 33: % - represents strain imaging, 1/s – represents strain rate, ASR -contraction, CA – catheter ablation, ESR -conduit, ms- milliseconds, SSR – reservoir, TSA – thoracoscopic surgical ablation

4.3.2.2 COMPARISON OF LA STRAIN AND STRAIN RATE PARAMETERS BETWEEN SINUS RHYTHM AND AF RECURRENCE

Among the 54 patients, SR was maintained throughout follow up in 30 (56%) patients, whereas AF recurrence was recorded in 24 (44%) patients. Similar proportions of patients in each of the CA and TSA groups had AF recurrence during follow up.

In the SR group (Table 23), LA SSR, LA SSR' and LA ESR were significantly higher at 3 months compared to baseline with no further change thereafter. LA ESR' was similar at all 3 time points and LA ASR and LA ASR' were similar at 3 months and 12 months.

In the AF group (Table 23), LA SSR, LA SSR' and LA ESR were significantly higher at 3 months compared to baseline with no further change thereafter. LA ESR' was similar at all 3 time points and LA ASR and LA ASR' were similar at 3 months and 12 months.

Table 23: Within group analyses of strain and strain rate measurements al all three study time points, based on heart rhythm in follow up.

SR, n = 30						
LA parameter	**a. baseline**	**b. 3 months**	**c. 12 months**	**p value a vs. b**	**p value b vs. c**	**p value a vs. c**
LA strain time to peak (ms)	353 ± 57	390 ± 41	378 ± 56	0.007	0.165	0.108
LA SSR; %	12.3 ± 4.3	22.2 ± 8.1	19.6 ± 6.9	<0.001	0.081	<0.001
LA ESR; %	6.4 ± 2.6	13.8 ± 5.9	11.6 ± 5.2	<0.001	0.064	<0.001
LA SSR'; 1/s	0.59 ± 0.24	0.88 ± 0.28	0.79 ± 0.34	<0.001	0.124	0.008
LA ESR'; 1/s	0.89 ± 0.49	0.9 ± 0.39	1.1 ± 1.7	0.96	0.63	0.6
LA ASR; %		8.4 ± 3.3	8 ± 3.7		0.57	
LA ASR'; 1/s		0.76 ± 0.3	0.67 ± 0.4		0.17	
AF, n = 24						

LA parameter	a. baseline	b. 3 months	c. 12 months	p value a vs. b	p value b vs. c	p value a vs. c
LA strain time to peak (ms)	358 ± 60	408 ± 50	372 ± 60	0.001	0.004	0.5
LA SSR; %	9.8 ± 3.7	16.4 ± 4.9	17.2 ± 6.2	<0.001	0.53	<0.001
LA ESR; %	5.1 ± 2.2	11 ± 4.4	10.5 ± 5	<0.001	0.53	<0.001
LA SSR'; 1/s	0.48 ± 0.14	0.73 ± 0.23	0.65 ± 0.22	<0.001	0.14	0.004
LA ESR'; 1/s	0.73 ± 0.32	0.84 ± 0.6	0.57 ± 0.25	0.38	0.052	0.071
LA ASR; %		5.5 ± 2.1	6.7 ± 2.2		0.052	
LA ASR'; 1/s		0.49 ± 0.23	0.44 ± 0.19		0.24	

Footnote 34: % - represents strain imaging, 1/s – represents strain rate, ASR -contraction, CA – catheter ablation, ESR -conduit, ms- milliseconds, SSR – reservoir, TSA – thoracoscopic surgical ablation

Between group comparisons showed that LA SSR and LA SSR' at baseline and 3 months were higher in the SR group compared to the AF group, but were not significantly different at 12 months (Table 24). LA ESR was significantly higher in the SR group at baseline, but with no significant differences at follow-up. LA ESR' was higher in the SR group at 3 months only. LA ASR and LA ASR' were significantly higher in the SR group at 3 months, and LA ASR' remained higher at 12 months.

Table 24: Comparison of LA strain and strain rate between the SR and AF groups at baseline, 3 months and 12 months following ablation.

LA strain/strain rate parameter	Study time point	AF (n = 24)	SR (n = 30)	P value
LA strain time to peak (ms)	Baseline	358 ± 60	353 ± 57	0.76
	3 months	408 ± 50	392 ± 41	0.23
	12 months	372 ± 60	378 ± 56	0.71
LA SSR; %	Baseline	9.8 ± 3.7	12.3 ± 4.3	0.024
	3 months	16.4 ± 4.9	22.2 ± 8.1	0.002
	12 months	17.2 ± 6.2	19.6 ± 6.9	0.191
LA ESR; %	Baseline	5.1 ± 2.2	6.4 ± 2.6	0.042
	3 months	11 ± 4.4	13.8 ± 5.9	0.7
	12 months	10.5 ± 5	11.6 ± 5.2	0.44
LA SSR'; 1/s	Baseline	0.48 ± 0.14	0.59 ± 0.24	0.048
	3 months	0.73 ± 0.23	0.88 ± 0.28	0.031
	12 months	0.65 ± 0.22	0.79 ± 0.34	0.19
LA ESR'; 1/s	Baseline	0.73 ± 0.32	0.9 ± 0.49	0.141
	3 months	0.84 ± 0.6	0.9 ± 0.39	0.048
	12 months	0.57 ± 0.25	1.1 ± 1.7	0.14
LA ASR; %	3 months	5.5 ± 2.1	8.4 ± 3.3	0.001
	12 months	6.7 ± 2.2	8 ± 3.7	0.121
LA ASR'; %	3 months	0.49 ± 0.23	0.75 ± 0.3	0.001
	12 months	0.44 ± 0.19	0.67 ± 4	0.008

Footnote 35: % - represents strain imaging, 1/s – represents strain rate, ASR -contraction, CA – catheter ablation, ESR -conduit, ms- milliseconds, SSR – reservoir, TSA – thoracoscopic surgical ablation

4.3.2.3 LA STRAIN AND STRAIN RATE AS PREDICTORS OF AF RECURRENCE

Table 25 provides a summary of univariable and multivariable analyses of the baseline demographic data and LA parameters. This is followed by multivariable analysis of the LA parameters at 3 months when added to the demographic data.

Univariable analysis of the baseline parameters showed LA SSR to have a significant negative association with AF recurrence. Body mass index achieved borderline statistical significance and all other parameters were not significantly related to AF recurrence. Multivariable analysis also showed LA SSR to be the only independent baseline predictor of AF recurrence. Univariable analysis of the data from 3 months follow-up time point, showed LA ASR and LA ASR' to have significant negative associations with AF recurrence. In multivariable analysis LA ASR at 3 months to be an independent predictor of AF recurrence. Re-analysis of the 3 months data, by excluding LA SSR, LA ESR and LA ASR and keeping only the strain rate data showed that LA ASR' became an independent predictor of AF recurrence.

Table 25: Univariable and multivariable analyses of AF recurrence and association with LA function measured by strain and strain rate.

Timeline	Parameter	Univariable			Multivariable		
		OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Baseline	BMI	1.118	0.998 – 1.25	0.053	1.116	0.988 – 1.26	0.077
	AF duration	1	0.998 – 1.001	0.69			

	Age	1.05	0.99 – 1.11	0.11			
	Male	1.667	0.44 – 6.3	0.45			
	Hypertension	1.4	0.47 – 4.13	0.54			
	Respiratory disease	0.299	0.056 – 1.597	0.16			
	DM	1.128	0.407 – 3.125	0.82			
	CAD	2.8	0.47 -16.8	0.26			
	Thyroid disorders	2.04	0.634 – 6.53	0.23			
	CVD	0.609	0.052 – 7.146	0.69			
	CKD	2	0.31 – 13	0.47			
	Smoker	0.75	0.29 – 1.95	0.55			
	Alcohol	1.016	0.674 – 1.53	0.94			
	LA SSR (%)	0.843	0.719 - 0.989	0.036	0.845	0.716 – 0.998	0.047
	LA SSR (1/s)	0.064	0.003 – 1.249	0.07			
	LA ESR (%)	0.781	0.608 – 1.004	0.054			
	LAESR (1/s)	0.355	0.082 – 1.538	0.166			
3 months	LA SSR (%)	0.862	0.775 – 0.959	0.006			
	LA SSR (1/s)	0.091	0.009 – 0.909	0.041			
	LA ESR (%)	0.892	0791 – 1.007	0.064			
	LA ESR (1/s)	0.786	0.247 – 2.495	0.68			
	LA ASR (%)	0.64	0.481 – 0.851	0.002	0.669	0.507 – 0.882	0.004
	LA ASR (1/s)	0.02	0.002 – 0.262	0.003			

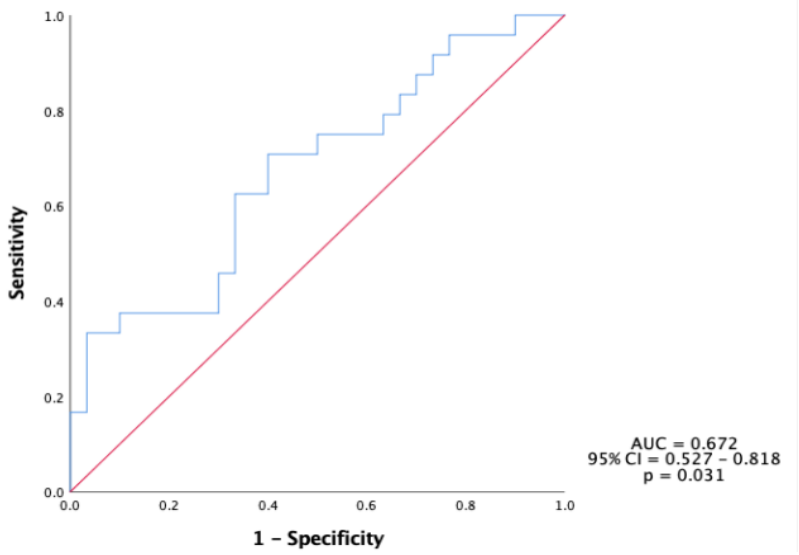
Footnote 36: % - represents strain imaging, 1/s – represents strain rate, ASR -contraction, CA – catheter ablation, CAD – coronary artery disease, CKD – chronic kidney disease, CVD –

cerebrovascular disease, DM – diabetes mellitus, ESR -conduit, ms- milliseconds, SSR – reservoir, TSA – thoracoscopic surgical ablation

ROC curve analysis for LA SSR at baseline showed strain (area under the curve (AUC) = 0.672, p = 0.03) was a strong predictor of AF recurrence in follow-up with optimal cut-off point being 10.3% (sensitivity = 70.8% and specificity = 60%).

Kaplan-Meier survival curve analysis showed a LA SSR cut-off of <10.3% was associated with 41.4% freedom from atrial arrhythmias, while >10.3% was associated with 72% freedom from atrial arrhythmias (HR = 2.73, 95% CI = 1.13 – 6.62, p = 0.026), Figure 42.

A:



B:

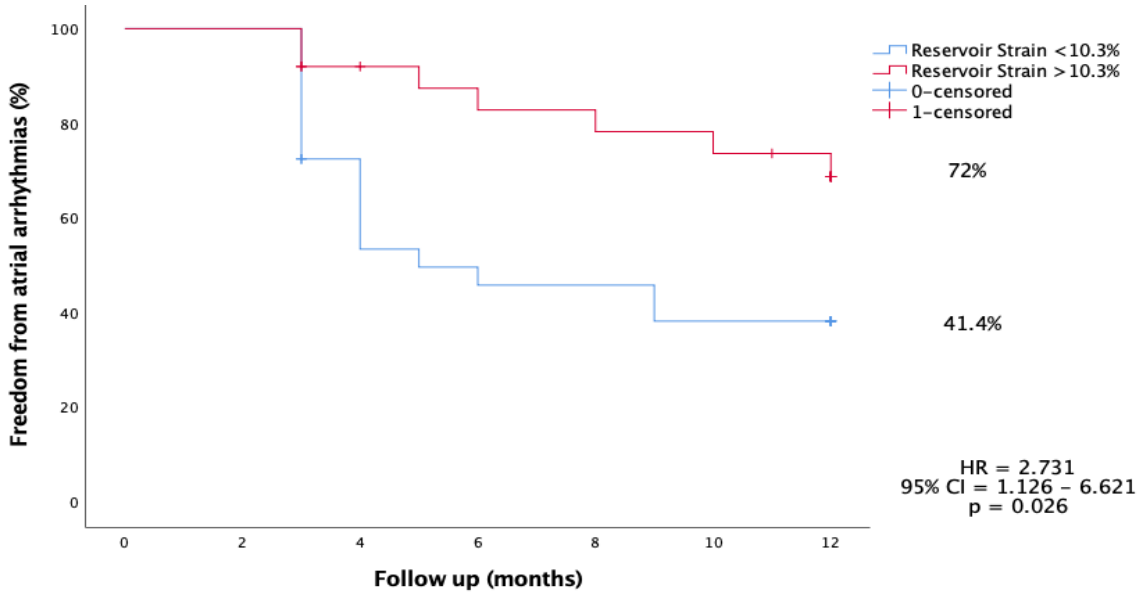
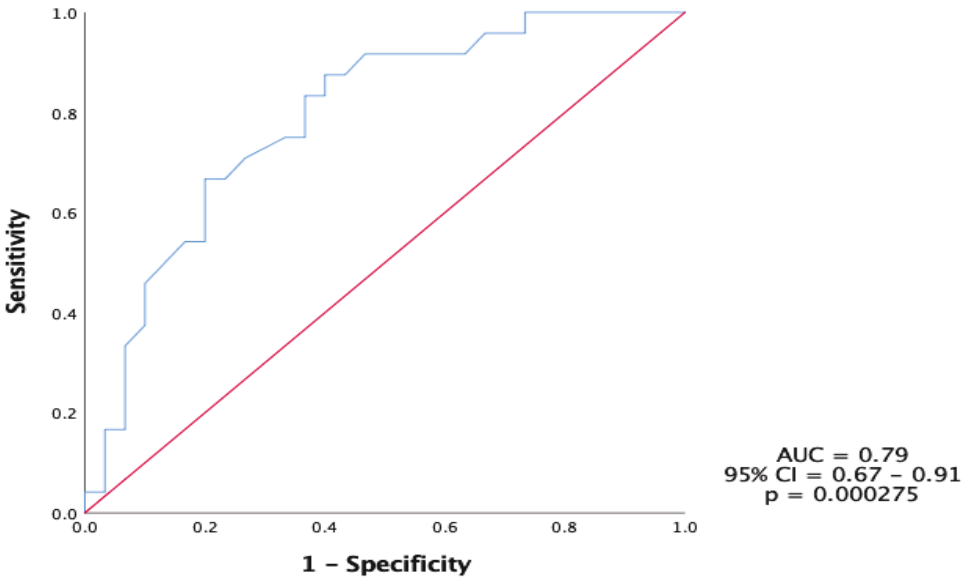


Figure 42: Baseline LA SSR ROC curve analysis showed strain (AUC = 0.672, p = 0.03) was a strong predictor of AF recurrence in follow-up with optimal cut-off being 10.3% ***(A)****. Kaplan Maier survival curves showing that reservoir strain <10.3% is strongly associated (P=0.026) with SR maintenance (72%)* ***(B)****.*

Using ROC curve analysis for LA ASR from 3 months follow up showed strong prediction for AF recurrence (AUC = 0.79, p = <0.001) with optimal cut-off of 7.5% (sensitivity = 88% and specificity = 60%). At 3 months following ablation, a cut-off of LA ASR >7.5% was associated with 85.7% freedom from atrial arrhythmias, while ASR <7.5% was associated with 36.4% freedom from atrial arrhythmias (HR 5.94, 95% CI = 1.76 – 20.1, p = 0.004), Figure 43.

A:



B:

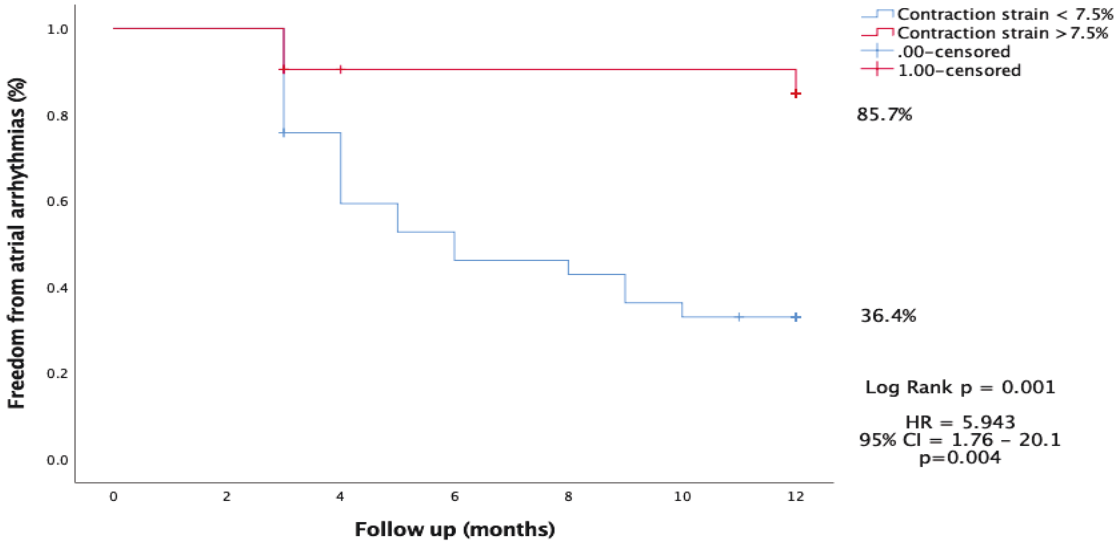


Figure 43: ROC curve of LA contraction using 2D speckle tracking strain at 3 months following ablation as a predictor for AF recurrence over 12 months follow up **(A)**. Kaplan Meier curve analysis of freedom from AF recurrence LA reservoir strain at 3 months categorised as < or > 7.5% **(B)**.

4.3.3 TISSUE DOPPLER IMAGING DATA

A total of 52 patients (45%) had technically adequate TTE scans for analysis of TDI parameters in CASA AF Trial cohort. Of these, 33 were common to the strain analysis and 19 were a different subset of patients. Among the 52 patients, 50% underwent CA. Baseline demographic characteristics and clinical data were similar in both groups apart from greater digoxin use in the CA group, 34.6% compared to 11.5% (Table 26).

Table 26: Baseline characteristics of study participants in TDI analysis

BASELINE CHARACTERISTICS	**CA (n=26)**	**TSA (n=26)**	**P value**
Age (mean years, ±SD)	64 ± 8.9	67.4 ± 8.3	0.15
Sex, n = male (%)	20 (76.9%)	20 (76.9%)	1
Body mass index, kg/m^2 (mean ± SD)	30.8 ± 4.6	29.5 ± 4.6	0.32
Smoking, n (%)	2 (7.7)	0	0.15
Hypertension, n (%)	10 (38.5)	17 (65.4)	0.095
Diabetes mellitus, n (%)	2 (7.7)	2 (7.7)	1
Stroke, n (%)	0	2 (7.7)	0.15
Coronary artery disease, n (%)	5 (19.2)	4 (15.4)	0.714
Renal disease, n (%)	3 (11.5)	1 (3.8)	0.3
Respiratory disease, n (%)	4 (15.4)	4 (15.4)	1
Thyroid disorders, n (%)	1 (3.8)	3 (11.5)	0.3
Alcohol, n (%)	15 (57.7)	12 (46.2)	0.6
MEDICATIONS			

Beta-blocker, n (%)	21 (80.8)	21 (80.8)	1
Digoxin, n (%)	9 (34.6)	3 (11.5)	0.048
Calcium channel blocker, n (%)	3 (11.5)	3 (11.5)	1
ACE/ARB, n (%)	12 (46.2)	13 (50)	0.78
Diuretic, n (%)	6 (23)	11 (42.3)	0.24
AADs, n (%)	1 (3.8)	1 (3.8)	1
Statin, n (%)	16 (61.5)	14 (53.9)	0.78

Footnote 37: AADs – antiarrhythmic drugs, ACE -angiotensin converting enzyme, ARB – angiotensin receptor blocker, CA -catheter ablation, TSA -thoracoscopic surgical ablation.

4.3.3.1 COMPARISONS OF THE LA TDI PARAMETERS IN THE CA AND TSA GROUPS

Table 27 shows measurements and comparison of TDI parameters in CA and TSA groups. In the CA group, compared to baseline, S' and SSR were higher at 12 months, whereas ESR was lower at 3 months and remained lower at 12 months. There was a significant increase in ASR from 3 months to 12 months, but no change in TACT or LV septal A' during this time period.

In the TSA group, compared to baseline, S' was lower at 3 months and 12 months. There was no significant change in SSR, whereas there was a reduction in ESR at 3 months and 12 months. ASR and TACT remained unchanged from 3 months to 12 months. Finally, there was a trend towards lower LV septal A' at 12 months compared to 3 months.

Table 27: Within group analyses of LA TDI parameters

CA, n = 26						
Global Parameter	**Time point**			**P values**		
	a. baseline	**b. 3 months**	**c. 12 months**	**a vs. b**	**b vs. c**	**a vs. c**
S' (cm/s)	7.2 ± 2.1	6.8 ± 1.9	7.7 ± 2.2	0.31	0.35	0.009
SSR (cm/s)	6.2 ± 1.3	6.6 ± 1.3	7.3 ± 1.4	0.183	0.011	0.002
ESR (cm/s)	8.9 ± 2.2	7.7 ± 1.2	7.8 ± 1.3	0.016	0.64	0.035
ASR (cm/s)		6.3 ± 1.9	6.9 ± 2		0.043	
TACT (ms)		156.2 ± 27.9	161.2 ± 30.1		0.67	
LV Septal A'		6.2 ± 2	6.4 ± 1.6		0.59	
TSA, n = 26						
Global Parameter	**Time point**			**P values**		
	a. baseline	**b. 3 months**	**c. 12 months**	**a vs. b**	**b vs. c**	**a vs. c**
S' (cm/s)	8.1 ± 2	6.6 ± 1.8	7.2 ± 2	0.002	0.115	0.031
SSR (cm/s)	6.5 ± 1.3	6.6 ± 1.4	7.2 ± 1.7	0.8	0.05	0.12
ESR (cm/s)	10.1 ± 2.9	7.9 ± 1.8	8.1 ± 1.9	0.002	0.81	0.003
ASR (cm/s)		6 ± 1.6	6 ± 1.5		0.89	
TACT (ms)		168 ± 34	171.6 ± 22.2		0.66	
LV Septal A'		7 ± 1.9	6.2 ± 1.9		0.05	

Footnote 38: ASR -contraction, CA – catheter ablation, ESR -conduit, ms- milliseconds, LV septal A' – late diastolic A velocity representing effect of left atrial contraction on the LV septum, S' – isovolumic LA contraction, SSR – reservoir, TACT -total atrial contraction time, TSA – thoracoscopic surgical ablation

As shown in Table 28 there were no between group differences in LA TDI parameters at the 3 equivalent time points.

Table 28: Global LA function comparisons between CA and TSA

Study time point	Parameter	CA, n= 26	TSA, n = 26	P Value
Global Baseline	S' (cm/s)	7.2 ± 2.1	8.1 ± 2	0.13
	SSR (cm/s)	6.2 ± 1.3	6.5 ± 1.3	0.36
	ESR (cm/s)	8.9 ± 2.2	10.1 ± 2.9	0.1
Global Month 3	S' (cm/s)	6.7 ± 1.8	6.6 ± 1.8	0.8
	SSR (cm/s)	6.6 ± 1.8	6.6 ± 1.3	0.9
	ESR (cm/s)	7.7 ± 1.2	8.1 ± 2	0.38
	ASR (cm/s)	6.2 ± 1.9	6.1 ± 1.6	0.73
	TACT (ms)	156.2 ± 27.9	168 ± 34	0.33
	LV Septal A'	6 ± 2	7 ± 1.9	0.14
Global Month 12	S' (cm/s)	7.7 ± 2.2	7.2 ± 2	0.45
	SSR (cm/s)	7.3 ± 1.4	7.2 ± 1.7	0.85
	ESR (cm/s)	7.8 ± 1.3	8.1 ± 1.9	0.38
	ASR (cm/s)	6.8 ± 1.9	5.9 ± 1.6	0.06
	TACT (ms)	159.5 ± 29.4	171.6 ± 22.2	0.23
	LV Septal A'	6.5 ± 1.5	6.1 ± 1.9	0.61

Footnote 39: ASR -contraction, CA – catheter ablation, ESR -conduit, ms- milliseconds, LV septal A' – late diastolic A velocity representing effect of left atrial contraction on the LV

septum, S' – isovolumic LA contraction, SSR – reservoir, TACT -total atrial contraction time, TSA – thoracoscopic surgical ablation

4.3.3.2 LONGITUDINAL EFFECTS OF CA AND TSA ON REGIONAL LA WALL MOTION AND FUNCTION

Individual ablation strategies can have different effects on regional LA wall motion and function which can evolve over time. We compared changes in regional and global LA functions at baseline, 3 and 12 months post ablation as shown in Table 28 and Table 29.

There were no significant differences in the regional functions of the LA at baseline and in septal and inferior LA regions at 3 months and 12 months between CA and TSA. However, patients in the TSA group had reduced contraction at the lateral LA region (4.8 ± 1.7 cm/s vs 6.2 ± 2.8 cm/s, p= 0.045) and the anterior LA region (5.5 ± 2.3 vs 7.1 ± 2.4 cm/s, p=0.02) when compared to CA at 12 months follow up. This effect does not translate into a change in the global LA function between the two groups at 3 or the 12 months follow up. The reduced contractile function at the anterior and lateral wall in the SA group at 12 months might be a medium to long-term effect of mechanical LAA exclusion using epicardial compression device.

Within the CA and TSA groups, there is noticeable increase in regional expansion following CA in most regions except lateral wall with nonsignificant changes following TSA at 12 months follow up 9 (Table 30 and Table 31).

Global conduit function significantly reduced from baseline to 3 months and 12 months, in both CA and TSA groups (more inferior and lateral for the CA group; more anterior and inferior for the TSA group). More of the LA walls showed improved reservoir function in the CA group (inferior, septal, anterior) compared to none in the TSA group.

Table 29: Regional wall TDI measurements: comparison of CA and TSA treatment groups

Location	Parameter	Timeline	CA (26)	TSA (26)	P value
Septum	S’	Baseline	6.6 ± 2.7	7.8 ± 2.2	0.08
		3 months	6.8 ± 2	7.1 ± 2.3	0.57
		12 months	8.2 ± 2.9	8.2 ± 2.7	0.96
	Reservoir	Baseline	5.3 ± 1.5	5.6 ± 1.4	0.56
		3 months	6 ± 1.3	5.7 ± 1.8	0.52
		12 months	6.5 ± 2.1	6.3 ± 2.3	0.67
	Conduit	Baseline	7.4 ± 2.2	7.6 ± 2.6	0.76
		3 months	6.9 ± 2.1	6.3 ± 2.1	0.3
		12 months	6.3 ± 2.3	6.5 ± 2.2	0.75
	Booster	3 months	6.1 ± 1.9	6 ± 1.9	0.86
		12 months	6.5 ± 2.1	6 ± 1.9	0.37
Lateral	S’	Baseline	6.9 ± 2.7	7.9 ± 2.8	0.21
		3 months	6 ± 2.1	5.9 ± 1.9	0.8
		12 months	6.7 ± 2.6	6.3 ± 2.7	0.65
	Reservoir	Baseline	6.7 ± 1.8	7.1 ± 2.2	0.53
		3 months	7.1 ± 1.6	7.1 ± 2	0.97
		12 months	7.5 ± 2.1	7.9 ± 2.1	0.56
	Conduit	Baseline	10.6 ± 2.6	11.2 ± 4.3	0.55

		3 months	8.5 ± 1.3	9.9 ± 3.8	0.07
		12 months	8.7 ± 1.5	10.3 ± 3.2	0.03
	Booster	3 months	5.7 ± 2.4	5.2 ± 1.7	0.45
		12 months	6.2 ± 2.8	4.8 ± 1.7	0.045
Anterior	S’	Baseline	7.1 ± 2	8.2 ± 2.5	0.09
		3 months	6.7 ± 2.3	5.7 ±2.2	0.11
		12 months	7.5 ± 2.9	6.1 ± 2.3	0.05
	Reservoir	Baseline	6.6 ± 2	7.1 ± 1.8	0.4
		3 months	6.8 ± 2.1	7.3 ± 1.5	0.33
		12 months	7.7 ± 1.6	7.4 ± 2	0.52
	Conduit	Baseline	10.7 ± 2.8	12.2 ± 4.4	0.16
		3 months	8.4 ± 2.7	8.7 ± 2.5	0.65
		12 months	8.7 ± 1.7	8.6 ± 2.3	0.84
	Booster	3 months	6.4 ± 2.5	5.8 ± 2.2	0.41
		12 months	7.1 ± 2.4	5.5 ± 2.3	0.02
Inferior	S’	Baseline	8.1 ± 3.2	8.4 ± 2.9	0.67
		3 months	7.3 ± 2.6	7.6 ± 2.7	0.63
		12 months	8.3 ± 2.9	8.3 ± 2.1	0.92
	Reservoir	Baseline	5.9 ± 1.4	6.4 ± 1.6	0.31
		3 months	6.5 ± 1.8	6.5 ± 1.8	1
		12 months	7.4 ± 1.9	7.3 ± 2.1	0.82
	Conduit	Baseline	8.3 ± 2.2	9.5 ± 3.2	0.11
		3 months	6.8 ± 1.7	7.3 ± 2.3	0.44

		12 months	7.3 ± 2.1	7.1 ± 2.2	0.81
	Booster	3 months	6.8 ± 2.1	7.2 ± 2.2	0.49
		12 months	7.4 ± 1.9	7.1 ± 2.7	0.66

Table 30: TDI regional measurements at different time points in CA treatment arm.

Location	**Parameter**	**a. baseline**	**b. 3 months**	**c. 12 months**	**P value a vs. b**	**P value b vs. c**	**P value a vs. c**
Septum	S’	6.6 ± 2.7	6.8 ± 2	8.2 ± 2.9	0.69	0.011	0.018
	Reservoir	5.3 ± 1.5	6 ± 1.3	6.5 ± 2.1	0.088	0.21	0.007
	Conduit	7.4 ± 2.2	6.9 ± 2.1	6.3 ± 2.3	0.31	0.3	0.034
	Booster	-	6.1 ± 1.9	6.5 ± 2.1	-	0.24	-
Lateral	S’	6.9 ± 2.7	6 ± 2.1	6.7 ± 2.6	0.16	0.098	0.72
	Reservoir	6.7 ± 1.8	7.1 ± 1.6	7.5 ± 2.1	0.36	0.17	0.06
	Conduit	10.6 ± 2.6	8.5 ± 1.3	8.7 ± 1.5	0.001	0.5	0.003
	Booster	-	5.7 ± 2.4	6.2 ± 2.8		0.17	-
Anterior	S’	7.1 ± 2	6.7 ± 2.3	7.5 ± 2.9	0.43	0.14	0.46
	Reservoir	6.6 ± 2	6.8 ± 2.1	7.7 ± 1.6	0.68	0.082	0.037
	Conduit	10.7 ± 2.8	8.4 ± 2.7	8.7 ± 1.7	0.012	0.46	0.014
	Booster	-	6.4 ± 2.5	7.1 ± 2.4		0.28	-
Inferior	S’	8.1 ± 3.2	7.3 ± 2.6	8.3 ± 2.9	0.35	0.053	0.74
	Reservoir	5.9 ± 1.4	6.5 ± 1.8	7.4 ± 1.9	0.21	0.034	0.002
	Conduit	8.3 ± 2.2	6.8 ± 1.7	7.3 ± 2.1	0.004	0.37	0.054
	Booster	-	6.8 ± 2.1	7.4 ± 1.9		0.092	-

Table 31: TDI regional measurements at different time points in TSA treatment arm.

Location	Parameter	a. baseline	b. 3 months	c. 12 months	P value a vs. b	P value b vs. c	P value a vs. c
Septum	S’	7.8 ± 2.2	7.1 ± 2.3	8.2 ± 2.7	0.23	0.099	0.5
	Reservoir	5.6 ± 1.4	5.7 ± 1.8	6.3 ± 2.3	0.7	0.039	0.13
	Conduit	7.6 ± 2.6	7.6 ± 2.6	6.5 ± 2.2	0.011	0.65	0.13
	Booster	-	6 ± 1.9	6 ± 1.9	-	0.86	-
Lateral	S’	7.9 ± 2.8	5.9 ± 1.9	6.3 ± 2.7	0.005	0.4	0.036
	Reservoir	7.1 ± 2.2	7.1 ± 2	7.9 ± 2.1	0.97	0.077	0.17
	Conduit	11.2 ± 4.3	9.9 ± 3.8	10.3 ± 3.2	0.23	0.58	0.35
	Booster		5.2 ± 1.7	4.8 ± 1.7	-	0.57	-
Anterior	S’	8.2 ± 2.5	5.7 ±2.2	6.1 ± 2.3	<0.0001	0.28	0.0001
	Reservoir	7.1 ± 1.8	7.3 ± 1.5	7.4 ± 2	0.6	0.84	0.59
	Conduit	12.2 ± 4.4	8.7 ± 2.5	8.6 ± 2.3	0.002	0.88	0.001
	Booster	-	5.8 ± 2.2	5.5 ± 2.3	-	0.76	-
Inferior	S’	8.4 ± 2.9	7.6 ± 2.7	8.3 ± 2.1	0.33	0.3	0.8
	Reservoir	6.4 ± 1.6	6.5 ± 1.8	7.3 ± 2.1	0.98	0.027	0.094
	Conduit	9.5 ± 3.2	7.3 ± 2.3	7.1 ± 2.2	0.004	0.77	0.002
	Booster	-	7.2 ± 2.2	7.3 ± 2.7	-	0.91	-

4.3.3.3 LONGITUDINAL EFFECTS OF REGIONAL LA WALL MOTION AND FUNCTION ON THE RHYTHM

We compared changes in the regional LA function at baseline, 3 months and 12 months between rhythm groups of sinus rhythm maintenance and AF recurrence. There were no differences in S' and conduit function in all LA regions between rhythm groups. There was only a significant improvement in the reservoir function of the inferior wall at 12 months for patients who maintained SR (8.2 ± 1.2cm/s vs. 6.9 ± 2.1cm/s, p = 0.008). There were significant improvements in the contraction at 3 months of the lateral LA wall (7.1 ± 2.1 cm/s vs. 4.6 ± 1.6 cm/s, p <0.001) and the anterior LA wall (7.8 ± 2.3 cm/s vs 4.6 ± 1.6 cm/s, p = 0.001) in patients who maintained SR compared to patients with AF recurrence that persists for 12 months (Table 32, Table 33 and Table 34). The improved contraction in these two regions translates to improved global LA contraction for those patients who maintained SR.

Table 32: Regional TDI measurements contrasting groups in SR and AF

Location	Parameter	Timeline	AF (35)	SR (17)	P value
Septum	S'	Baseline	7.4 ± 2.8	6.8 ± 1.7	0.35
		3 months	7 ± 2.2	7 ± 2.1	0.95
		12 months	8.3 ± 2.9	8 ± 2.6	0.78
	Reservoir	Baseline	5.5 ± 1.6	5.4 ± 1.1	0.79
		3 months	5.7 ± 1.7	6.2 ± 1.3	0.24
		12 months	6.1 ± 1.9	7 ± 2	0.14
	Conduit	Baseline	7.3 ± 2.5	7.9 ± 2.1	0.36

		3 months	6.7 ± 2.2	6.4 ± 1.8	0.66
		12 months	6.4 ± 2.1	6.5 ± 2.6	0.82
	Booster	3 months	5.6 ± 1.9	6.9 ± 1.7	0.066
		12 months	5.9 ± 1.8	7.2 ± 2.3	0.1
Lateral	S’	Baseline	7.6 ± 2.5	6.8 ± 3.2	0.34
		3 months	6 ± 2.1	5.9 ± 1.9	0.93
		12 months	6.7 ± 2.9	6.2 ± 2.1	0.53
	Reservoir	Baseline	7 ± 2.2	6.8 ± 1.6	0.79
		3 months	6.8 ± 1.8	7.7 ± 1.5	0.068
		12 months	7.6 ± 2.2	8 ± 1.8	0.41
	Conduit	Baseline	11.1 ± 3.7	10.4 ± 3.1	0.5
		3 months	8.9 ± 2.8	9.9 ± 3	0.26
		12 months	9.6 ± 2.5	9.5 ± 3	0.89
	Booster	3 months	4.6 ± 1.6	7.1 ± 2.1	0.00015
		12 months	5.1 ± 1.8	6.9 ± 2.9	0.08
Anterior	S’	Baseline	8.2 ± 2.3	6.4 ± 1.7	0.003
		3 months	6.6 ± 2.4	5.5 ± 1.9	0.08
		12 months	6.8 ± 2.8	6.9 ± 2.6	0.86
	Reservoir	Baseline	7.1 ± 2	6.4 ± 1.6	0.19
		3 months	6.9 ± 2	7.5 ± 1.5	0.28
		12 months	7.3 ± 1.8	8.1 ± 1.7	0.19
	Conduit	Baseline	12 ± 3.6	10.2 ± 3.8	0.13
		3 months	8.5 ± 2.8	8.9 ± 2.1	0.75
		12 months	8.6 ± 2.1	8.9 ± 2	0.78
	Booster	Baseline	4.6 ± 1.6	7.8 ± 2.3	0.001

		3 months	5.1 ± 1.8	7.8 ± 2.5	0.004
Inferior	S’	Baseline	8.8 ± 3.1	7.1 ± 2.4	0.039
		3 months	7.5 ± 2.8	7.6 ± 2.4	0.97
		12 months	8.4 ± 2.5	8.2 ± 2.7	0.77
	Reservoir	Baseline	6.1 ± 1.6	6.3 ± 1.4	0.67
		3 months	6.3 ± 1.8	6.9 ± 1.6	0.21
		12 months	6.9 ± 2.1	8.2 ± 1.2	0.008
	Conduit	Baseline	9 ± 2.4	8.7 ± 3.5	0.72
		3 months	7 ± 2.2	7.1 ± 1.3	0.83
		12 months	7 ± 2.1	7.4 ± 1.9	0.91
	Booster	3 months	6.5 ± 2.2	7.8 ± 2	0.056
		12 months	6.9 ± 2.4	8.2 ± 2	0.071

Table 33: Regional TDI measurements in AF group (n = 35).

Location	**Parameter**	**a. baseline**	**b. 3 months**	**c. 12 months**	**P value a vs. b**	**P value b vs. c**	**P value a vs. c**
Septum	S’	7.4 ± 2.8	7 ± 2.2	8.3 ± 2.9	0.36	0.11	0.018
	Reservoir	5.5 ± 1.6	5.7 ± 1.7	6.1 ± 1.9	0.57	0.17	0.086
	Conduit	7.3 ± 2.5	6.7 ± 2.2	6.4 ± 2.1	0.18	0.47	0.089
	Booster	-	5.6 ± 1.9	5.9 ± 1.8	-	0.48	-
Lateral	S’	7.6 ± 2.5	6 ± 2.1	6.7 ± 2.9	0.002	0.12	0.07
	Reservoir	7 ± 2.2	6.8 ± 1.8	7.6 ± 2.2	0.76	0.044	0.22
	Conduit	11.1 ± 3.7	8.9 ± 2.8	9.6 ± 2.5	0.005	0.19	0.035

	Booster	-	4.6 ± 1.6	5.1 ± 1.8	-	0.17	-
Anterior	S’	8.2 ± 2.3	6.6 ± 2.4	6.8 ± 2.8	0.0001	0.66	0.002
	Reservoir	7.1 ± 2	6.9 ± 2	7.3 ± 1.8	0.63	0.3	0.59
	Conduit	12 ± 3.6	8.5 ± 2.8	8.6 ± 2.1	<0.0001	0.76	<0.0001
	Booster	-	4.6 ± 1.6	5.1 ± 1.8	-	0.43	-
Inferior	S’	8.8 ± 3.1	7.5 ± 2.8	8.4 ± 2.5	0.044	0.082	0.49
	Reservoir	6.1 ± 1.6	6.3 ± 1.8	6.9 ± 2.1	0.77	0.083	0.058
	Conduit	9 ± 2.4	7 ± 2.2	7 ± 2.1	0.0004	0.87	0.0004
	Booster	-	6.5 ± 2.2	6.9 ± 2.4	-	0.38	-

Table 34: Regional TDI measurements in SR group (n = 17)

Location	**Parameter**	**a. baseline**	**b. 3 months**	**c. 12 months**	**P value a vs. b**	**P value b vs. c**	**P value a vs. c**
Septum	S’	6.8 ± 1.7	7 ± 2.1	8 ± 2.6	0.73	0.086	0.12
	Reservoir	5.4 ± 1.1	6.2 ± 1.3	7 ± 2	0.031	0.056	0.008
	Conduit	7.9 ± 2.1	6.4 ± 1.8	6.5 ± 2.6	0.003	0.89	0.045
	Booster	-	6.9 ± 1.7	7.2 ± 2.3	-	0.68	-
Lateral	S’	6.8 ± 3.2	5.9 ± 1.9	6.2 ± 2.1	0.33	0.55	0.5
	Reservoir	6.8 ± 1.6	7.7 ± 1.5	8 ± 1.8	0.006	0.32	0.012
	Conduit	10.4 ± 3.1	9.9 ± 3	9.5 ± 3	0.53	0.46	0.2
	Booster	-	7.1 ± 2.1	6.9 ± 2.9	-	0.69	-
Anterior	S’	6.4 ± 1.7	5.5 ± 1.9	6.9 ± 2.6	0.18	0.001	0.55
	Reservoir	6.4 ± 1.6	7.5 ± 1.5	8.1 ± 1.7	0.042	0.13	0.022

	Conduit	10.2 ± 3.8	8.9 ± 2.1	8.9 ± 2	0.29	0.88	0.28
	Booster	-	7.8 ± 2.3	7.8 ± 2.5	-	0.96	-
Inferior	S’	7.1 ± 2.4	7.6 ± 2.4	8.2 ± 2.7	0.61	0.26	0.25
	Reservoir	6.3 ± 1.4	6.9 ± 1.6	8.2 ± 1.2	0.22	0.0004	0.001
	Conduit	8.7 ± 3.5	7.1 ± 1.3	7.4 ± 1.9	0.065	0.6	0.19
	Booster	-	7.8 ± 2	8.2 ± 2	-	0.4	-

4.3.3.4 COMPARISON OF LA TDI PARAMETERS IN THE SINUS RHYTHM AND AF RECURRENCE GROUPS

Out of the 52 patients, 17 remained in sinus rhythm (33%) and 35 developed recurrent AF over the 12 months follow up period. The LA TDI parameters were assessed in both groups at baseline, 3 months and 12 months.

In the SR group, there were significant increases in SSR from baseline to 3 months and from 3 months to 12 months. All other parameters remained unchanged (Table 35).

In the AF recurrence group, S’ and SSR showed no significant change from baseline to 12 months, whereas ESR was lower at 3 months with no further change at 12 months. There were no significant differences in ASR, TACT and LV septal A’ from 3 months to 12 months (Table 35).

Table 35: Within group comparisons of TDI measured parameters in patients remaining in SR and those with AF recurrence

SR, n = 17						
	Time point			**P values**		
Global Parameter	**A baseline**	**B 3 months**	**C 12 months**	**A vs. B**	**B vs. C**	**A vs. C**
S' (cm/s)	6.8 ± 1.3	6.5 ± 1.5	7.3 ± 2.1	0.57	0.036	0.37
SSR (cm/s)	6.2 ± 1.1	7.1 ± 1.2	7.8 ± 1.3	0.014	0.003	0.001
ESR (cm/s)	9.3 ± 2.6	8.1 ± 1.2	8 ± 1.4	0.078	0.99	0.05
ASR (cm/s)		7.4 ± 1.5	7.5 ± 1.9		0.77	
TACT (ms)		151.9 ± 27.6	164.8 ± 19.9		0.18	
LV Septal A'		7.8 ± 1.5	7.5 ± 1.3		0.60	
AF, n = 35						
	Time point			**P values**		
Global Parameter	**A baseline**	**B 3 months**	**C 12 months**	**A vs. B**	**B vs. C**	**A vs. C**
S' (cm/s)	8 ± 2.2	6.8 ± 1.9	7.5 ± 2.2	0.002	0.03	0.196
SSR (cm/s)	6.4 ± 1.4	6.4 ± 1.4	6.9 ± 1.6	0.97	0.033	0.1
ESR (cm/s)	9.6 ± 2.7	7.8 ± 1.8	7.9 ± 1.7	<0.001	0.63	0.002
ASR (cm/s)		5.5 ± 1.5	5.9 ± 1.5		0.171	
TACT (ms)		169.9 ± 32.7	168.8 ± 29.3		0.91	
LV Septal A'		5.9 ± 1.9	5.6 ± 1.6		0.32	

Footnote 40: ASR -contraction, CA – catheter ablation, ESR -conduit, ms- milliseconds, LV septal A' – late diastolic A velocity representing effect of left atrial contraction on the LV septum, S' – isovolumic LA contraction, SSR – reservoir, TACT -total atrial contraction time, TSA – thoracoscopic surgical ablation

Comparison of SR and AF groups showed higher S' at baseline in the SR group with no differences at 3 months and 12 months (Table 36**).** There was a gradual increase in SSR which became significant at 12 months in the SR group. There were similar reductions in ESR from baseline to 12 months in both groups. Most notably, ASR and LV septal A' were significantly higher at 3 months in the SR group compared to the AF group and these differences were maintained at 12 months. TACT was similar at all time points in both groups.

Table 36: LA function analysed by TDI and its relation to clinical outcomes

Study time point	**LA Wall**	**Parameter**	**AF, n=35**	**SR, n= 17**	**P Value**
Baseline	Global	S' (cm/s)	8 ± 2.2	6.8 ± 1.3	0.017
		SSR (cm/s)	6.4 ± 1.3	6.2 ± 1.1	0.64
		ESR (cm/s)	9.6 ± 2.7	9.3 ± 2.6	0.73
3 months	Global	S' (cm/s)	6.7 ± 1.9	6.5 ± 1.5	0.56
		SSR (cm/s)	6.4 ± 1.4	7.1 ± 1.1	0.09
		ESR (cm/s)	7.8 ± 1.8	8 ± 1.2	0.61
		ASR (cm/s)	5.5 ± 1.5	7.4 ± 1.5	<0.001
		TACT	169.9 ± 32.7	151.9 ± 27.6	0.13
		LV Septal A'	5.9 ± 1.9	7.8 ± 1.5	0.004
12 months	Global	S' (cm/s)	7.5 ± 2.2	7.3 ± 2.1	0.76
		SSR (cm/s)	7 ± 1.6	7.8 ± 1.2	0.048
		ESR (cm/s)	7.9 ± 1.7	8 ± 1.4	0.88
		ASR (cm/s)	5.9 ± 1.5	7.4 ± 1.9	0.008
		TACT	168.8 ± 29.3	162 ± 20.3	0.51

		LV Septal A’	5.6 ± 1.6	7.4 ± 1.3	0.001

Footnote 41: ASR -contraction, CA – catheter ablation, ESR -conduit, ms- milliseconds, LV septal A’ – late diastolic A velocity representing effect of left atrial contraction on the LV septum, S’ – isovolumic LA contraction, SSR – reservoir, TACT -total atrial contraction time, TSA – thoracoscopic surgical ablation

4.3.3.5 LA TDI PARAMETERS AS PREDICTORS OF AF RECURRENCE

As shown in Table 37 univariable and multivariable logistic regression analyses of baseline parameters were not able to identify any predictors of AF recurrence, but ASR measured at 3 months was a negative independent predictor of AF recurrence in both analyses.

Table 37: Univariable and multivariable analyses of LA TDI parameters and association with AF recurrence

Timeline	**Parameter**	**Univariable**			**Multivariable**		
		OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Baseline	BMI	0.967	0.853 – 1.097	0.6			
	AF duration	0.999	0.998 – 1.001	0.29			
	Age	1.043	0.974 – 1.117	0.23			
	Male	1.615	0.375 – 6.951	0.52			
	Hypertension	0.661	0.205 – 2.133	0.49			
	Respiratory disease	0.419	0.091 – 1.936	0.266			
	DM	1.225	0.38 – 3.949	0.734			

	CAD	4.741	0.542 – 41.4	0.16			
	Thyroid	1.225	0.38 – 3.949	0.734			
	CVD	0.471	0.028 – 8	0.6			
	CKD	0.412	0.08 – 2.118	0.29			
	Smoker	1.028	0.51 – 2.1	0.94			
	Alcohol	1.415	0.868 – 2.3	0.164			
	S’	1.405	0.998 – 1.979	0.052			
	Reservoir	1.115	0.694 – 1.791	0.65			
	Conduit	1.042	0.827 – 1.312	0.73			
3 months	S’	1.099	0.785 – 1.539	0.58			
	SSR	0.704	0.453 – 1.094	0.12	1.026	0.58 – 1.83	0.93
	ESR	0.92	0.643 – 1.316	0.65			
	ASR	0.442	0.264 – 0.74	0.002	0.371	0.186 – 0.74	0.005
	LV septal A’	0.527	0.311 – 0.892	0.17			

Footnote 42: ASR -contraction, BMI – body mass index, CA – catheter ablation, CAD – coronary artery disease, CKD – chronic kidney disease, CVD – cerebrovascular disease, DM – diabetes mellitus, ESR - conduit, ms- milliseconds, LV septal A’ - late diastolic A velocity representing effect of left atrial contraction on the LV septum, S’ – Isovolumetric contraction of LA, SSR – reservoir, TSA – thoracoscopic surgical ablation.

As illustrated in Figure 44, ROC curve analysis showed ASR at 3 months to have an AUC of 0.797 ($p<0.001$) for the prediction of AF recurrence. At the optimum cut-off value of 6cm/s, ASR was associated with 66% sensitivity and 81% specificity for the prediction of AF

recurrence. Patients with ASR >6cm/s were more likely to remain in SR during follow up compared to those with ASR < 6cm/s.

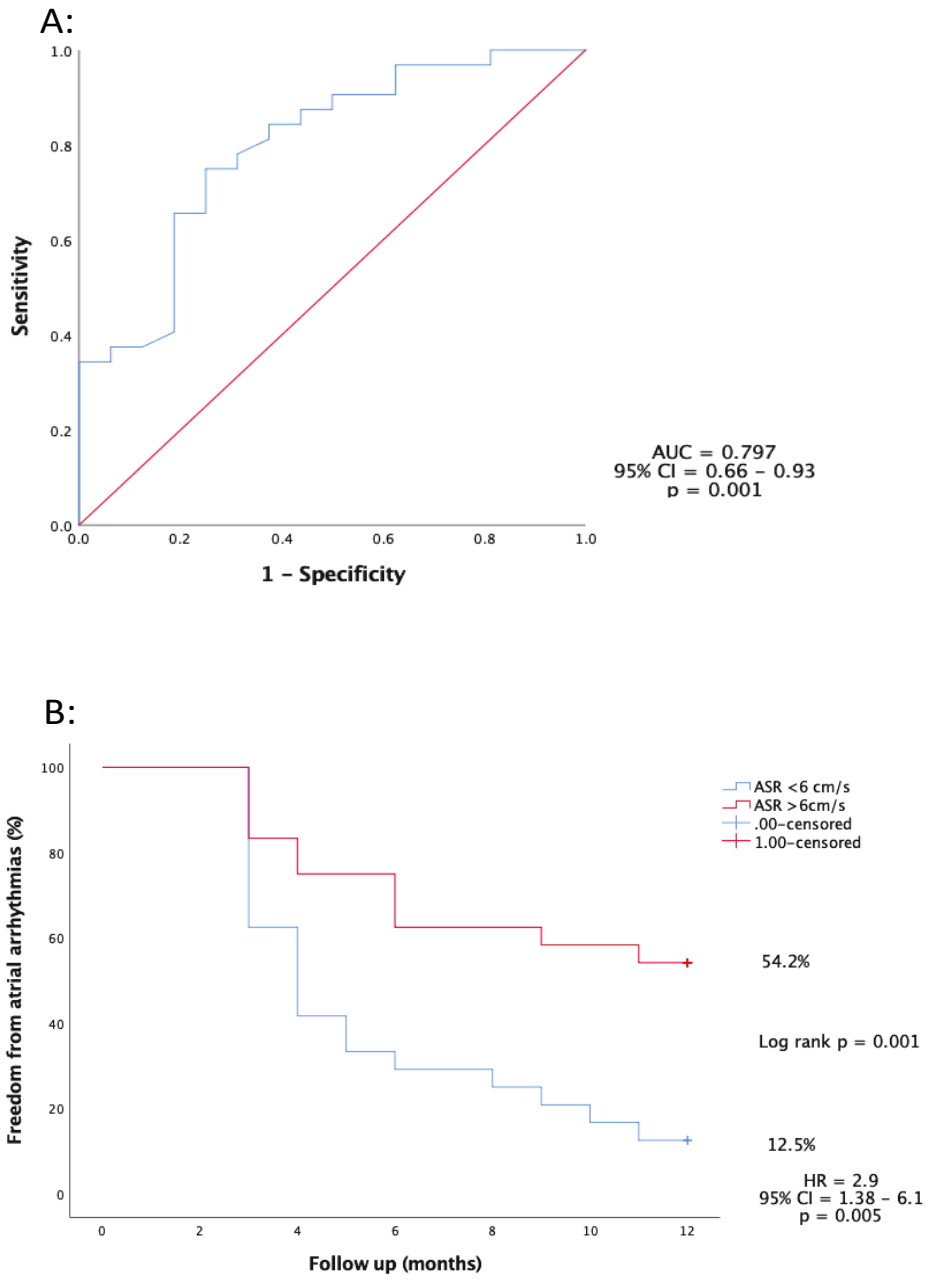


Figure 44: ROC curve analysis of ASR at 3 months with sensitivity and specificity related to detecting AF recurrence (A). In Kaplan-Meier survival analysis, ASR at 3 months < 6 cm/s was associated with 88.5% AF recurrence while >6cm/s was associated with 45.8% AF recurrence over 12 months follow up (B).

4.4 DISCUSSION

Impairment of LA mechanical function may provide indirect information about the presence of fibrosis before or after ablation. It can be comprehensively assessed by using multiple echocardiographic modalities and this was done in a number of earlier studies focussing on patients with PAF and persistent AF. To our knowledge, this is the first randomised controlled study to perform a comprehensive assessment of LA function after CA and TSA in patients with LSPAF.

The main findings of this sub study of the CASA AF randomised trial are as follows:

(i). CA and TSA result in significant reduction in the LA volume and improvement in LAEF, LA reservoir function, TDI and speckle tracking strain and strain rate at 3 months and 12 months of follow-up. There was an increased reduction of the LA maximum volume in the CA group compared to TSA group, however this was not associated with SR maintenance. There was no difference between two groups in the LA volume (max, min and p-wave volume) and LA TDI based function assessment at 3 months and 12 months. However, strain reservoir and conduit functions were higher in the CA group at 12 months compared to TSA group.

(ii). LA volume was significantly reduced in patients who maintained SR after ablation during the 12 months follow up, but volumetric assessment of LA function did not show significant difference between patients who maintained SR in follow up and those who

experienced AF recurrence. However, LA function assessed by TDI and speckle tracking strain and strain rate was significantly better in patients who maintained SR.

(iii). At baseline, increasing LA max volume and reduced LA reservoir function using strain were the only independent predictor of AF recurrence during 12 months follow up. At 3 months, LA volume at p wave and LA contraction using speckle tracing strain were independent predictors of AF recurrence.

(iv). LAA mechanical exclusion as part of TSA to treat LSPAF results in reduced LA contraction at the anterior and lateral walls during the 12 months follow up. Mitral isthmus line as part of CA to treat LSPAF results had no impact on the inferior LA wall function at 3 and 12 months follow up scans.

Ablation and LA volumes

In both treatment arms, the ablation procedure led to a reduction in LA volumes and an increase in LAEF. There was only a non-significant trend towards less reverse remodelling in the TSA group at 12 months. There was also improvement in reservoir function as assessed by the volumes and strain data. Volumetrically assessed conduit function was similar in both groups after ablation, but conduit strain (LA ESR) was better at 3 months and 12 months in the CA group. This may indicate improved recoil and long axis function during passive emptying in the CA group, but for uncertain reasons may not translate to an increased volume of emptying. Notably, there was no improvement in conduit strain rate following ablation with either technique suggesting that the degree of myocardial shortening and not

the rate of shortening was the more important factor. In the sub-group of patients who underwent TDI, conduit function based on myocardial velocities was reduced in both groups. This might reflect either a lesser contribution of conduit function from the left atrial walls just below the mitral annulus sampled by pulsed wave TDI, or systematically poor sampling of the LA walls during the motion caused by passive emptying. LA speckle tracking strain measurements tend to be more robust than pulsed wave TDI as they take into account long axis function from all walls and are not angle dependent or confounded by motion artefact. In both treatment groups, contractile function derived from LA volumes and strain/strain rate assessment was similar after ablation.

In summary, the impact of both ablation strategies was similar with respect to reducing LA volumes and improving reservoir function with similar effects on contractile function. Conduit function by strain assessment was better in the CA group, and there was a non-significant trend towards an increase in LA volume at 12 months in the TSA group.

AF recurrence and LA function

Analysis of the study population based on heart rhythm response following ablation showed that baseline LAmax was significantly higher in the AF recurrence group compared to those who remained in SR throughout follow-up. Although the percentage reduction in LAmax and LAmin after ablation were similar in both groups, LAmin and LA p-wave volume were significantly higher in the AF group at 3 months and 12 months. There were improvements in volume-derived reservoir function in both groups after ablation, but a trend towards lower reservoir function in the AF group compared to the SR group at both 3 months and 12

months. Strain and strain rate assessment showed improvement in reservoir function after ablation in both groups, but significantly lower values in the AF group at baseline and 3 months. TDI also showed lower reservoir function in the AF group compared to the SR group at 12 months. There were also subtle indications of better conduit function in the SR compared to the AF recurrence group with higher baseline conduit strain, higher conduit strain rate at 3 months and trends towards better volume-derived conduit function at 3 months and 12 months. Although contractile function derived from LA volumes was similar in both groups, contractile strain and strain rate were clearly higher in the SR group following ablation. The TDI data also showed better LA contractile function in the SR group during follow-up.

Predictors of AF recurrence

It is important to acknowledge that the measurement of LAmax is a part of the minimum dataset for performing transthoracic echocardiography in routine clinical practice whereas assessment of LA strain remains a research tool. Therefore, when performing multivariable analysis for the prediction of AF recurrence, the initial model was performed with clinical data and LA volumes alone. Baseline LAmax was found to be an independent predictor of AF recurrence and the optimal cut-off value of 42 ml/m^2 was within the range reported in individual studies and in a recent meta-analysis [502,503]. Analysis of the data at the 3 months follow-up timepoint during sinus rhythm, showed that the LA p-wave volume (the left atrial volume just prior to active atrial contraction) was a stronger independent predictor of AF recurrence, but that LAmax remained significant if LA p-wave volume was removed from the model. The inclusion of the strain data in multivariable analysis showed that LA reservoir

strain was a stronger predictor of AF recurrence than LAmax at baseline and that LA contractile strain was the best predictor at 3 months. The optimal baseline LA reservoir strain and 3 months LA contractile strain cut-off values for the prediction of AF recurrence were 10.3% and 7.5%, respectively. LA contractile strain at 3 months had the highest area under the curve. Therefore, despite being in AF for greater than 12 months, baseline LA reservoir strain may be used to select patients who might be suitable for ablation. Our results are in line with Moreno-Ruiz et al. (2019) who suggested global LA reservoir strain of <10.75% as a predictor for AF recurrence following DCCV of patients with LSPAF [772].

A number of studies have assessed LA sphericity by CT and CMR as predictors of AF recurrence with variable results[533,814]. A small study showed LA sphericity index by echocardiography to predict AF recurrence following DC cardioversion[815]. Our findings did not show any predictive value of LA sphericity index for AF recurrence when taking into account LA volumes and strain-derived components of function in keeping with a recent study by Mulder et al. (2020) showing LA sphericity to be related to restraints in the thoracic cavity rather than AF remodelling [816].

The assessment of pulsed wave myocardial tissue velocities by TDI has inherent limitations related to angle dependency and motion artefact. In addition, a global assessment of LA function by this technique is time consuming and prone to variability as multiple sites have to be sampled to derive an average value. Importantly, in our study the subgroup of patients who underwent TDI were not the same as those who had the complete 2D volumes and strain data. Despite these limitations, it was interesting to note that LA contractile function represented by the A' velocity at 3 months was a strong predictor of AF recurrence.

This finding was entirely consistent with the LA contractile strain data and the areas under the curves were similar. Longer duration of TACT derived from TDI has been shown to be related to recurrence of AF following CA and cardiac surgery. The longer TACT may represent slow conduction in the tissue due to scar or large LA size [613,614,796,812,817], and local atrial wall segment conduction times have been used as a marker of AF recurrence following cardioversion[818]. In our study, there was no difference in TACT between CA and SA likely due to similar lesion sets and similar changes in LA volumes and function between the two ablation techniques. Moreover, TACT did not predict AF recurrence following ablation.

The LA volumes measured by TTE in our study were nearly two-fold higher than in a healthy population of a similar age [819]. Consistent with previous studies of AF ablation, pre-procedural LA size is an important predictor of successful ablation [502,503,506,820]. Our study also shows that atrial compliance, the ability of the LA to expand during the filling phase, was the more dominant factor in predicting heart rhythm response following ablation. Increased LA myocardial stiffness or rigidity, may indicate greater fibrotic change and increased likelihood of AF recurrence. Passive recoil of the LA during the early emptying phase did not influence AF recurrence, perhaps because the pressure difference between the LA and LV during the early phase of emptying was the dominant factor in LA emptying without the need for a significant elastic recoil effect to be important. Notably, with the return of sinus rhythm and mechanical atrial contraction following ablation, the size of the LA just prior to atrial contraction at 3 months was an important predictor of AF – the smaller the size, the less the likelihood of AF recurrence. However, the extent of atrial contraction as measured by longitudinal myocardial shortening was the best predictor of AF recurrence as judged by the high area under the curve in ROC curve analysis. This finding is supported

by the predictive value of LA TDI A wave velocity which had similarly high areas under the curve of 0.79 for the prediction of AF recurrence.

. Using echocardiography, LA substrate remodelling may be assessed most effectively by measuring strain and less so by evaluating myocardial tissue velocities using TDI [821,822] or volume-derived measurements of LA function. LA function as assessed by volumes and strain analysis in our study population was markedly reduced at baseline and improved following ablation. Despite these improvements of LA function following ablation and with restoration of SR, 44% of the patients had AF recurrence in this sub-study of the CASA AF trial. The proportion of patients with AF recurrence is lower in comparison to the overall trial results but this is most likely due to exclusion of patients who were not in SR at the time of the scan.

The AF recurrence group had significant reductions in LA volumes and improvement in reservoir function from baseline to 3 months which could be attributed to being predominantly in SR. However, the group with maintained sinus rhythm throughout follow-up had better reservoir and contractile function assessed by strain and strain rate at 3 months when compared to the AF recurrence group. Strain rate analysis also showed a significant improvement in LA conduit function at 3 months in the sinus rhythm group. This is very important in understanding the possible reasons for AF recurrence, one of which could be LA fibrosis leading to a stiffer left atrium and a more advanced pathological substrate affecting atrial expansion, recoil and contractility. It is also important to note that LA strain values, although improved after ablation remained substantially lower than levels observed in a healthy population [823]. Pathan et al. (2017) conducted a meta-analysis of

strain values in 2542 normal individuals from 40 studies and found the mean LA reservoir strain was 39.4%, LA conduit strain was 23% and LA contractile strain was 17.4% [805]. In our study population of LSPAF, LA reservoir strain, conduit strain and contractile strain improved following ablation to only 18%, 11% and 7.5%, respectively.

As discussed earlier, LA function is determined by many factors including duration of AF and associated cardiovascular risk factors [615,824-826]. The two rhythm groups in our study were well matched in this regard with no significant differences in cardiovascular risk factors.

The AF ablation strategies evolved over the last few decades with increased lesions sets usually by a stepwise Bordeaux approach [827]. The impact of linear lesions and epicardial approaches on LA anatomy and function have not been extensively studied. Thomas et al. assessed LA function in patients who had treatment for AF, ablation (CA or TSA) or cardioversion, and compared it to measurements in healthy controls. Patients who had treatments, linear lesions during ablation and patients who were cardioverted, had larger LA size than the healthy controls [828]. LA function was also reduced in patients with linear lesions compared to those who underwent cardioversion [828]. A small study by De Maat et al showed that thoracoscopic surgical ligation of the LAA by a clip did not seem to have a detrimental effect on LA contractile function[621]. Similarly, in our study, all TSA patients underwent LAA exclusion by AtriClip™ without any detectable impact on global LA function despite a regional reduction in contraction in the anterolateral LA walls compared to CA group. On the contrary, patients with mitral isthmus lesion did not have any reduction in lateral LA wall function without impact on global LA function compared to the TSA group.

4.5 LIMITATIONS

The main limitation of this study is the reduced sample size, which was determined by the availability of good quality TTE images for all relevant time points. Further limitation was additional selection of patients who had to be in SR at the time the scan in order to enable measurements of all the components of LA function at different time points reduced the overall number of patients. However, this can be advantageous in order to understand how LA function using advanced Echocardiography can be used in other forms of AF such as persistent AF. This had an impact on the proportion of patients in SR/AF recurrence groups which was different from the primary outcome in the trial. However, the baseline characteristics of the patients within these subgroups were no different to the rest of the trial sample.

Good quality images were particularly difficult to obtain for LA strain and tissue Doppler measurements due to breathing affecting the movement of the LA myocardial edge. The sonographers were trained in the early phase of the trial recruitment so some sub-optimal quality scans in this period had to be excluded from the analysis.

Although LA volumes derived from 2D echocardiography tend to be systematically lower than CMR measurements, there is a high correlation between the two techniques [829] so the use of echo-derived measurements for serial assessment is justified, particularly as echocardiography is easily accessible, less time consuming and inexpensive [830]. 3D echocardiography may have provided more accurate LA volume measurements, but the technique is technically challenging, requires very high quality images and would almost

certainly have led to further reductions in the number of patients available for these analyses. Performing multivariable adjustments for predicting factors responsible for AF recurrence can result in underestimation a potentially useful predictor. We try to minimise this by using variables that had a significance of <0.15 to limit the confounding effects. There are some factors that are shown to be borderline and due to small numbers, their true potential prediction strength is underestimated.

4.6 CONCLUSION

LA function in LSPAF improves after ablation by both CA and TSA as shown by reduced LA volumes, improved LA reservoir function and restored atrial contraction. LA maximum volume of <42ml/m^2 at baseline and reservoir strain of >10.3% in LSPAF patients are strongly associated with sinus rhythm maintenance. LA volume and contractile strain at 3 months following restoration of sinus rhythm are predictive of sinus rhythm maintenance over the follow up period. Further studies are required to analyse the effect of isolated lesions on regional LA wall motion and for longer periods of time.

CHAPTER 5

VOLUMATIC, STRUCTURAL AND FUNCTIONAL CHANGES FOLLOWING ABLATION ASSESSED BY CARDIAC MAGNETIC RESONANCE IMAGING IN THE CASA-AF TRIAL

5.1 BACKGROUND

Atrial remodelling in the presence of AF consists of biochemical, electrical, autonomic and structural changes with or without fibrosis.[97,98] The remodelling process can be interrupted by the restoration of sinus rhythm using anti-arrhythmic drugs, cardioversion or ablation, which should be done in the early stages of AF. Maintaining sinus rhythm then leads to reverse remodelling, effectively a reduction in the LA volume, which was shown to be a predictor of clinical success following ablation. [509,831,832]

In the previous chapter, we have analysed changes in LA volumes and function following ablation by catheter ablation (CA) and surgical ablation (TSA) using echocardiography. Here the objectives were to evaluate the same parameters using CMR which is considered to be the gold standard imaging modality due to its superior spatial resolution.[530,532] We also present the results of RA size and function assessments, which is not possible to assess with the same degree of consistency using echocardiography. Changes in bi-atrial sizes and function will be correlated to the ablation modalities and AF recurrence in our cohort of difficult to treat patients with LSPAF. Using CMR images, we also evaluate changes in pulmonary veins diameter following ablation and define greater than 50% stenosis or occlusion as serious procedure-related adverse events. [833,834]

5.2 METHODS

5.2.1 CMR PROTOCOL

A 1.5-Tesla MR system with 18-channel transmit/receive body coil, and 32-channel transmit/receive spine coil (Magnetom Avanto, Siemens Healthcare, Germany) was used to scan patients. Images of the atria were acquired in the two-chamber and four-chamber orientation using a breath-hold ECG-gated steady-state free precession cine sequence. Breath-hold ECG-gated steady-state free precession cine acquisitions (echo time = 1.2 ms; repetition time = 2.8 ms; spatial resolution = 1.5 mm x 1.5 mm x 8 mm; correct temporal resolution = 28 ms) were performed in two- and four-chamber orientations, followed by stacks of short axis and transverse acquisitions covering the whole heart. ECG gating was retrospective for patients in SR and prospective for patients in AF to reduce HRV artefacts.

5.2.2 MEASURING ATRIAL VOLUMES AND FUNCTION WITH CMR

LA max and LA min were defined as LA volume just prior to the mitral valve opening and closure, respectively. RA max and RA min were defined as the RA volume just prior to the tricuspid valve opening and closure, respectively. For LA volume calculation, the biplane area-length method was used, but the complex RA morphology including right atrial appendage was measured from a stack of contiguous trans-axial cines encompassing the entire RA (as shown in Figure 45A and B, respectively). [835,836] LA volumes at P wave were not calculated by CMR, and so conduit function and contractile function could not be assessed.

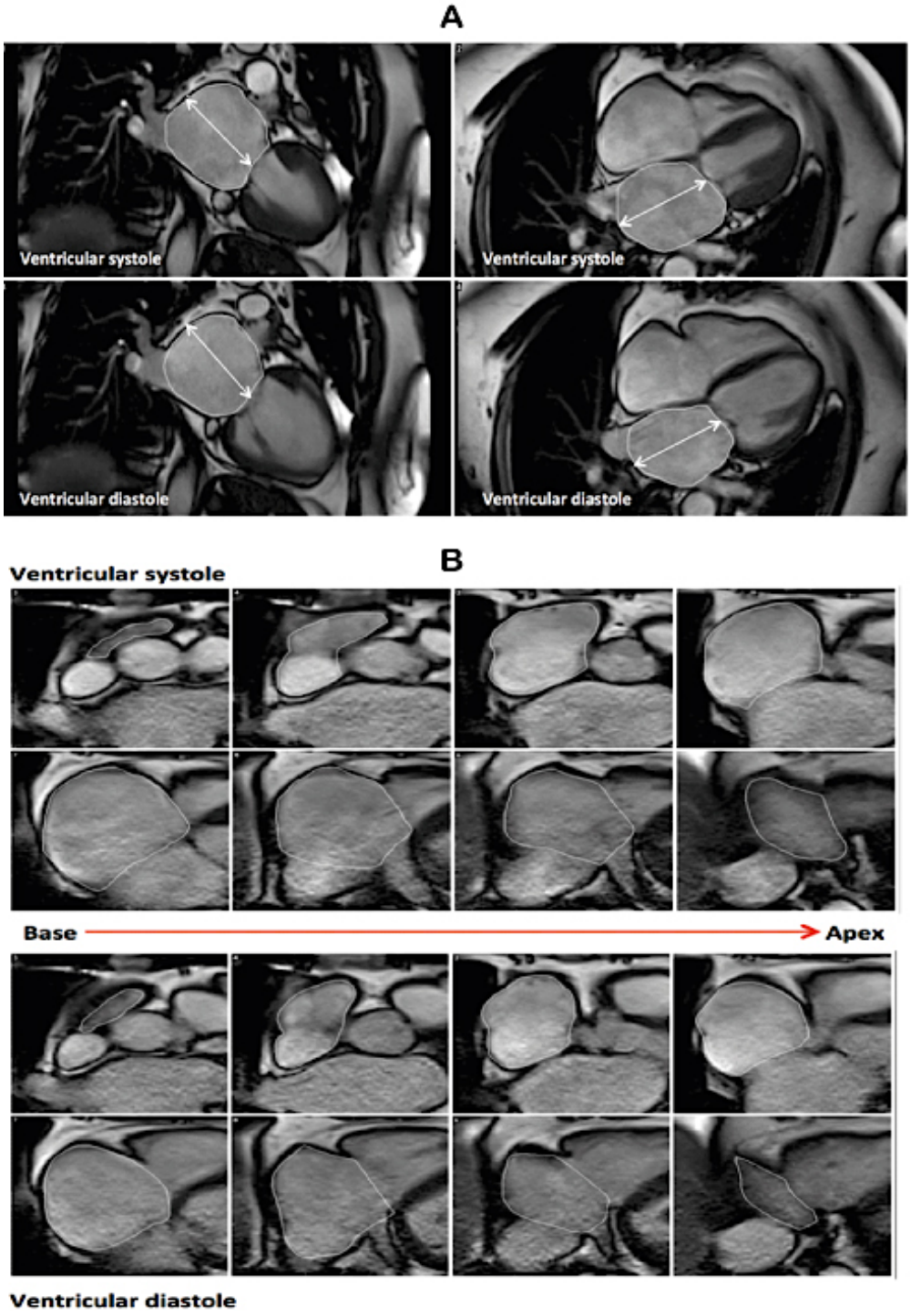


Figure 45: Figure A: Biplane area-length method for LA volume measurements. Areas were measured in two chamber (Left panel) and four chamber (right panel) views at the ventricular end-systole (LA max) and end-diastole (LA min) with the exclusion of LAA and the ostia of the PVs. Figure B: Example of transaxial RA stack cines used to calculate RA volumes. RA endocardial borders were delineated in all slices in both ventricular end-systole (RA max) and end-diastole (RA min) with the inclusion of the atrial appendage and exclusion of the cava veins and the coronary sinus orifice

From LA max measurements we calculated the reverse remodelling (RRM) which is defined as the percentage reduction in LA volume following ablation from baseline to 6 months' follow up:

$$LA\ RRM = \frac{LAmaxfollowup\ - LAmax\ baseline}{LAmax\ baseline}\ x\ 100$$

Atrial emptying fraction was measured using the following equations:

$$LA\ EF = \frac{(\mathrm{LAmax} - \mathrm{LAmin})}{\mathrm{LAmax}}\ x\ 100.$$

$$RA\ EF = \frac{(\mathrm{RAmax} - \mathrm{RAmin})}{\mathrm{RAmax}}\ x\ 100.$$

Active and passive phasic functions of the atria are not considered in this study.

Absolute values of LA volume measurements using two imaging modalities are different, but we observed a high correlation (p =0.0001) between dimensions of LA max measured with echocardiography and magnetic resonance (correlation coefficient 0.82, 95% CI = 0.647-0.993 and Beta coefficient 0.749).

Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM corporation, Armonk, New York, USA). Continuous variables that followed parametric distribution are presented as mean and standard deviation and Student's t-test was used to assess differences between groups. Paired sample t-test was used to assess differences within

groups from baseline to 6 months. Non-parametric continuous variables are presented as median and inter-quartile ranges and between group comparisons were done using the Mann-Whitney test. Categorical values were tested using Chi-square. Baseline demographic variables as shown in below were included in univariate binary logistic regression analysis apart from medications. Variables with p value <0.15 in univariate analyses were included in the multivariable logistic regression backward (Wald) stepwise model to identify independent predictors of AF recurrence. ROC curve was used to identify cut-off values for significant variables derived from multivariate analysis and both positive and negative predictive values for those variables were calculated. Cox regression analysis was used to calculate hazard ratio and Kaplan Meier curve analysis was used to show freedom from AF recurrence of the strongest predictor derived from ROC curve analysis. All p values >0.15 were categorised as non-significant. Throughout the analysis, p values ≤ 0.05 were considered statistically significant.

5.3 RESULTS

5.3.1 PATIENTS

A total of 115 patients with LSPAF underwent CA or TSA in the CASA AF trial. Eleven patients did not undergo CMR at baseline for the following reasons: 2 patients had permanent pacemaker, 3 were claustrophobic, 1 patient had renal disease, and 5 patients did not have the study done due to long waiting lists. Following ablation, a further 8 patients did not attend the follow up appointment, 8 patients had additional catheter ablation prior to 6 months follow-up CMR, 2 patients had PPM inserted due to bradycardia, 2 patients were in

another hospital for management of another condition and one patient died. We have therefore analysed data from 83 patients who had both baseline and 6 months CMR scans of whom 45 underwent CA and 38 had TSA.

Baseline demographic data of the two treatment groups were similar apart from a higher prevalence of respiratory disease in the TSA group (Table 38).

Table 38: Baseline characteristics for patients randomised to CA or TSA with analysis of MRI data

DEMOGRAPHIC DATA	**CA (n=45)**	**TSA (n=38)**	**P value**
Age, years	62.3 ± 10.1	63.1 ± 9.8	0.70
Sex, male	33 (73.3)	28 (73.6)	0.59
AF duration, days	575 (429 – 848)	686 (495 – 1053)	N/S
Body mass index, kg/m^2	30.7 ± 4.9	29.6 ± 4.1	0.26
Smoking	3 (6.7)	4 (10.5)	0.53
Hypertension	21 (46.7)	20 (52.6)	0.37
Diabetes	4 (8.9)	4 (10.5)	0.8
Stroke	0 (0)	2 (5.3)	0.12
Coronary artery disease	7 (15.6)	4 (10.5)	0.5
Respiratory disease	4 (8.9)	10 (26.3)	0.035
DRUG THERAPY			
Betablocker	38 (84.4)	29 (76.3)	0.26
Digoxin	14 (31.1)	7 (18.4)	0.14

Calcium channel blocker	4 (8.9)	7 (18.4)	0.2
ACEi/ARB	23 (51.1)	18 (47.4)	0.45
Diuretic	12 (26.7)	12 (31.6)	0.4
AADs	5 (11.1)	6 (15.8)	0.38

Footnote 43: AADs – antiarrhythmic drugs, ACE – angiotensin converting enzyme inhibitor, AF -atrial fibrillation, ARB – angiotensin receptor blocker, CA – catheter ablation, kg – kilograms, TSA -thoracoscopic surgical ablation.

5.3.2 ATRIAL VOLUMES, EF AND REVERSE REMODELLING: COMPARISONS BETWEEN TREATMENT ARMS (CA VS TSA)

Left atrial volumes reduced in size significantly six months after ablation in both treatment arms (*Table 39*). LA max was reduced by 12.7 ± 13.4 ml/m^2 in CA arm (p = <0.001) and 5.6 ± 11.5 ml/m^2 in TSA arm (p =0.005). LA min was reduced by 18.4 ± 13.9 ml/m^2 in CA arm (p =<0.001) compared to 12.1 ± 11.1 ml/m^2 in TSA arm (p = <0.001).

Right atrial volumes were also significantly reduced following ablation. RAmax was reduced by 12.9 ± 16 ml/m^2 in CA ablation group (p = <0.001) and by 8.2 ± 11.1 ml/m^2 in TSA group (p = <0.001). RAmin was reduced by 24.6 ± 16.2 ml/m^2 in CA arm (p = <0.001) compared to 20.9 ± 11.1 ml/m^2 in TSA arm (p = <0.001).

Emptying fractions of both atria improved significantly following ablation in both treatment arms and the increase was particularly marked for the RA. RAEF was significantly poorer in TSA arm at baseline but the significance was lost in the post-ablation period.

Table 39: Within and between group measurements of atrial volumes, EF and reverse remodelling (mean ± SD) in CA and SA group

Parameters	Timepoint	CA (n = 45)	TSA (n = 38)	P value
LA max, ml/m^2	Baseline	62 ± 13.4	63.8 ± 17	0.61
	6 months	49.3 ± 14	58.2 ± 16.7	0.011
	p value	<0.001	<0.01	
LA min, ml/m^2	Baseline	51.8 ± 13.4	52.7 ± 13.2	N0.75
	6 months	33.8 ± 13.3	39.9 ± 14.6	0.052
	p value	<0.001	<0.001	
LAEF, %	Baseline	17.4 ± 9.4	16.8 ± 8.8	0.77
	6 months	32.9 ± 9.9	30.9 ± 9.5	0.36
	p value	<0.001	<0.001	
RA max, ml/m^2	Baseline	71.4 ± 17.9	66 ± 16.2	0.17
	6 months	58 ± 15.6	57.6 ± 14.7	0.9
	p value	<0.001	<0.001	
RA min, ml/m^2	Baseline	60.9 ± 18.1	59.3 ± 14.8	0.68
	6 months	36 ± 12.7	38.7 ± 12	0.37
	p value	<0.001	<0.001	
RAEF, %	Baseline	15.2 ± 10.7	10 ± 6.3	0.009
	6 months	37.7 ± 12.4	33.1 ± 8.4	0.066
	p value	<0.001	<0.001	
LA RRM, %		-19.6 ± 20.6	-7.6 ± 17.8	0.006
RA RRAM, %		-15.9 ± 24.1	-10.6 ± 16.6	0.28

Footnote 44: CA – catheter ablation, EF – emptying fraction, LA – left atrium, max – maximum volume, min – minimum volume, RA – right atrium, RRM – reverse remodelling

Between group comparisons, suggest that LA max volume was significantly more reduced in CA arm compared to TSA arm, p = 0.011. The difference in the LA min reduction was also almost significant, p = 0.052.

Significant reductions in RA volumes were observed in both treatment arms but there was no difference in the extent of the reduction in RA max or RA min between treatment arms.

Left atrial ejection fraction was similar between treatment arms at baseline and at the 6 months follow up. Right atrial ejection fraction was significantly better in CA arm at baseline and remains better in follow up compared to TSA arm.

There was significantly more reverse remodelling in the left atrium in the catheter ablation group when compared to thoracoscopic surgical ablation group (-19.6 ± 20.6% vs. -7.6 ± 17.8%, p= 0.006). Reverse remodelling of the RA was not significantly different between the treatment arms.

5.3.3 ATRIAL VOLUMES, EF AND REVERSE REMODELLING: COMPARISONS BETWEEN SINUS RHYTHM AND AF RECURRENCE

After ablation, patients were followed up for 12 months, and their rhythm was assessed from continuous monitoring by ILR. Of the 83 patients with CMR data, SR was achieved throughout the follow-up period in 26 patients whereas 57 patients developed recurrences of AF. Similar proportion of patients in each treatment arm had AF recurrence (68%).

Significant reductions in left and right atrial volumes were seen in patients who maintained SR throughout follow up and those who experienced AF recurrence, as shown in Table 40. LA max values at baseline (61.6 ± 13 ml/m^2 vs. 63.4 ± 16 ml/m^2, p=0.58) and 6 months after ablation (52.1 ± 16.9 ml/m^2 vs. 53.9 ± 15.5 ml/m^2, p = 0.63) did not differ significantly between patients who maintained SR throughout follow up and those who experienced AF recurrence. Also, LA min values at baseline (49.4 ± 11.9 ml/m^2 vs. 53.5 ± 13.8, p = 0.18) and at 6 months follow up (35.1 ± 15.7 ml/m^2 vs. 37.3 ± 13.5 ml/m^2, p = 0.56) were similar in both groups.

RA max values were larger at baseline in patients with recurrent AF compared to those who maintained SR, but this was not significant (71.6 ± 15.6 ml/m^2 vs. 63.5 ± 19.6 ml/m^2, p=0.08). RA max measurements at follow up were significantly smaller in patients who were in SR throughout follow up (51.7 ± 16.9ml/m^2 vs 60.8 ± 13.2 ml/m^2, p = 0.026).

CMR measurements of the EF in both atria show significant improvements following ablation but the values did not differ between patients in SR and those with AF recurrence at both time points.

Table 40: Evaluation of atrial volumes, ejection fractions and reverse remodelling based on recurrence of AF. The values in the table are means ± SD.

Parameters	**Timepoint**	**AF (n = 57)**	**SR (n = 26)**	**P value**
LA max, ml/m^2	Baseline	63.4 ± 16	61.6 ± 13	0.48

	6 months	53.9 ± 15.5	52.1 ± 16.9	0.63
	p value	<0.001	<0.001	
LA min, ml/m^2	Baseline	53.5 ± 13.8	49.4 ± 11.9	0.18
	6 months	37.3 ± 13.5	35.1 ± 15.7	0.56
	p value	<0.001	<0.001	
LAEF, %	Baseline	16 ± 8.2	19.5 ± 10.4	0.15
	6 months	31.2 ± 10.1	33.8 ± 8.6	0.25
	p value	<0.001	<0.001	
RA max, ml/m^2	Baseline	71.6 ± 15.6	63.5 ± 19.6	0.08
	6 months	60.8 ± 13.2	51.7 ± 16.9	0.026
	p value	<0.001	<0.01	
RA min, ml/m^2	Baseline	62.1 ± 14.9	56.1 ± 19.5	0.17
	6 months	39 ± 12.4	33.8 ± 11.9	0.088
	p value	<0.001	<0.001	
RAEF, %	Baseline	13.1 ± 8.8	12.3 ± 10.5	0.77
	6 months	36.3 ± 11.1	34.1 ± 10.5	0.41
	p value	<0.001	<0.001	
LA RRM, %		-12.9 ± 21.9	-15.9 ± 15.6	0.48
RA RRM, %		-14.2 ± 22.5	-11.9 ± 18	0.63

Footnote 45: CA – catheter ablation, EF – emptying fraction, LA – left atrium, max – maximum volume, min – minimum volume, RA – right atrium, RRM – reverse remodelling

5.3.4 PREDICTORS OF AF RECURRENCE

Univariable and multivariable logistic regression analysis was performed to identify factors associated with AF recurrence (Table 41).

Using multivariable analysis, an increasing RA maximum volume at baseline (OR =1.046, 95% CI = 1.01 – 1.09, p value = 0.015) was an independent predictor of AF recurrence. Coronary artery disease and history of respiratory illness were also independent predictors of AF recurrence although the analyses were based on very small sample.

At 6 months, multivariable analysis also showed an increasing RA maximum volume (OR = 1.052, 95% CI = 1.01 – 1.096, p = 0.015) to be an independent predictor for AF recurrence during follow up.

Table 41: Univariable and multivariable regression analysis of cardiac structures associated with AF recurrence

Timeline	Parameter	Univariable			Multivariable		
		OR	95% CI	P value	OR	95% CI	P value
Baseline	Age	1.008	0.962 – 1.057	0.73			
	Sex (male)	1.785	0.578 – 5.52	0.31			
	AF duration	1	0.999 – 1.001	0.64			
	BMI	1.03	0.93- 1.142	0.57			
	Smoking	1.16	0.64 – 2.1	0.62			

	Hypertension	0.77	0.3 – 1.96	0.58			
	Diabetes	1.87	0.64 – 5.48	0.25			
	Stroke	0.45	0.03 – 7.4	0.57			
	CAD	5.3	0.644 – 44	0.121	18.1	1.46 – 226	0.024
	Respiratory disease	0.27	0.08 – 0.87	0.028	0.14	0.03 – 0.67	0.14
	LA max	1.009	0.977 – 1.04	0.61			
	LA min	1.025	0.987 – 1.065	0.53			
	LAEF	0.959	0.91 – 1.01	0.12			
	RA max	1.03	0.999 – 1.062	0.059	1.046	1.01 – 1.09	0.015
	RA min	1.024	0.993 – 1.056	0.14			
	RAEF	1.009	0.96 – 1.063	0.75			
6 months	CAD				9.93	0.943 - 1.04	0.056
	Respiratory disease				0.175	0.04 – 0.81	0.026
	LA max	1.008	0.978 – 1.04	0.61			
	LA min	1.011	0.98 -1.05	0.53			
	LAEF	0.972	0.924 – 1.022	0.27			
	RA max	1.046	1.007 – 1.086	0.02	1.052	1.01 – 1.096	0.015
	RA min	1.039	0.993 – 1.087	0.095	0.978	0.89 – 1.08	0.65
	RAEF	1.019	0.973 -1.068	0.41			

Footnote 46:AF -atrial fibrillation, BMI – body mass index, CA – catheter ablation, CAD - coronary artery disease, CI -confidence interval, EF – emptying fraction, LA – left atrium, max – maximum volume, min – minimum volume, RA – right atrium, RRM – reverse remodelling

Receiver operative characteristic (ROC) curve analysis showed RA max volume (ml/$m^{2,}$) measured at baseline (AUC = 0.636, 95% CI =0.494 – 0.779, p value = 0.053) and 6 months (AUC = 0.673, 95% CI = 0.527 – 0.818, p value = 0.017) after ablation, to be strongly associated with AF recurrence (Figure 46).

At baseline, a cut-off value of RA max volume 54.9ml/m^2 had a sensitivity of 86.8% and specificity of 44% resulting in positive predictive value of 76.7% and negative predictive value of 61.1%.

At 6 months, a cut-off value of RA max volume 49.9ml/m^2 had a sensitivity of 81.6% and specificity of 56.5% resulting in positive predictive value of 80% and negative predictive value of 59.1% (Figure 46).

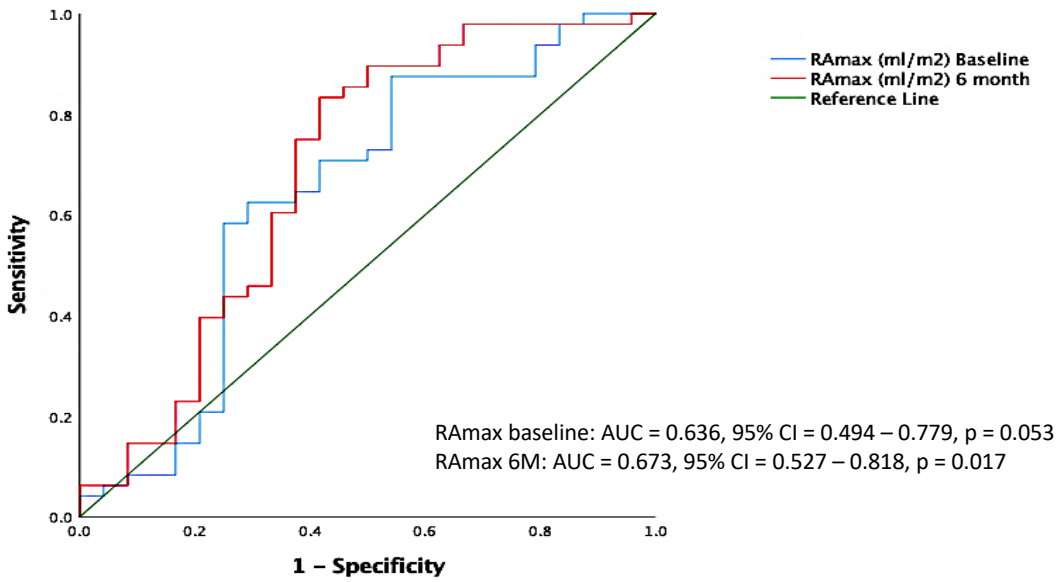


Figure 46: ROC analyses of RA max values (ml/m^2) at baseline and 6 months associated with AF recurrence

Values of RA max at two different time points were used in Kaplan-Meier survival curves to illustrate the relationship between this parameter and recurrence of AF (Figure 47).

Using Cox regression model analysis, baseline RA max >54.9 ml/m^2 was predictive of AF recurrence in follow up (HR = 2.5, 95% CI = 1.13 – 5.56, p = 0.024) and associated with arrhythmia free survival of 23.3%, log rank p = 0.01.

Using data at 6 months follow up with Cox regression model analysis, we found that RA max volume >49.9 ml/m^2 was significantly predictive of AF recurrence (HR = 2.67, 95% CI = 1.29 – 5.53, p = 0.008) and associated with arrhythmia free survival of 20%, log rank p = 0.003.

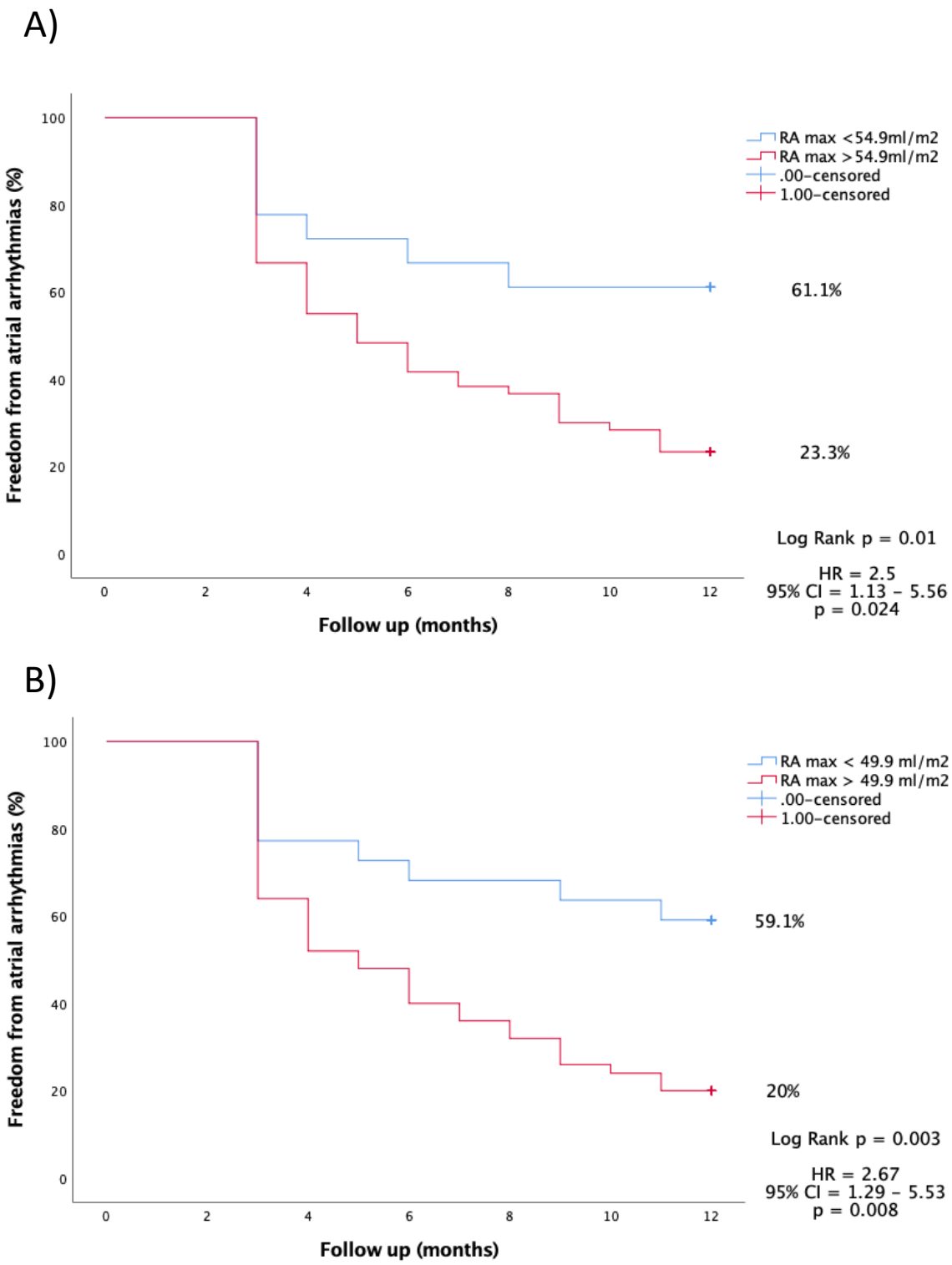


Figure 47: Kaplan-Meier survival curves predicting AF recurrence using RA max values measured at baseline (A) and at 6 months follow up (B).

5.3.5 PULMONARY VEIN MEASUREMENTS

Pulmonary veins (PV) measurements obtained from magnetic resonance images suggest small reductions post ablation amounting to 5-11%.

The reductions in the CA group of all the PV were significant whereas in the TSA group only the left inferior PV was significantly reduced in size following ablation (Table 42).

Table 42: PV measurements (mm ± SD) showing within and between group comparisons

PV		CA (n = 45)	TSA (n = 38)	P value
RSPV	Baseline	18.9 ± 3.1	18.1 ± 2.6	0.21
	6 months	17.5 ± 2.8	17.2 ± 2.2	0.55
	p value	<0.01	0.08	
RIPV	Baseline	18 ± 3	16.8 ± 3.1	0.076
	6 months	16.5 ± 2.9	15.7 ± 2.9	0.25
	p value	<0.01	0.07	
LSPV	Baseline	16.3 ± 3	15.9 ± 2.8	0.54
	6 months	14.9 ± 2.8	14.9 ± 3.2	0.99
	p value	<0.001	0.061	
LIPV	Baseline	15.8 ± 2.7	15.8 ± 2.7	0.98
	6 months	14.2 ± 3.6	13.2 ± 2.4	0.12
	p value	<0.001	<0.001	

Footnote 47: CA – catheter ablation, LIPV – left inferior pulmonary vein, LSPV – left superior pulmonary vein, PV – pulmonary vein, RIPV – right inferior pulmonary vein, RSPV – right superior pulmonary vein, TSA – thoracoscopic surgical ablation.

These data were also analysed to establish if any of the study participants suffered moderate severity stenosis (≥50%) following ablation. One patient in TSA arm had symptomatic PV stenosis of the left inferior pulmonary vein and occlusion of the left superior pulmonary vein which required treatment with percutaneous stent insertion. One patient in the CA arm (had 50% stenosis of the left inferior pulmonary which was asymptomatic and did not require any treatment. In our intent to treat analyses, similar proportions of patients had moderate stenosis of PVs following ablation: 1/55 (1.8%) in TSA and 1/60 (1.7%) in CA arm.

Sizes of PV diameters at baseline and at the 6 months' follow up time point were similar when patients were compared in groups on the basis of AF recurrence as shown in *Table 43*.

Table 43: PV sizes (mm ± SD) pre- and post-ablation grouped according to AF recurrence

PV		AF (n = 57)	SR (n = 26)	P value
RSPV	Baseline	18.4 ± 3	19 ± 2.7	0.39
	6 months	17.5 ± 2.6	17.2 ± 2.6	0.6
	p value	0.017	0.009	
RIPV	Baseline	17.3 ± 3	17.8 ± 3.3	0.5
	6 months	16.2 ± 3	16.1 ± 2.8	0.97

	p value	0.007	0.048	
LSPV	Baseline	16.1 ± 3	16.2 ± 2.5	0.96
	6 months	14.8 ± 3.3	15 ± 2.3	0.82
	p value	0.002	0.029	
LIPV	Baseline	15.9 ± 3.1	15.5 ± 2.9	0.63
	6 months	13.4 ± 3.1	14.4 ± 3.3	0.23
	p value	<0.0001	0.073	

Footnote 48: CA – catheter ablation, LIPV – left inferior pulmonary vein, LSPV – left superior pulmonary vein, PV – pulmonary vein, RIPV – right inferior pulmonary vein, RSPV – right superior pulmonary vein, TSA – thoracoscopic surgical ablation.

5.4 DISCUSSION

Atria are complex anatomical structures responsible for ventricular late diastolic filling and improvement of ventricular ejection fraction. Assessment of atrial function by imaging modalities not only provides information about mechanical function but also indirectly about fibrosis that might be present before or after ablation.

Significant findings of this study are as follows:

1. Advanced LA mechanical remodelling associated with LSPAF is reversible following CA and TSA.

2. Atrial reverse remodelling is significantly greater in the CA group compared to TSA group but occurs irrespective of arrhythmia outcome.

3. Significant improvements in left and right atrial EF are seen following ablation regardless of the type of the procedure or maintenance of SR.

4. Larger RAmax volumes at baseline and 6 months are associated with AF recurrence during the 12 months follow up period.

5. PV diameters appear to be reduced following either CA or TSA with reductions being more pronounced in the CA arm.

ATRIAL VOLUMES

In this trial we evaluated LA sizes using both modalities and are able to report high correlation between them, however, the volumes were underestimated by echocardiogram as shown in other studies. Therefore, cut-off values obtained from different modalities cannot be used interchangeably as supported by Rabbat et al. (2015)[830]. They compared LA volume using TTE, CMR with area-length method and multi-slice trace method (MSM) along with invasive measurement using CARTO 3D mapping systems. They showed that LA volume measured by the CMR area-length method can be used instead of CMR-MSM as they correlated well. On the contrary, TTE LA volume correlated poorly with CMR-MSM and with CARTO mapping systems. The values obtained for prediction have to be used cautiously as

the cut-offs are higher in CMR compared to TTE. In our patients, LA volume in AF recurrence was 63.4mls vs 54.7mls(p=0.016) using CMR against TTE.

LA max measured by CMR at baseline has been used to predict AF recurrence in previous studies[502,506,820,837,838], and we have shown similar results using echocardiography but not CMR. Studies that show LA volume at baseline to be a predictor for AF recurrence usually have patients that are predominantly PAF and early persistent with less substrate modification represented by LA scar less than 20% (92% of patients) as shown by Den Uijl et al. in 2018 [837]. However, our measurements based on CMR data did not support baseline LA volume to be a predictor for AF recurrence and might represent more advanced substrate modification supported by larger volumes for all patients recruited in the CASA AF trial compared to reported literature. A recent study conducted by Gunasekaran et al. (2020) shows similar findings to our study where LA volume were smaller than those in our LSPAF study population measured by CMR and not predictable for AF recurrence in a population of 100 patients with PAF (67 patients) or early persistent AF (33 patients)[839].

Our CMR data shows that RA max at baseline and at 6 months are strongly associated with AF recurrence and this finding is in agreement with earlier published reports.[840,841] However, the data examining the function of the RA in patients with AF are sparse as clinical investigations prior to treatment do not usually involve CMR. Measuring RA volume using TTE is very difficult and not accurate due to the non-spherical shape of the RA rendering equations like area-length method useless as shown by Lambertz et al. (1986)[842]. There are high degrees of variability in the RA volume measurements by other modalities such as CT

compared to CMR dictated by techniques of acquisition including breath-hold, rate of contrast media flow, RA shape and differences in heart rate at time of acquisitions[843].

REVERSE REMODELLING

LA reverse remodelling occurred in both treatment arms but was more pronounced in the CA group. CA of the pulmonary vein ostia causes LA reverse remodelling measured by CMR as reported in literature [844]. The differences in the lesion sets between CA and TSA that could account for these significant differences could be mitral line and CTI line resulting in higher LA and RA reverse remodelling respectively. LA reverse remodelling measured by TTE or CT following CA and surgical reduction of LA have been shown to be related to improved SR maintenance post ablation,[510,513,831,845,846] but there is scarcity of data using CMR. Our data using both CMR and TTE does not support LA reverse remodelling to be a predictor for maintaining SR following either CA or TSA. This is likely due to the complex AF substrate in LSPAF patients which may require more than the demonstrable atrial reverse remodelling to support SR in the long term.

Furthermore, the changes in left atrial dimensions may be due to the extensive lesions sets used in the study which involved linear lesions particularly mitral isthmus line and cavotricuspid isthmus line, wide area circumferential ablation, or complex fractionated atrial electrograms ablation.[847] It has been suggested that LA volume reduction could be simply a consequence of post-ablation contraction due to scarring in addition to restoration of sinus rhythm which may lead to improved atrial contraction. [509,848]

TSA in our study was equally successful as CA in restoring SR in patients with LSPAF, particularly in those with improving LAEF following ablation. This is in contrast to Compier et al., whose patient cohort was a diverse spectrum of AF population with concomitant ischemic and valvular heart disease which they reported as a possible mechanism to be loss of atrial contraction.[849] In our patients, there was no clinical ischemia and no valvular heart disease, and similar lesion sets were used by the two ablation techniques. Our findings suggest that the anatomical changes that occurred before or during LSPAF can be reversed with ablation, at least partially, although this does not necessarily provide long lasting rhythm control.

It is important to highlight RA reverse remodelling which also occurred in our patients receiving TSA although ablation of the RA tissues was not performed. RA reverse remodelling was higher in the CA group due to scarring caused by ablation of the cavo-tricuspid isthmus line performed in this group. Itakura et al. recently demonstrated similar effects in patients with persistent AF who had pulmonary vein isolation and cavo-tricuspid isthmus ablation. The authors reported reduction in RA volume, reduction in right atrial annulus diameter and reduction in severity of tricuspid regurgitation.[848]

PULMONARY VEIN DIAMETER

Wide area circumferential ablation (WACA) in the CA group and visually sparing pulmonary veins in the TSA group should minimise the damage to the pulmonary veins during ablation. We observed very mild stenosis (5-11%) in all PV diameters; these changes appeared to be significant in CA group but considerably lower than reported in recent literature[850]. LIPV is situated very close to the inferior ablation line on the posterior LA wall and we have two

patients in the study, one in each treatment arm, with stenosis of ≥50% in the LIPV. Small number of studies show left sided PVs to be vulnerable for pulmonary vein stenosis due to oval shape of the ostia compared to circular right sided PVs, and in particular higher risk is LIPV due to external compression by the descending aorta[851,852]. One of the patients in TSA arm had occlusion of the LUPV and required treatment with percutaneous stent insertion.

Acquired PV stenosis is a known complication in both TSA and CA but is on the decrease and opening or recanalization can be achieved in majority of the cases by stenting and in rare cases by surgery[853-856]. In intent to treat analyses in this trial the incidence of moderate and severe stenosis was 1.8% of patients in TSA group and 1.7% in CA group, which is low overall in published literature or in line with reported high volume centres.[833,857,858] Incidence of pulmonary vein stenosis has gradually been reducing with change in ablation techniques, technology advancements with more accurate 3D LA maps and higher control of lesion delivery with irrigation catheters and contact force technology[858]. The techniques of isolating pulmonary veins have shifted from pulmonary vein lumen ablation to ostial and now wide area circumferential ablation around the ostia of the pulmonary veins. The change in ablation lesions has resulted in reducing incidences of moderate to severe pulmonary vein stenosis, occlusion resulting in occlusive pulmonary hypertension from as high as 28% to 0.7%[850,859,860]. TSA has an advantage over CA because the ostia of the pulmonary veins can be more clearly visualised compared to a 3D computer generated model of LA in CA and lesions can be more safely delivered away from the ostia into the LA body reducing the chances of PV stenosis. Studies have shown regression on pulmonary vein stenosis with time if no further ablations are not delivered in future redo CA cases[861].

5.5 LIMITATIONS

The analyses presented in this chapter are subgroup analyses which are most likely underpowered, affecting the reproducibility of the results as well as the reported effects/effect sizes. Multifactor testing with potentially clinically irrelevant variables as predictors of AF recurrence can underestimate significance of a factor.

All baseline data using CMR was collected during atrial fibrillation and hence contractility of the atria could not be measured as a surrogate marker of fibrosis prior to ablation. Compared to echocardiography, LA volumes were not measured at the onset of p wave on ECG and hence conduit and contractile functions were not measured in CMR analysis.

Using CMR is technically challenging, due to the thin-walled atria, and image quality can be reduced by heart rate interval variability. When possible, cine data were acquired with retrospective ECG gating to provide images throughout the entire cardiac cycle. However, if heart rate variability was sufficient to reduce image quality, this was switched to prospective gating. So-called arrhythmia rejection techniques – which exclude data acquired in heart rate intervals outside of a user-defined window – were not used as they lead to long and unpredictable breath-hold durations and often reduce image quality due to poor respiratory control. Real-time cine imaging – which allows imaging in a single cardiac cycle – was another option. However, the spatial and temporal resolution in these circumstances reduce substantially.

5.6 CONCLUSIONS

We have shown reductions in LA and RA volumes and higher LAEF and RAEF after both CA and TSA indicating that bi-atrial dilation in symptomatic LSPAF is potentially reversible. Greater reduction in LA and RA volumes and therefore more reverse remodelling was noted in the CA group which can be related to mitral isthmus line or CTI line without association in preventing AF recurrence. More research is required to establish whether the reverse remodelling is a reflection solely due to either restoration of sinus rhythm, mitral line, CTI line or a combination of these.. Baseline RA max volume measured by CMR might be a useful predictor of AF recurrence and may help with appropriate patient selection in the future. More research is required to establish cost effectiveness of CMR against TTE particularly if procedures are going to be decided based on atrial volumes.

CHAPTER 6

CARDIAC MAGNETIC RESONANCE EVALUATION OF LEFT ATRIAL SCAR QUANTIFICATION

6.1 BACKGROUND

Structural remodelling of the left atrium (LA) is marked by increased fibrosis which raises risks of stroke and heart failure and is associated with poorer outcomes following ablation.[862 91,863] Atrial fibrosis was traditionally considered a consequence of AF, but it has been shown that it also exists in patients in sinus rhythm, particularly those with comorbidities like hypertension and diabetes many years before development of AF.[52 862,864,865] Accurate identification and quantification of fibrosis would be useful as an adjunctive tool to stratify patients and identify those that might benefit the most from ablative interventions. In addition, it may be used to help guide ablation and reduce the need for repeat procedures.[866] The current clinical gold standard for assessment of atrial scarring is electro-anatomical mapping (EAM), performed during an electrophysiological (EP) study.[21,76,549] However, this is an invasive technique which uses ionizing radiation and its accuracy is suboptimal, with reported errors of up to 10 mm in the localization of scar tissue.[867-869]

Delayed enhancement magnetic resonance imaging (DE-MRI) is an established non-invasive technique for detecting myocardial scar tissue.[870,871] Non-invasive evaluation of atrial tissue has been a significant advancement in interventional electrophysiology with atrial 3D DE-

MRI used to assess patient suitability for AF ablation by identifying potential non-responders,[558,871-878] and to define the most appropriate ablation approach.[873,874,876,879]

Marrouche's group in Utah demonstrated that the burden of atrial fibrosis can predict the success of AF ablation. [558,561,587,591,593,873,880-886] However, the techniques and results have been challenging to replicate by other centres around the world.[588,887-889] Furthermore, all the MRI data used in these papers were exclusively acquired in normal sinus rhythm. Low voltage areas instead of delayed enhancement have been suggested to be areas of increased arrhythmogenesis and target for ablation strategies.[890]

Segmentation of atrial scar from DE-MRI images is often very challenging due to poor image quality. This is a result of heart rate variability, residual respiratory motion related artefacts, low signal-to-noise ratio (SNR), and contrast agent wash-out during the long acquisition. Accuracy of the scar delineation is often impaired by enhancement from nearby structures (e.g. valves and aortic wall) and blood flow. In addition, distinguishing scar tissue in a thin walled LA is difficult even for skilled MRI experts.

A grand challenge for evaluation and benchmarking of various atrial scar segmentation methods has shown promising results although most techniques relied on manual segmentation of the LA wall and PV and assumed fixed thickness of the LA wall.[564,577,866202,227,228] Manual segmentation is labour intensive and prone to human error and exhibits both intra- and interobserver variation affecting reproducibility in multi-centre and multi-scanner studies.[577,866,891]

Our clinical interest is in patients with LSPAF who are difficult to electrically cardiovert and maintain sinus rhythm long enough to conduct a cardiac MRI with prospective ECG gating. Our goal in this sub-study was to use the technique of acquiring MRI in patients who are in AF at the time and to then develop the methodology for automatic segmentation and quantification of the scar. We then planned to use this technique to evaluate scar prior to and following ablation and to compare the results in groups based on the ablation treatment and on the heart rhythm in follow up. Here we describe multi-view two-task segmentation (MVTT) technique which is effective and efficient at automated LA and PV segmentation combined with quantification of LA scar.[595]

6.2 METHODS

6.2.1 DATA ACQUISITION

Cardiac MR data were acquired on a Siemens Magnetom Avanto 1.5 tesla scanner (Siemens Medical Systems, Erlangen, Germany). Transverse navigator-gated 3D DE-MRI was performed using an inversion prepared segmented gradient echo sequence (echo time (TE)/repetition time (TR) 2.2 ms/5.2 ms) 15 min after gadolinium administration (Gadovist™-gadobutrol, 0.1 mmol/kg body weight, Bayer-Schering, Berlin, Germany). The inversion time was set to null the signal from normal myocardium and varied on a beat-by-beat basis (depending on the patient's RR interval) to maintain nulling.[578] Detailed scanning parameters are: 30-34 slices at 1.5 x 1.5 x4 mm^3, reconstructed to 60-68 slices at 0.75 x 0.75 x 2 mm^3, field-of-view 380 x 380 mm^2, acceleration factor of 2 using generalized auto-calibrating partially parallel acquisition (GRAPPA), acquisition window 125 ms positioned

within the subject-specific rest period, single R-wave gating, chemical shift fat suppression, flip angle 20°. Data were acquired during free-breathing using a crossed-pairs navigator positioned over the dome of the right hemi-diaphragm with navigator acceptance window size of 5 mm and continuously adaptive windowing strategy (CLAWS) respiratory motion control.[891] The navigator-restore pulse was delayed by 100ms to reduce artefactual signal in the right pulmonary veins.[892] The nominal acquisition duration was 204–232 cardiac cycles assuming 100% respiratory efficiency. [892]

Prior to contrast agent administration, coronal navigator- gated 3D b- steady-state free precession (TE/TR 1/2.3 ms) Roadmap data were acquired with the following parameters: 80 slices at 1.6 x 1.6 x 3.2 mm^3, reconstructed to 160 slices at 0.8 x 0.8 x 1.6 mm^3, field-of-view 380 x 380 mm^2, acceleration factor of 2 using GRAPPA, partial Fourier 6/8, acquisition window 125 ms positioned within the subject-specific rest period, chemical shift fat suppression, flip angle 70°. Off resonant blood from the lungs arriving in the LA and PV can result in signal loss, which in our application, is minimized by using the shortest TE/TR possible.[893] This was achieved by using nonselective radiofrequency excitation.[894]

6.2.2 SEGMENTATION

DEEP LEARNING BASED METHOD

Although conventional machine learning and pattern recognition based methods previously described by our group can achieve promising results for LA chamber and PV segmentation with accurate atrial scar localisation, the requirement of additional roadmap data may be a

hurdle for a reproducible study and not all centres have roadmap data available.[595]Recently, we proposed a deep learning based method to tackle this limitation.[565]

Medical imaging analysis is an extremely important research area that combines advanced multidisciplinary topics. Recently, deep learning-based methods showed very promising results in medical image computing mainly due to the fast accumulation of medical data and the GPU powered computing resources. Deep learning is a new 'artificial intelligence' trend that uses multi-layer perceptron network that contains multiple hidden layers and is therefore called a deep learning structure. [895] According to Shen et al. [896], in terms of input types, we can consider deep models as typical multilayer hierarchical neural networks, which take non-structured vector formatted values as input or convolutional neural networks (CNN) that take structured 2D or 3D values as input. Due to the abundant information embedded in the neighbour-hood voxels especially for the structural medical images that normally represent anatomical characteristics of the imaged organs, CNN have been widely used in medical image analysis.

In this study, we have developed a combined multi-view two-task segmentation (MVTT) deep learning paradigm with recursive attention that can work directly on 3D LGE CMR images to segment the LA (and proximal pulmonary veins) and delineate the scar on the same dataset.

Our deep learning method imitates the inspection method of radiologists who go through 2D axial slices to locate associated details, while still utilizing complementary orthogonal views details. Thus, we divide the volume of 3D LGE CMR into contiguous 2D slices and

conduct 2D slice segmentation. This has two main advantages: 1) it improves abundant training data and 2) it provides greater memory capacity in 2D convolution. Our MVTT method consists of three major subnetworks – a multi-view learning network, a dilated residual network, and a dilated attention network – which automatically and concurrently execute LA and proximal PV and LA scars segmentations.

The MVTT system consists primarily of a multi-view learning network and a dilated concentration network. The multiview learning network uses a sequential learning subnetwork to know the association between 2D axial slices. At the same time, in the sagittal and coronal views, two dilated residual subnetworks learn the complementary details. Then, we combine the two forms of complementary details into the axial slice features to get fused multiview features to accomplish the LA anatomy segmentation. Since LA wounds are very small, the dilated attention network learns from the picture of an attention map to force our network to concentrate on certain tiny regions and suppress background noise effect. The LA anatomy and LA scars share the multiview functionality in our MVTT to manage the two segmentation functions, which can therefore reduce the issue of error accumulation.

Each dataset was scrutinised before MVTT was applied. Acquired images were scored by a senior cardiac MRI physicist on a Likert-type scale: 0 (non-diagnostic), 1 (poor), 2 (fair), 3 (good), and 4 (very good) depending on the level of SNR, quality of normal myocardial nulling and the existence of navigator beam and ghost artefacts. The datasets used had to have the Likert scale score >2.

The quantity of scar is expressed as the percentage of surface area of the LA. The accuracy of the automatic segmentation and scar measurement was established by comparison to the manual ground truth model of scar quantification. We found that automatic segmentation measurements were highly correlated with manual measurements having a mean Dice score of 0.82±0.05, correlation coefficient 0.902, $p<0.0001$.

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM corporation, Armonk, New York, USA). Continuous variables that followed parametric distribution are presented as mean and standard deviation and Student's t-test was used to assess differences between groups. Paired sample t-test was used to assess differences within groups from baseline to 6 months. Non-parametric continuous variables are presented as median and inter-quartile ranges and between group comparisons were done using the Mann-Whitney test. Categorical values were tested using Chi-square. Baseline demographic variables as shown in Table 1 below were included in univariable binary logistic regression analysis apart from medications. Throughout the analysis, p values ≤ 0.05 were considered statistically significant.

6.3 RESULTS

Of 97 patients enrolled in the CASA AF randomised control trial at the Royal Brompton and Harefield NHS Trust 17 did not have an MRI performed, 13 at baseline and 4 at follow up. The reasons were: withdrawal prior to treatment (n = 3), claustrophobia (n = 2), no available

slot for MRI (n = 5), advanced renal disease or another condition precluding MRI (n = 6) and death (n = 1). We have excluded MRI studies of 7 patients who had an additional ablation in follow up to ensure comparisons of scarring between ablative modalities are not compromised.

Of the remaining 73 patients 27 did not have appropriate image quality for analyses; 22 at baseline scan and 5 at the follow up scan so they too were excluded (30%). Forty-six patients in this study had CMR at baseline and 6 months following ablation and their images were of appropriate standard for MVVT and scar assessment (Figure 48).

The patients considered in these analyses were 62.4 ± 8.6 years old, 36 were male (78.3%); 27 were randomised to catheter ablation and 19 to thoracoscopic surgical ablation. Their baseline characteristics were the same as in the remainder of the trial participants (see Table 13).

The median time from baseline MRI to treatment was 48 days (34-68.5). LA scar measurements using MVTT are presented below in Table 44.

Pre-ablation left atrial scar in patients randomised to catheter ablation was 9.8 ± 4.9% and in those allocated to surgical ablation it was 13.4 ± 5.8%. The difference in size between the two treatment groups appears to be significant, as p=0.034.

Table 44: Proportion of scar tissue in LA at baseline and 6 months after ablation based on multi-view two task segmentation method

	CA n= 27	**TSA n = 19**	**P value**	**SR in follow up n = 16**	**AF in follow up n = 30**	**P value**
LA scar - baseline, %	9.8 ± 4.9	13.4 ± 5.8	0.034	13 ± 5.2	10.4 ± 5.6	0.12
LA scar - 6 months, %	29.4 ± 8.7	29.7 ± 11.9	0.92	31.1 ± 10	28.6 ± 10.1	0.42
Δ scar, %	19.5 ± 8.9	16.3 ± 10.8	0.2	18.2 ± 8.6	17.5 ± 10.5	0.8
P value	<0.0001	<0.0001		<0.0001	<0.0001	

Footnote 49: Δ – delta change, AF-atrial fibrillation, CA – catheter ablation, SR – sinus rhythm, TSA – thoracoscopic surgical ablation

Post-ablation CMR was performed on average 173 ± 45 days after ablation. The scar area increase (Δ scar) was significant in both treatment arms following ablation: 19.5 ± 8.9% in CA arm and 16.3 ± 10.8% in TSA arm, p<0.0001 for both groups.

The proportion of scar in LA measured at 6 months follow up did not appear to differ significantly between treatment groups (p=0.92).

Thirty patients had AF recurrence during the follow-up period. Scar measurements at baseline were similar in patients with AF recurrence and those who maintained sinus rhythm throughout follow up (10.4 ± 5.6% compared to 13 ± 5.2%, p =0.12).

At 6 months follow up there was a significant increase in proportion of scar in patients who maintained SR (Δ scar 18.2 ± 8.6%, p<0.0001) and in those who experienced AF recurrence (Δ scar 17.5 ± 10.5%, p<0.0001). The size of the increase was similar in both groups (p=0.8).

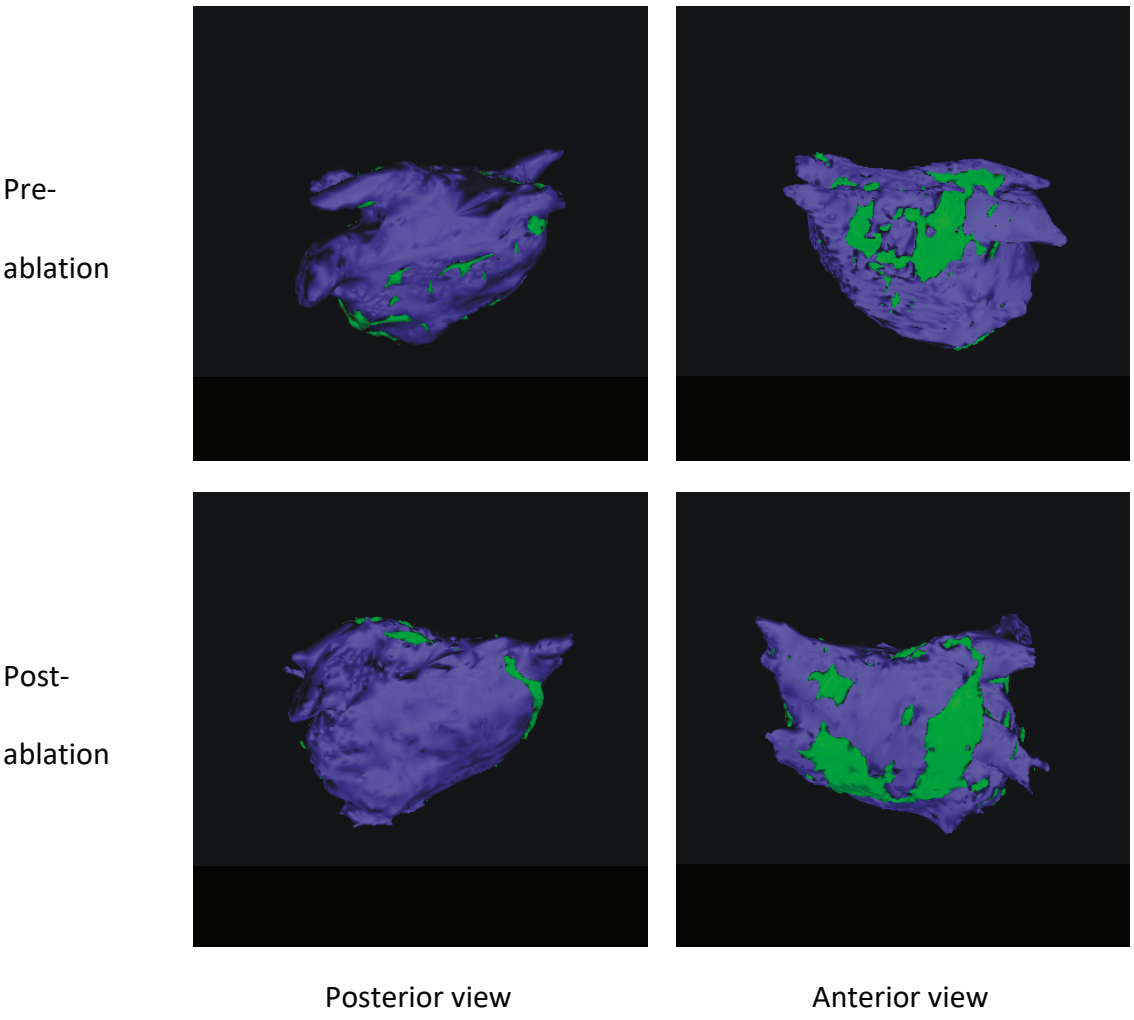


Figure 48: Scar distribution (green rendering) based on 3D DE MRI scan, pre- and post-ablation.

6.4 LA SCAR AS A PREDICTOR OF AF RECURRENCE

We used demographic and clinical variables in this subgroup of patients in univariable analyses to identify a possible predictor of AF recurrence. In addition, we used LA scar measurements (MVTT and manual) at baseline and at 6 months to establish the correlation between fibrosis and AF recurrence. None of the variables in univariable analysis model appeared to achieve a significance of 0.2 to merit further testing (see Table 45).

Table 45: Univariable analyses of data from patients in MRI scar assessment study and AF recurrence. LA scar measurements using both multi-view two task segmentation method (MVTT) and manual measurements (GT) are included for comparison.

Timeline	**Parameter**	**Univariable**		
		OR	95% CI	P value
Baseline	Age	1.001	0.934 – 1.073	0.97
	Sex (male)	1.04	0.263 – 4.1	0.96
	AF duration	0.999	0.998 – 1.001	0.61
	Body mass index	1.02	0.9- 1.12	0.76
	Smoking	1.73	0.71 – 4.2	0.23
	Hypertension	1.19	0.36 – 3.89	0.77
	Diabetes	1.265	0.39 – 4.08	0.69
	Stroke	0.5	0.03 – 8.5	0.63
	Coronary artery disease	0.49	0.097 – 2.1	0.31
	Respiratory disease	0.33	0.06 – 1.66	0.18

	LA scar MVTT	0.92	0.82 – 1.027	0.132
	LA scar GT	0.92	0.82 – 1.035	0.169
6 months	LA scar MVTT	0.97	0.92 – 1.03	0.35
	LA scar GT	0.98	0.92 – 1.05	0.62

6.5 DISCUSSION

We have developed a novel fully automatic segmentation method to detect atrial scarring in LGE MRI images acquired uniquely during AF and validated it against manual ground truth segmentation by experienced imaging cardiologists.[565,595]This methodology was applied in this study to quantify LA scar prior to and after ablation in patients with LSPAF.

The main findings of the study are:

1. LA scar is significantly increased following both ablation strategies.

2. LA scar was not predictive of AF recurrence.

One of the key issues in LA scar segmentation is to distinguish the LA and the scar from the high enhancement regions which we successfully accomplished. [595] In addition, we scanned patients in AF by adopting MRI acquisition strategies including beat-to-beat changes in

inversion time and navigator artefact reduction schemes. Despite these improvements, almost 30% of the acquired datasets in our study were not of the required standard, largely due to the suboptimal heart rate control in our patients, which affected our sample size. The multi-atlas LA auto-segmentation in our study was strongly correlated with manual ground truth delineation as shown by consistent Dice score of >90.[595] The development of deep learning methods renders the analysis of scar less time consuming and the methodology probably represents the future of image related analyses. However, scar identification and assessment within the same dataset changes with different learning methods so accuracy and reproducibility still need to be resolved.[564,577,895-897]

In our study, the amount of fibrosis identified at baseline with automatic segmentation was larger in patients in the TSA group, but this may be due to a Type II error as our sample size was defined by the quality of the acquired images.

Quantification of scar at baseline was less than 20% of the total LA surface in our patients so they would be classified as being in stage 1 and 2 of fibrosis as defined by the investigators of DECAAF study.[558] In their trial, 92 patients had persistent or permanent AF and pre-ablation scar measurements for 61% of them(n=56) were in categories 1 (<10%) and 2 (>10, <20%) which were associated with only 15% of AF recurrence in follow up.

Following ablation, the percentage of scar in the LA the patients in our study increased to around 30% which is largely in line with literature reports of electro-anatomical mapping quantification of scar and low-voltage post ablation in patients with chronic AF.[242,898] This is

surprising as scar estimates with electro-anatomical mapping during catheter ablation are significantly higher than those obtained with LGE-MRI.[593,899]

A number of studies reported discrepancies in scar quantification using different methodologies and at this point we still lack a gold standard.[888,897,899,900] Quantification of scar is highly influenced by the CMR acquisition sequences and post processing methods which then leads to non-generalisable results.[887,900,901] The imaging technologies as well as electro-anatomical mapping most likely need further histological validation before being universally adopted to identify and quantify scar so that it can be used in clinical decision making.

All our patients had an ILR implanted at the end of the ablation procedure so the artefact from the ILR can be seen in the intrathoracic space in about a third of the cases. It is possible that this artefact interfered with automatic LA segmentation although the published literature suggests otherwise, and our own ground truth measurements were highly correlated with values from automatic segmentation.[577,900,902]

6.6 CONCLUSIONS

In this study we made significant progress by acquiring DE-MRI datasets in AF and developing a fully automated segmentation tool for LA and PV geometry and LA scar delineation. This tool has allowed us to assess the LA scar burden pre- and post-ablation and showed that both ablative techniques increase the scar in LA. However, the size of the scar does not appear to be predictive of AF recurrence. Further work is required to refine our segmentation and LA scar quantification techniques.

CHAPTER 7

EFFECT OF GANGLIONIC PLEXI ABLATION IN THORACOSCOPIC SURGICAL ABLATION ON AUTONOMIC NERVOUS SYSTEM. ANALYSIS OF CONTINUOUS HEART RATE VARIABILITY OVER 1 YEAR FOLLOW UP

7.1 BACKGROUND

AF initiation and maintenance of AF are due to very complex mechanisms that are not fully understood. Many theories have been postulated to understand the mechanisms and target the causal factors to improve the management of AF and its associated comorbidities[18]. Amongst many factors that lead to AF initiation, one of them is due to autonomic or neural imbalance leading to parasympathetic overstimulation and sympathetic inhibition. The imbalance leads to bradycardia and intercellular increase in calcium particular around the atria and PVs leading to early depolarisations and late after depolarisations[903]. The autonomic nervous system plays an integral role in AF initiation and maintenance of AF via imbalances of the sympathetic and parasympathetic nervous system[658,904]. Treating AF with PVI and linear lesions in the LA caused a change in the autonomic tone of the subjects[668].

The cardiac autonomic nervous system comprises of extrinsic and intrinsic autonomic components. The stellate ganglion is part of the extrinsic cardiac autonomic system while GPs are neural clusters present on the epicardial surface of the atria with higher densities around PV ostia are part of the intrinsic autonomic nervous system[905]. Modulating the nervous system around the cardiac chambers can be difficult as most of the ablation

strategies are limited to endocardial ablations and attempting to ablate the GP endocardially can be challenging due to multiple pathways signalling the GP centres and interconnections between GP[906,907]. The energy required to ablate epicardial structures via endocardial route is higher and carries increased of atrial perforation and associated comorbidities with complications. It is difficult to establish whether ablation was performed at a GP centre or its branches. From recent evidence GP ablation has become more accessible and more comfortable to perform, resulting in more complex lesion sets being performed with GP ablation not only via CA but also by TSA[641].

Earlier experience with minimal surgical ablation with GP ablation and its success over long-term follow up have not shown to be superior to CA for patients with PAF at five years[908]. Driessen et al. conducted a more extensive study (AFACT study) including persistent AF patients undergoing GP ablation with PAF patients serving as a control. Patients who had GP modification with PVI did not show a significant improvement in SR maintenance following ablation[909]. Berger et al. compared the 1:1 randomisation of surgical ablation with and without GP ablation as a sub-study of AFACT. There were no differences in AF recurrence between the two groups (11.8% vs 11%; GP ablation vs no GP ablation), although there were higher complication rates with sinus node dysfunction requiring pacemaker implantation, procedural bleeding, and pneumonia[292].

The early experience in comparing surgical thoracoscopic AF and CA was reported in a single randomised controlled trial (FAST trial) showing that the surgical approach is more effective when compared to CA (65.6% vs 36.5% clinical success, P=0.0022) [716]. It is still to debate

whether the higher effectiveness in minimally invasive TSA was due to transmural lesions, contiguous ablation lines, LAA ligation or GP ablation.

The largest RCT reported by Katrisis et al. showed a significant benefit of combining PVI with GP ablation instead of PVI or GP ablation alone [670]. However, a metanalysis in 2017 supported the adjunct of GP ablation to PVI by CA in the PAF cases. GP ablation in persistent AF did not clearly show a significant advantage in maintaining SR [910].

GP activity measured by HFS during the time of ablation can be inaccurate because it is dependent upon the activity of the centre being stimulated. There are suggestions of GP reactivation or recruitment from other regions following ablation. Zhao et al. in a canine study comparing GP ablation against sham control showed the GP ablation group had absent reflex acutely post-ablation, however, after eight weeks it was shown that the GP regions were easily stimulated with AF inducibility and higher levels of serum atrial natriuretic peptide [662].

Zdarska et al. (2017) performed a study of CA with GP ablation compared to a staged hybrid ablation with TSA performed first followed by CA and GP ablation. The group without hybrid procedure showed an accelerated heart rate in patients with GP ablation with significant differences in frequency and time domain measurements of autonomic function assessment while patients receiving CA as part of a staged hybrid procedure showed a blunted response of heart rate variability [911]. The absence of change in heart rate variability likely explained by coincidental GP ablation by the clamp and COBRA Fusion ™ (AtriCure®, USA) catheters

while isolating the pulmonary veins. However, there was no long-term follow up to see if the response persisted.

No studies are analysing the impact of GP ablation on the autonomic function over the long term and the overall effect of autonomic function on AF recurrence following ablation. To measure the effect of GP ablation, heart rate variability recorded by ILR using time-domain indices was measured daily over one year. HRV allows to analyse not only the impact of GP ablation but also to identify autonomic nervous system imbalance few minutes before AF initiation as shown in small studies. In one study by Marinkovi et al. (2020) used standard deviation of the normal-normal R-R intervals (SDNN) prior to CA in PAF population and after CA with follow up at 1 day, 1 month, 3 months, and 6 monthly after for median follow up of 33 months [912]. They showed a reduction in HRV early during follow up with gradual increase back to pre-ablation HRV in patients with AF recurrence, while reduced HRV persisted for those who maintained SR suggestive of association with parasympathetic suppression.

Heart rate fluctuates depending on stimulus related to level of mental stress, physiological stress from hormones, physiological stress from pregnancy and most commonly physical activity in the older subjects[913-921]. Physical activity can be in the form of habitual training comprised of regular high endurance training or activities of daily living [922,923]. Habitual training results in stable HRV parameters reflective of higher parasympathetic tone and reduced sympathetic tone [924-929]. Regular physical activity modulates the HRV over a long period and is not influenced with short burst of physical activities in the trained individuals and in the elderly physical activity appears dissociated with heart rate and HRV[927,928,930,931]. In subjects who are not training on a weekly basis, short periods of physical activity can

result in significant variations of HRV[919,927,931]. There are gender differences in HRV with women having more parasympathetic tone and men having more sympathetic tone when adjusted for similar age and physical activity[928,929,932].

We aim to investigate effect of GP ablation by measuring HRV captured by the ILR and represented as median difference in R-R interval calculated every 5 minutes and averaged over 24 hours. HRV will be measured daily by ILR and used to evaluate differences in autonomic nervous system response following GP ablation in the TSA group compared to CA group for a follow up duration of 1 year.

7.2 METHODS

7.2.1 GP STIMULATION AND ABLATION

Patients were part of the CASA AF Trial (CTN18250790) which randomised patients 1:1 to receive either CA or TSA. The outline of the trial has been reported and also included in chapter 2[698]. Patients who were randomised to receive TSA had the stimulation of the GP using a bipolar pen to deliver high-frequency stimulation (HFS) at pre-defined anatomical locations for 5 seconds (60ms burst, 25mA current, and pulse width 2ms). Locations were considered to have the presence of GP if there was a reduction in heart rate >50% or asystole 2 seconds (

Figure 49). GPs are ablated using the linear isolator pen at the identified GP locations and retested to ensure they are not excitable (Figure 50).

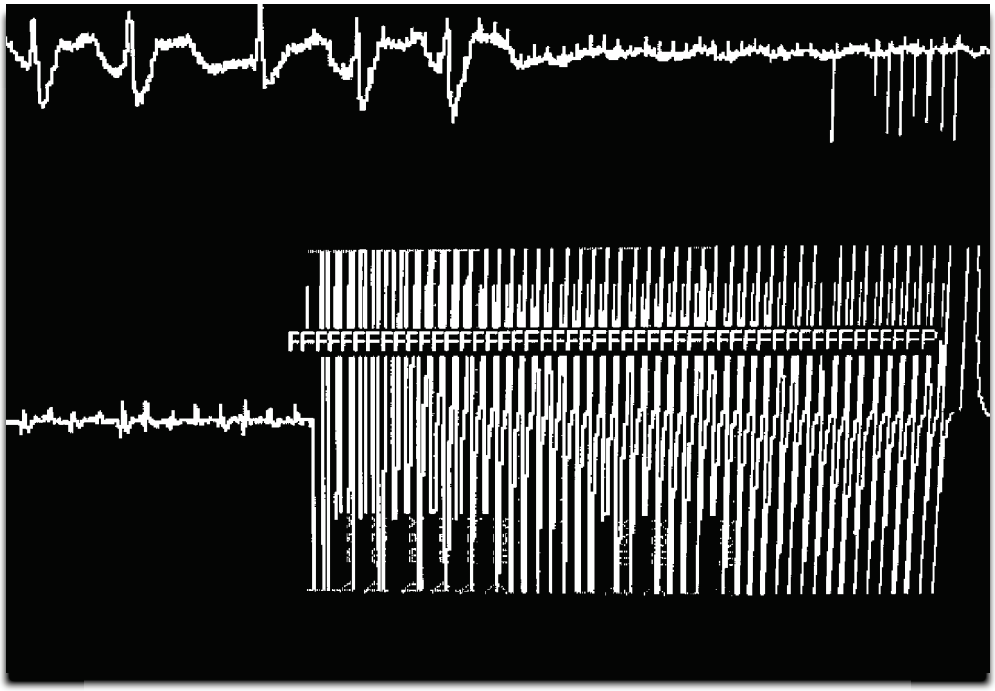


Figure 49: High-frequency stimulation (60ms burst, 25mA current, and pulse width 2ms) of ganglionic plexus resulting in a response of asystole.

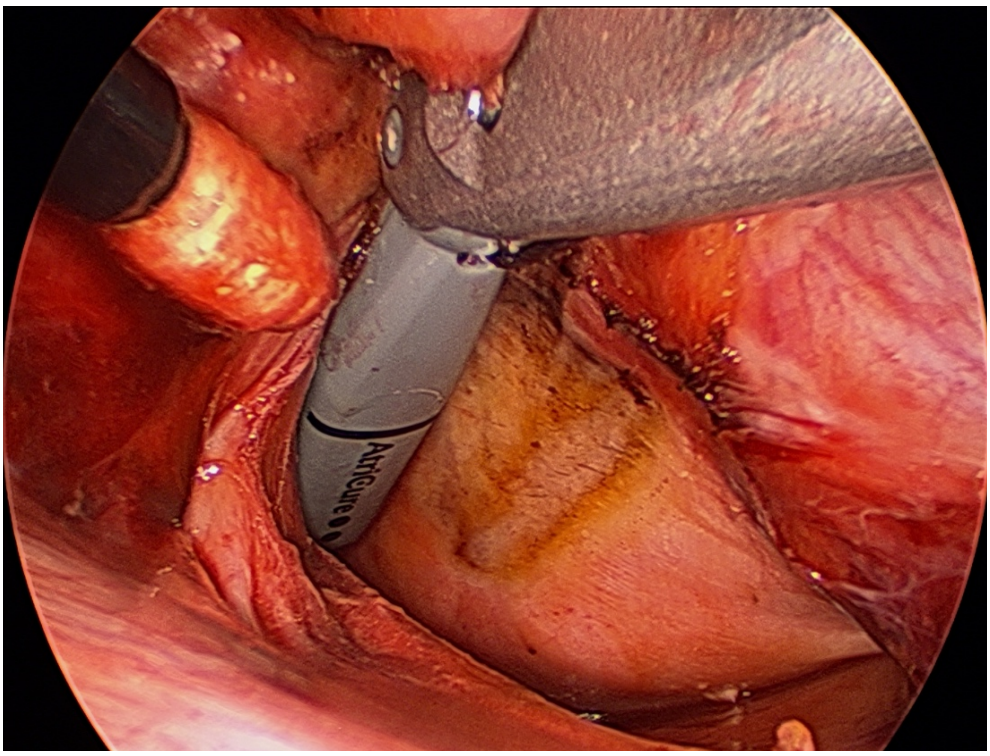


Figure 50: Ablation of Ganglionic plexi at the site of positive testing

7.2.2 HEART RATE VARIABILITY

Once the ablation was completed, patients had an ILR inserted along the anterior wall of their chest (Reveal LINQ™ - Medtronic, Minnesota, USA,) along with home monitoring using CareLink™ (Medtronic, Minnesota, USA). Cardiac compass summary was used to evaluate HRV and physical activity in the patients. CA subjects did not have GP ablation and served as controls for the study.

The ILR was programmed to capture any significant tachycardia, bradycardia and more importantly recurrences of AF and AT. Predetermined manufacturer's recording allowed to capture physiological data, including heart rate, heart rate variability (HRV), physical activity.

Heart rate variability was calculated using a surrogate derivative of the standard deviation of average normal R-R interval (SDARR / SDNN) in the following equation:

$$LTCT\ HRV = \sqrt{\frac{Sum(RR\ medians)^2 - \frac{(SumRR\ medians)^2}{nRR}}{nRR - 1}}$$

LTCT - Long Term Cardiac Trend

Heart rate variability based on the above equation is calculated every 5 minutes over a 24 hour period. The average of the 24 hour period is plotted as a single dot on the cardiac compass as shown in Figure 51. The plotted line graphs were digitised to extract the HRV using a custom developed C++ software, as shown below (Figure 51 and Figure 52). The software was calibrated to tag the days (yellow lines) located on the bottom of the graph as BMP files greater than 600dpi to ensure high resolution for digitisation (Figure 52). The peaks and troughs of the graph were then captured (red dots) and extracted in a numerical format after calibration to the scale located on the y-axis.

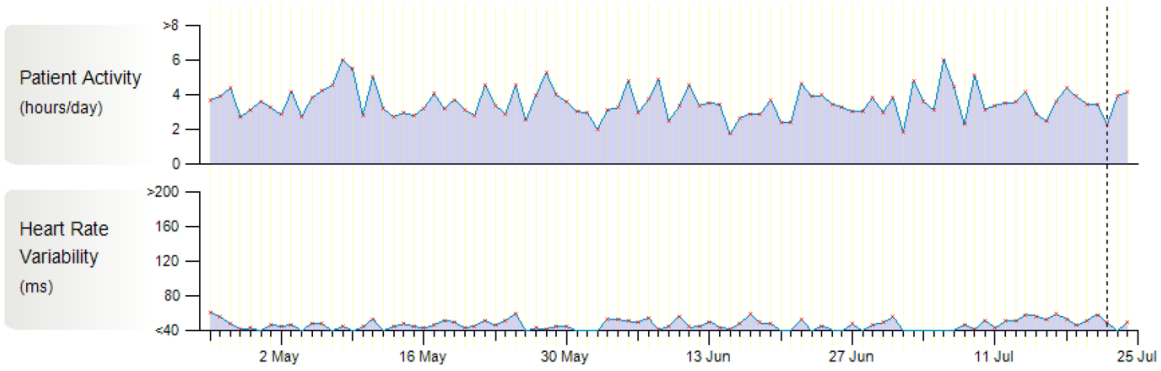


Figure 51: Cardiac Compass showing patient activity and heart rate variability over 90 days

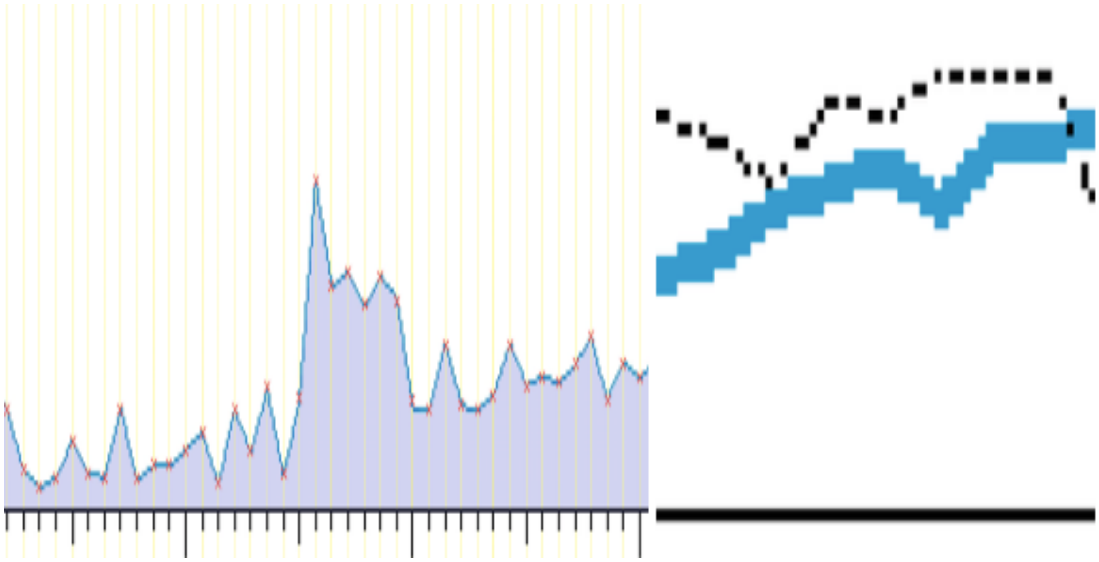


Figure 52: Digitization method of the graph with a minimum 600 dpi of the BMP images

According to the graph, the minimum HRV measure was 40ms. In order to ensure that lower points were not misrepresented, all data points on HRV of 40ms were discarded as the actual number could not be extracted.

7.2.3 STATISTICS

All continuous parametric data were shown as means and standard deviation while non-parametric data were shown as median and interquartile range. Linear regression was used to calculate regression residual estimates between HRV and physical activity. Student's t-Test was used to calculate mean differences between groups. Chi-square Test was used for categorical parametric data while the Mann-Whitney test was used for nonparametric data.

Mixed repeated measures model was used to see the trend of HRV over 12 months with a comparison between TSA and CA.

7.3 RESULTS

7.3.1 BASELINE

Seventy-one patients underwent randomisation (TSA = 30, CA = 41) as part of the CASA AF RCT. HRV data was not available in five patients due to prolonged periods of AF (Table 46). Of those five, two had pacemakers inserted due to sinus node dysfunction when not in AF. Five patients with AF within three months had cardioversion. Patients were followed up for 365 days with recording captured for 21019 days (87.2%) out of 24091 potential days. Three thousand seventy-two days were not measurable as subjects were in AF. Table 46 shows baseline characteristics for the subjects as below.

Table 46: Baseline characteristics of patients randomised to CA or TSA

Parameters	**All (n=66)**	**TSA (n=28)**	**CA (n=38)**	**P value**
Age		63.9 ± 11.8	64.4 ± 9	0.84
Male, n (%)	56 (84.8)	24 (85.7)	32 (84)	0.98
CAD, n (%)	9 (13.6)	3 (10)	6 (18.8)	0.60
Diabetes Mellitus, n (%)	5 (7.5)	2 (7.1)	3 (7.9)	0.92
Thyroid disease, n (%)	6 (9)	2 (7.1)	4 (10.5)	0.61

Hypertension, n (%)	31 (47)	18 (64)	13 (34)	0.7
CKD, n (%)	6 (9)	4 (14.3)	2 (5.2)	0.41
Smoker, n (%)	45 (68.2)	18 (64)	27 (71)	0.62
Alcohol, n (%)	11 (16.7)	3 (10.7)	8 (21)	0.29
Betablocker, n (%)	59 (89.4)	26 (92.8)	33 (86)	0.27
Ca Blocker, n (%)	9 (13.6)	3 (10.7)	6 (15.7)	0.72
ACEi/ARB, n (%)	30 (45.5)	18 (64.3)	12 (31.5)	0.64
Diuretic, n (%)	19 (28.8)	9 (32)	10 (26)	0.60
Statin, n (%)	33 (50)	15 (53.5)	18 (47.4)	0.64

Footnote 50: ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, CA – catheter ablation, CAD -coronary artery disease, CKD – chronic kidney disease

7.3.2 EFFECT OF GP ABLATION ON HRV DURING 1ST WEEK

All TSA patients had ablation of favourable GP stimulation locations. There was not a significant change in daily HRV over the first week between the two groups (Figure 53). However, there is a significant difference in physical activity between TSA and CA (Figure 54). Physical activity during the first week is limited in TSA as opposed to CA due to significant mobility restrictions due to chest drains associated with TSA to prevent pleural effusions and pneumothorax. A blunted response of HRV to physical activity was seen in the

TSA group when compared to CA (Figure 55). This suggests that ablation of GP does lead to an altered function of the autonomic nervous system as represented by HRV.

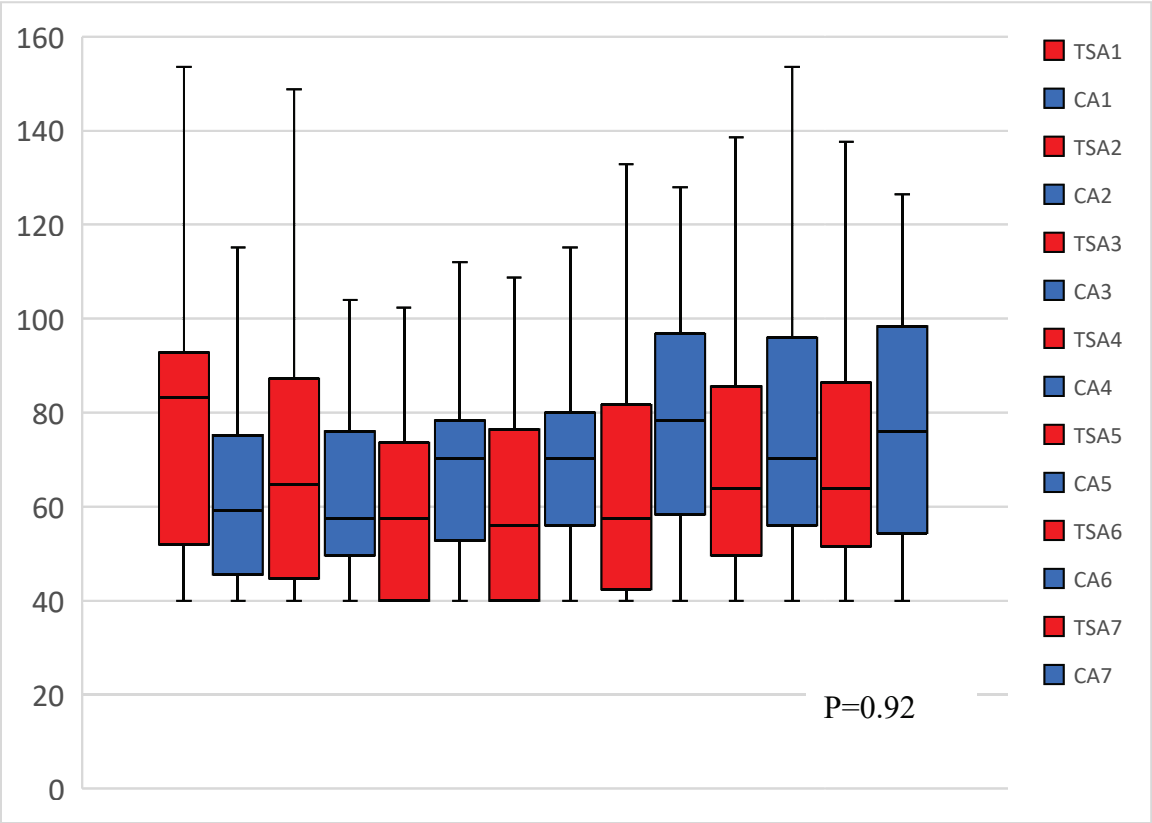


Figure 53: Comparison between CA and TSA with GP ablation for first-week post ablation

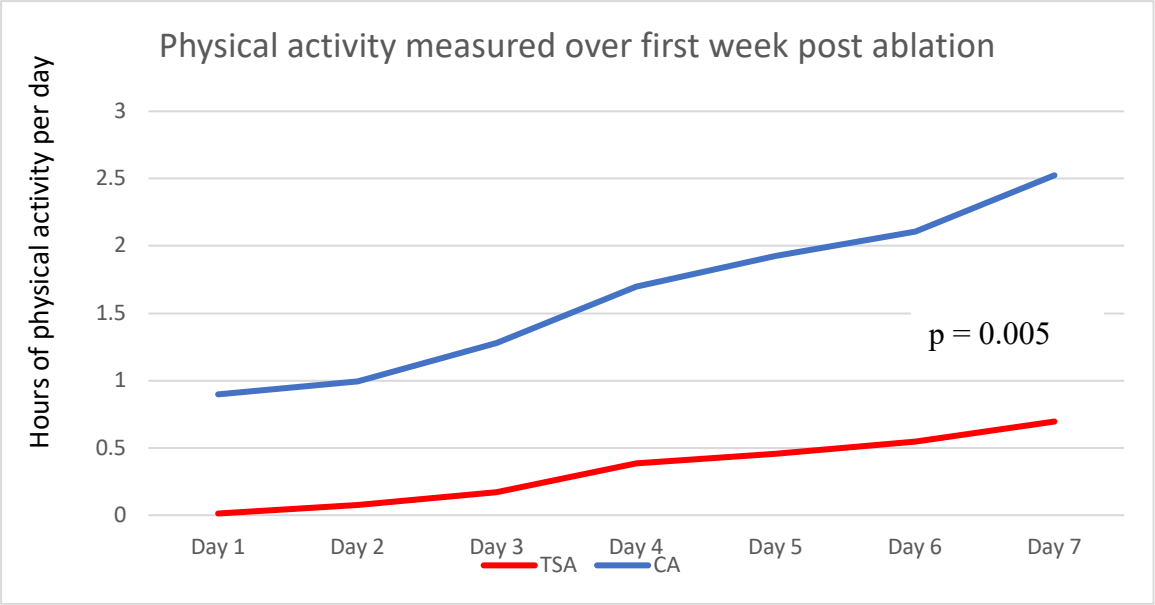


Figure 54: Level of physical activity between CA and TSA for the first week

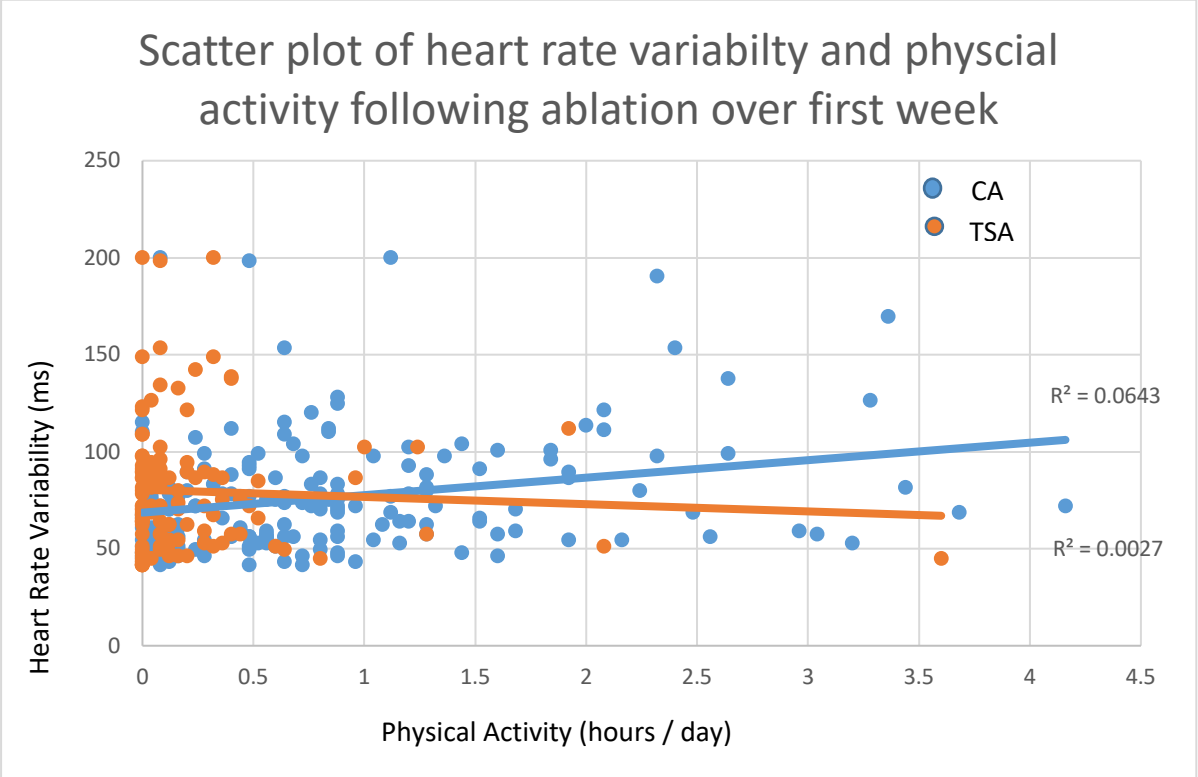


Figure 55: Scatter plot of heart rate variability and physical activity following ablation over the first week

7.3.3 EFFECT OF GANGLIONIC PLEXI ABLATION OVER 1 YEAR

Patients who received TSA take longer to recover and have a significant reduction of physical activity as measured by the ILR on the cardiac compass. Patients who received CA recovered to baseline at four weeks while TSA patients recovered at six weeks to a significantly lower physical activity that they maintained for the rest of the year (Figure 56). Over time there is a gradual increase in physical activity between in the CA group but not in the TSA group (Figure 56). The HRV response is reduced in the TSA group compared to CA group, and the response to physical activity is significantly reduced in the TSA group over 12 months follow up (Figure 57).

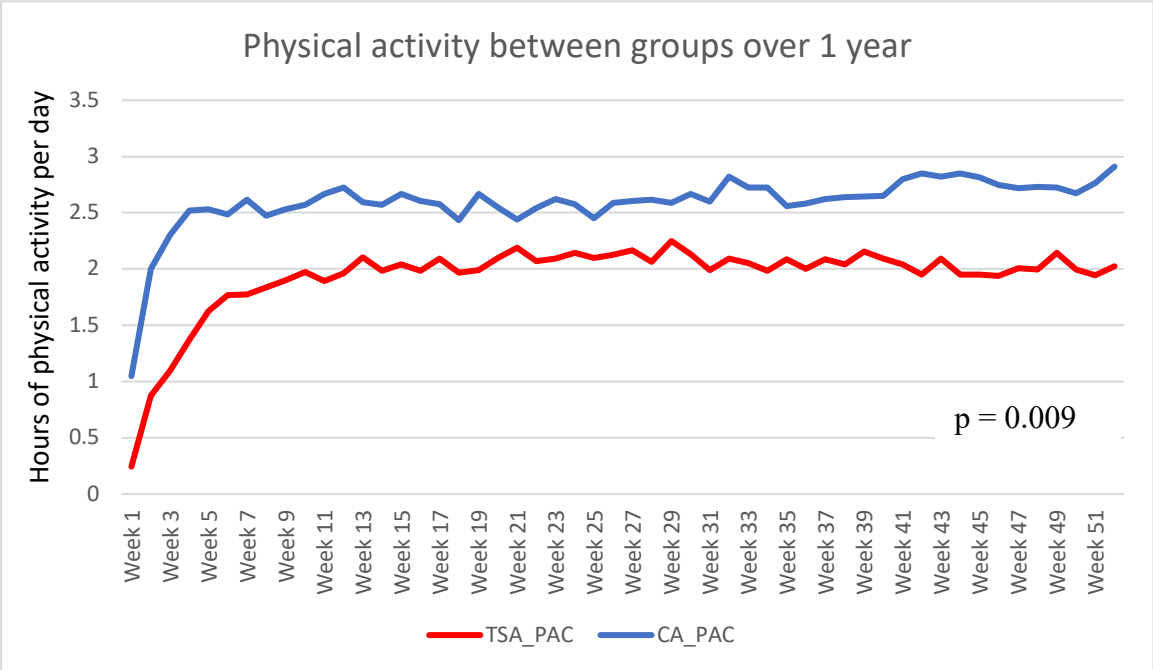


Figure 56: Physical activity (PAC) between thoracoscopic surgical ablation (TSA) and catheter ablation (CA) over one year.

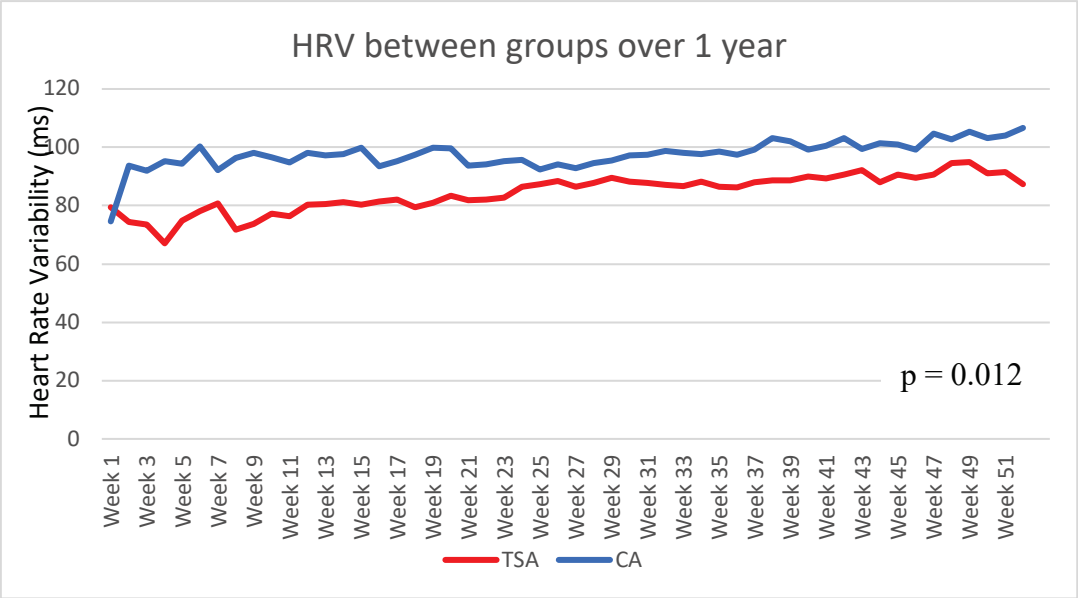


Figure 57: Heart rate variability (HRV) between groups over one year

The variability between HRV is not explained by the change in physical activity as shown by linear regression (R^2 =0.0252 vs R^2 <0.01: CA vs TSA, p = 0.000152) but the correlation is further reduced in the TSA group (Figure 58).

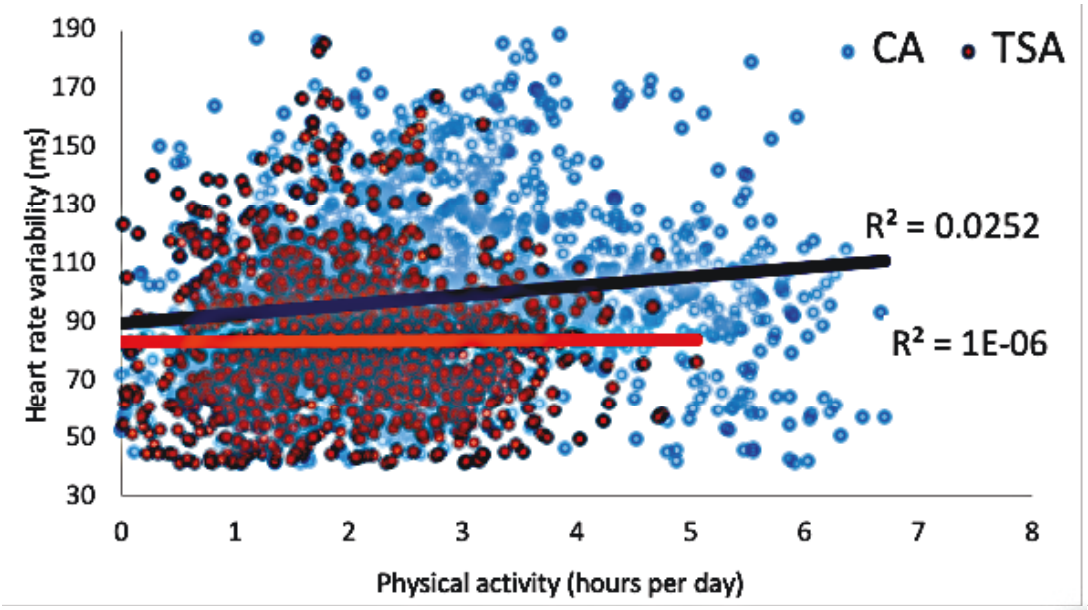


Figure 58: Linear regression/correlation curve of Heart rate variability and physical activity between CA and the TSA. P = 4.6e-50

Heart rates were lower in the CA group when compared to TSA group nocturnally when there was expected to be low levels or no levels of physical activity (67 ± 3.2 bpm vs 70.3 ± 7.7 bpm, $p<0.01$) (Figure 59). The opposite trend was noted in the day time with higher heart rates in the CA group (72.7 ± 3.2 vs 73.4 ± 8.9 bpm, $p<0.01$) when compared to the TSA group (Figure 59). Heart rate in the day time and night time varies due to activity. Influence from the autonomic nervous system can be more noticeable in the night when there is inhibition of sympathetic activity and unopposed parasympathetic activity. During the first three months, there was a more significant difference in the night heart rates. TSA showed a significantly higher night-time heart rate when compared to CA (74.7 ± 2.4 vs 67 ± 2.4 bpm, $p<0.01$). This effect is also seen in the day time (78 ± 3.6 bpm vs 73.8 ± 5.6 bpm, $p<0.01$) with exaggerated heart rate response in the CA group (7.8 ± 3.2 vs 3.3 ± 1.1 bpm, $p<0.01$). This would suggest that there is possibly an attenuated response of the sympathetic component of the GP due to their close proximity or in vicinity of the ablated site (Figure 59). Over the year there will also be variable autonomic responses due to different rates of healing and reconnections from the ablated GP resulting in either an increased sympathetic or return of parasympathetic effect.

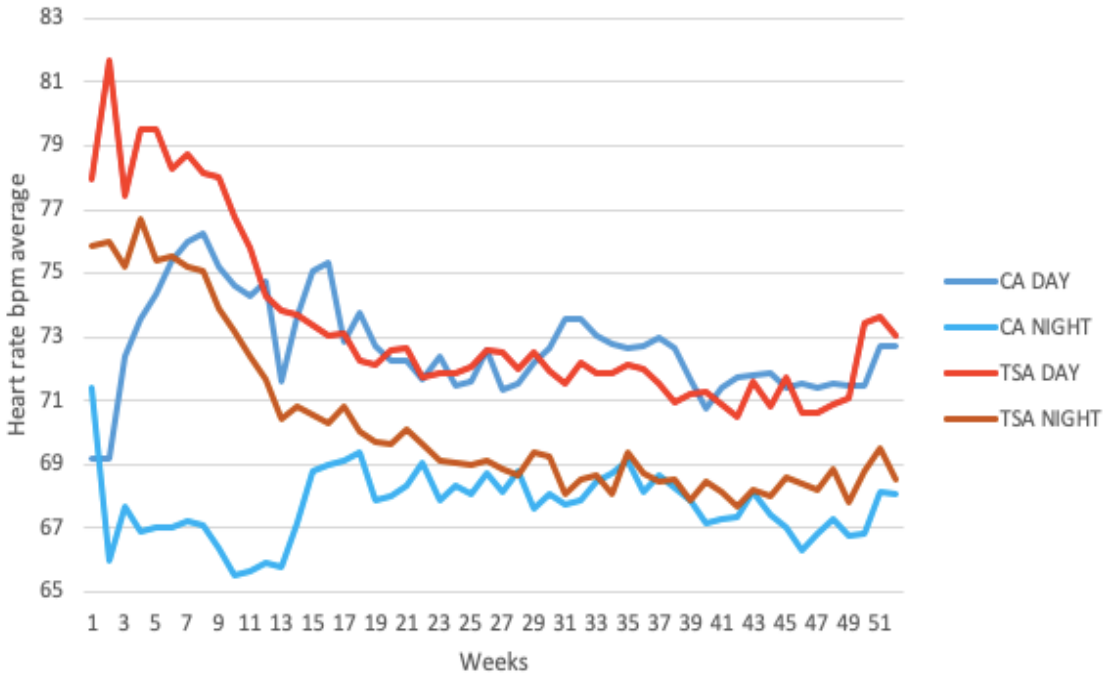


Figure 59: Heart rate weekly averages of day and night between CA and TSA

7.3.4 AUTONOMIC FUNCTION AND RELATIONSHIP TO AF RECURRENCE

Twenty-four patients from the CA group and 13 patients from the TSA group had AF recurrence (63% vs 46%, p=0.214) in this sub study of HRV. Patients who had AF recurrence had higher HRV over the 12 months follow up when compared to the patients who maintained SR (98.4 ± 34 ms vs 88 ± 27.4ms, p = 0.0011) as shown in Table 47. In the AF recurrence group, the HRV was higher in patients who had no GP ablation (CA) when compared to patients who had GP ablation (86.5 ± 26.6 ms vs 65.1 ± 16.2 ms, p = 0.0001) as shown in Table 47. One week before the AF recurrence, there was a small trend of HRV change in the GP ablation group when compared to the HRV of the same patients over the year (8 ± 15.5ms vs 3.8 ± 18.4ms, p=0.17) as shown in Figure 60.

Table 47: Heart rate variability of the patients who had GP ablation (TSA) compared to patients without GP ablation (CA) over the year and 1 week prior to AF recurrence.

Parameters	SR	AF (1 week prior)	P value
GP ablation	(n = 1306) 86.5 ± 26.6	(n=38) 65.1 ± 16.2	0.0001
No GP ablation	(n = 1706) 98.4 ± 34	(n= 105) 88 ± 27.4	0.0011
P value	<0.0001	<0.0001	

Footnote 51: n denotes number of patient equivalent weeks who maintained sinus rhythm or had AF recurrence.

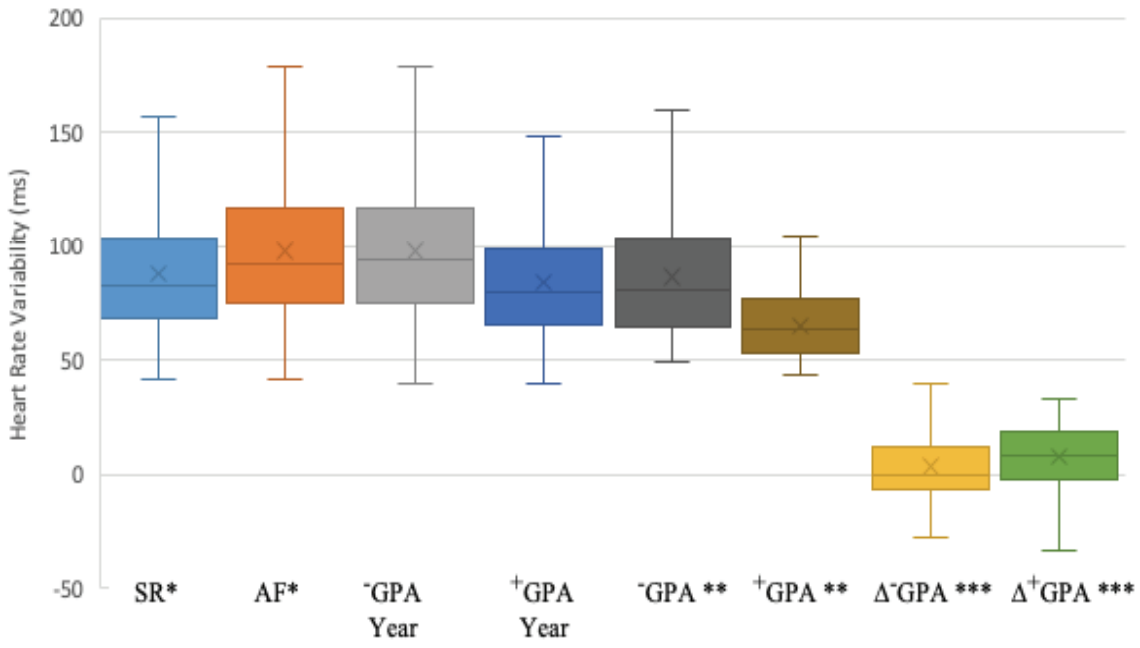


Figure 60: HRV assessment between patients who had targeted GP ablation as part of TSA compared to CA group and HRV differences between patients who had AF recurrence compared to patients who maintained SR.

Heart rate variability between AF and SR over one year follow up. **HRV during the week preceding AF recurrence between patients with and without GP ablation (TSA vs CA). * Differences in HRV before AF recurrence and annual HRV for the same patients. -GPA represents patients in the CA group, while +GPA represent patients in the TSA group. Δ - represent the difference in HRV between patients.*

In patients who had AF recurrence, shorter durations of AF were seen in the GP ablation group as compared to the non-GP ablation group (31.8 vs 88.8 days, p<0.0001) with frequencies and duration of the AF recurrence graphed in Figure 61.

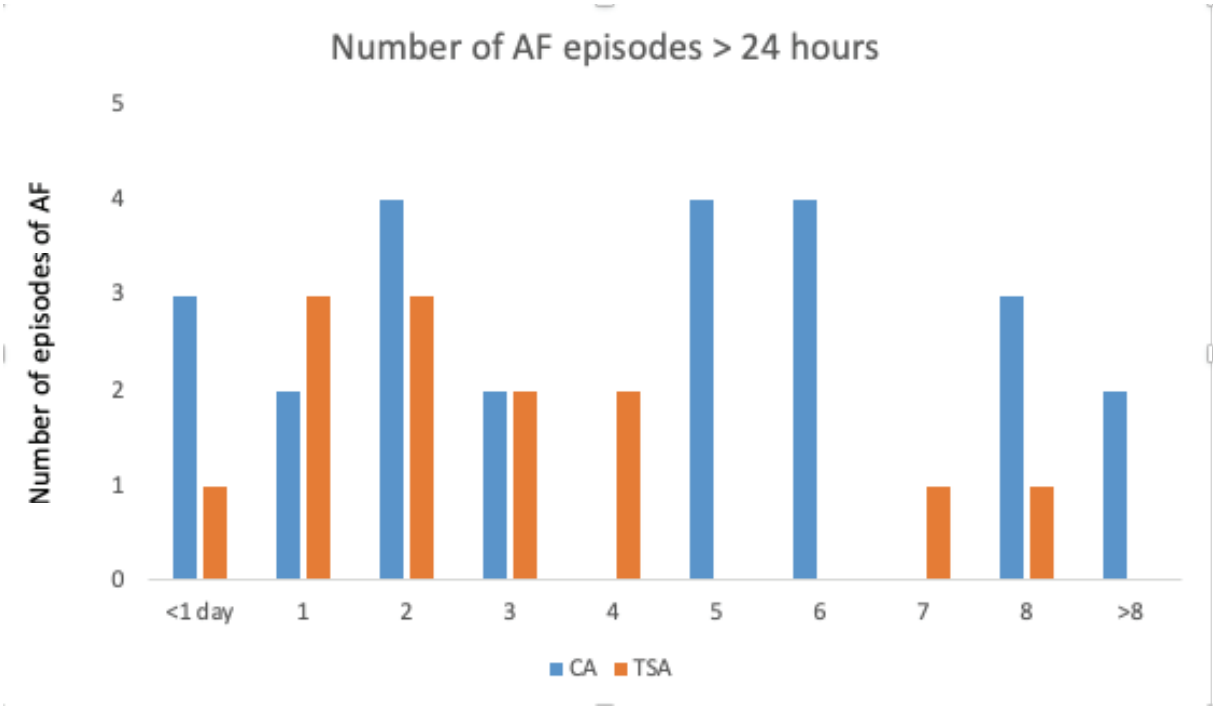


Figure 61: Bar chart showing the number of episodes of AF and the durations that those episodes lasted for patients who had an AF recurrence. CA - no GP ablation, TSA - with GP ablation.

Univariate analysis did not show HRV to be a predictor for AF recurrence.

7.4 DISCUSSION

In our study, HRV measured the impact of direct GP ablation as part of the strategy in TSA or indirect GP injury resulting from ablation of PV ostia in either TSA or CA groups. To my knowledge, this is the first study in humans evaluating HRV measured on a daily basis by an ILR for a follow period of up of 1 year.

Our study has the following key findings:

(1). Effect of GP can be accurately measured using HRV representing a time domain test.

(2). Effect of GP ablation on autonomic nervous system appears to continue over one year.

(3). HRV is not directly impacted by physical activity.

(4). Patients who had AF recurrence had a significantly lower HRV compared to the population who maintained SR irrespective of GP ablation.

(5). Patients who had GP ablation had a significantly lower HRV compared to patients who did not have GP ablation.

Scherlag et al. (2005,2006) have described the role of cardiac autonomic nervous system from canine study and followed by study in humans with AF (PAF and persistent AF) showing induction of AF by stimulation of neural plexus located close to PV junctions[903,933]. Ablation of these locations abolished the parasympathetic response and increased the success of ablation from 70% to 90% [933]. The autonomic response was also seen in another observational study conducted by Pappone et al. [668]. The vagal response was noted in 34.4% of the cases treated by CA and follow up showed an AF freedom in 99% of patients when compared to the group with no vagal response. In our study, all TSA patients had a response to GP stimulation before ablation with an absence of response following ablation. For the patients included in the study, AF recurrence did occur in the TSA group but was less than the CA group with no GP ablation (46% vs 63%). This is likely due to the sub-study being underpowered to detect a significance with the small number of patients. This study was not looking at the impact of TSA on AF recurrence but more to do with the impact of GP ablation on the autonomic nervous system.

GP ablation has historically targeted regions of parasympathetic(vagal) response, but it is important to note that the sympathetic system coexists in the same region. This was shown by the use of cholinergic agonist that slowed the response of increased heart rate in regions with parasympathetic responses. Couselo-Seijas et al. (2019) showed that there is upregulation of cholinergic (sympathetic) response in patients with increase epicardial adipose tissue and subsequent association with increased post-operative incidence of AF[934]. A closer relationship is observed between the parasympathetic and sympathetic system in initiating and maintaining AF. Sympathetic responses cause an increased calcium channel

release from sarcoplasmic reticulum resulting in higher levels of intracellular calcium, which is seen to be related to increased PV firing and triggered activity[935]. In our study, we targeted the parasympathetic response with the knowledge that sympathetic network coexists. The immediate effect of GP ablation on the heart is a higher unopposed sympathetic response leading to an increase in heart rate. The heart rate in our group was not measured immediately before ablation, and therefore, it is difficult to conclude that the response was unopposed. However, there was a significant difference in heart rate between TSA and CA during the first three months, and this effect continued in our patients throughout the follow-up period.

In our study, HRV was blunted in the TSA group compared to CA group, and this difference in the HRV continued throughout the year follow-up. Marinkovi et al. (2020) measured HRV prior to CA in PAF population and after CA with follow up at 1 day, 1 month, 3 months, and 6 monthly after for median follow up of 33 months [912]. They showed a reduction in HRV early post ablation with gradual increase back to baseline in patients with AF recurrence, while reduced HRV persisted for those who maintained SR suggestive of association with parasympathetic suppression. Zdarska et al. in 2017 showed a blunted HRV response in subjects with targeted GP ablation that persisted for the duration of the short to medium term follow up[911]. In our study, there was a gradual increase in the HRV in both CA and TSA associated with a gradual increase in physical activity, although a direct causal relationship during analysis was not recognised. It was surprising to note that there was a significant reduction in physical activity in the TSA group when compared to the CA group throughout the year follow-up. This might be reflective upon comorbidities or complications that could have occurred more readily in the TSA group such as phrenic nerve palsy, prolonged episode

of chest infection, pain from mini-thoracotomy incisions or other symptoms despite having more freedom from AF. The HRV also did not have a direct response to physical activity as was previously thought. There was a dramatic blunted response of HRV to physical activity in the TSA group as compared to the CA group that lasted throughout the year. This might be due to an accelerated heart rate in the TSA group due to the unopposed sympathetic cardiac nervous system following ablation of plexi with parasympathetic innervation. In CA, there is expected to be a higher parasympathetic drive at rest, and with resting bradycardia represented by nocturnal heart rate being lower in CA group (67.7 vs 70.3 bpm, $p<0.01$).

In our study, patients with AF recurrences had a lower HRV than compared to HRV from patients who remained in SR. In patients with AF recurrence, 1-week analysis of HRV before the event would suggest an increase in HRV due to an increase in parasympathetic activity leading to AF recurrence although this was not statistically proven and likely due to small numbers. The increased parasympathetic activity would suggest that there is likely reinnervation of the parasympathetic network in the ablation regions or recruitment of other dormant centres. This phenomenon was described in a canine study conducted by Zhao et al., where after eight weeks of ablation, there is higher parasympathetic innervation, and AF induction was quickly inducible[662]. Patients who had GP ablation endured shorter durations of AF than patients who did not have GP ablation.

7.5 LIMITATIONS

There are a few limitations in this study that are worth mentioning. The medications that can affect HRV were not stopped due to the clinical needs of suppressing atrial or

ventricular ectopics. Although there were no significant differences in the rate-limiting medications, it would have been more conclusive to see the HRV with no interference from medications. The lesion sets were not identical between TSA and CA. However, anatomical locations of the GPs would still be ablated in both approaches, albeit difficult from the endocardial approach. Our study ablated GP anatomically but also with HFS guided approach. Therefore, the impact on HRV can be a combined effect of the PV antral lesions and not HFS guided GP ablation alone. The CASA AF trial was powered for the primary outcome of AF recurrence in 1 year. Therefore, identifying an absolute criterion for HRV to be a predictor for AF recurrence was not possible as there was not a significant cut-off point with receiving operator characteristic (ROC) curve and during univariate logistic regression analysis. This can be due to the study being underpowered to detect small changes in HRV.

7.6 CONCLUSION

To our knowledge, this is the first study to show the effect of GP ablation acutely and over one year. There is a clear impact of GP ablation on the autonomic nervous system that can be measured using HRV. There is a role of autonomic function in the recurrence of AF, with the suggestion of increased parasympathetic activity before AF recurrence resulting in relative bradycardia and increased HRV. Ablation of GP is a safe and efficacious method of autonomic nervous system modification in patients with AF. This study will serve as a platform for a randomised control study to evaluate GP ablation using TSA in addition to maximum lesion sets, including LAA ligation and its impact on AF recurrence.

Chapter 8

CONCLUSION OF THE THESIS

My thesis aimed to investigate a potential new ablation modality of TSA to treat LSPAF. I have quantified LA function using features of TTE such as volume, TDI, strain using speckle tracking and CMR volume assessments. I have investigated the impact of ablation lesion sets in TSA and CA on regional LA wall function. Impact of autonomic nervous system modulation by ablation of GP was investigated by monitoring HRV continuously over one year. LA scar was quantified using a novel automatic segmentation algorithm developed in our centre to make analysis quicker and reproducible.

8.1 CHAPTER 3 – PRIMARY OUTCOMES OF CASA AF RANDOMISED CONTROL TRIAL

TSA showed similar clinical success compared to CA based on results from a randomised control study- CASA AF, although TSA had a higher incidence of adverse events including longer stay in hospital. PVs were isolated in 96% of the TSA group, with bidirectional block in 91% of roof line and only 84% of the inferior line. On the contrary in CA, only 75% had bidirectional block across the MIL, and 77% had bidirectional block across the roof line at the index procedure.

The rate of AF recurrence was higher compared to reported studies due to continuous monitoring by ILR. Sensitivity analysis of the data showed a reduced rate of captured AF with reducing monitoring intervals as seen in 24 hour or 1 week monitoring at 3 monthly

intervals. AF burden reduction of >75% resulting in freedom from AF was seen in > 70% of both ablation groups resulting in improvement in QOL that continued for the entire duration of follow up.

8.2 CHAPTER 4 – LA SIZE AND FUNCTION USING ADVANCED ECHOCARDIOGRAPHY

We showed a significant reduction in the LA volumes and LA reverse remodelling following ablation with both ablation modalities. Reservoir, conduit and contraction function measured by volume and strain improved significantly following both ablation modalities.

Regional impact of LAA exclusion using Atriclip ™ in TSA on the LA function was associated with anterolateral regional wall reduction of contraction measured by TDI without an impact on the overall LA function. Mitral isthmus line did not have detrimental effect on the function at the lateral LA wall or global LA function.

Patients who had AF recurrence had larger LA volumes and reduced LAEF at baseline and at 3months. AF recurrence was seen in patients with reduced reservoir function and conduit function at baseline measured by strain and TDI. At 3 months, reservoir, conduit and contraction function was reduced in the AF recurrence group. LA strain reservoir at baseline and contractile function at 3months were independent predictors for AF recurrence despite being in SR at the time of the scan.

8.3 CHAPTER 5 – LA VOLUME AND REVERSE REMODELLING SEEN USING CMR

CMR was used to investigate cardiac chamber volumes and reverse remodelling following ablation by TSA or CA. LA reverse remodelling was significantly higher in the CA group while RA reverse remodelling was not different between ablation modalities. There was no association of atrial reverse remodelling with maintenance of sinus rhythm contrary to reported literature.

Pulmonary vein diameter did not differ between CA and TSA from baseline to 6 months following ablation. Reduction in PV diameters was seen more often in the CA group compared to the TSA group.

8.4 CHAPTER 6 – LA SCAR MEASURED FROM CMR USING AUTOMATED SEGMENTATION

We developed a novel automatic segmentation and scar quantification algorithm at the Royal Brompton and Harefield NHS trust allowing for pre- and post-ablation quantification of LA scar. However, LA scar did not appear to be predictive of AF recurrence in our population of LSPAF subjected to either CA or TSA.

8.5 CHAPTER 7 – Ganglionic Plexi ablation and assessment using heart rate variability

I explored the impact of autonomic modulation in AF ablation. by measuring standard deviations of the averaged RR intervals recorded by Reveal LINQ™ ILR. The data supported the theory that GP ablation as part of TSA causes blunting of the parasympathetic system shown by a significant reduction in the HRV compared to CA. Gradual increase in HRV was observed in the AF recurrence group likely representing reconnection of the

parasympathetic component of the intrinsic cardiac nervous system.The change in the parasympathetic nervous system provides a useful mechanistic explanation in patients who have AF recurrences despite having isolated lesion sets on redo CA.

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CHAPTER 9

FUTURE CONSIDERATIONS

The CASA-AF randomised control trial is the first randomised control trial in a head-to-head comparison between catheter ablation and thoracoscopic surgical ablation in a population entirely consisting of non-valvular LSPAF and monitored by an ILR following ablation. CASA-AF trial has provided valuable information to fill some of the gaps in knowledge in the management of LSPAF using two ablation strategies and factors associated with failure to maintain sinus rhythm.

The knowledge gained from this thesis between ablation strategies, extensive assessment of LA function, scar assessment, and contribution of the autonomic nervous system in symptomatic LSPAF patients is invaluable. The chapters in the thesis have raised several clinical questions that will benefit from future research enumerated below and expanded further in corresponding paragraphs below:

1. What are the long-term outcomes between CA and TSA in achieving clinical success defined as ≥75% AF/AT burden reduction and improvement in AF symptoms measured by AFEQT score in the randomised CASA AF trial with and without AADs?

2. How can bidirectional blocks be more readily predicted in linear lesions such as the mitral isthmus line? Can this be achieved by using advanced imaging techniques to

identify regions of thinner myocardium to be able to deliver transmural lesions and use of better emerging catheter ablation technologies?

3. Can individual LA volume cut-off be used for each category of AF (PAF, persistent and LSPAF) to predict higher success in AF ablation?

4. Can ablation efficacy improve with the use of current advanced imaging identifying patients with higher LA reservoir and contractile function before ablation?

5. Can reduced LA function derived from advanced echocardiography such as strain be correlated with delayed enhancement identified by CMR after a histopathological validation?

6. Can autonomic dysfunction progression over a few years be measured using non-invasive techniques such as digital plethysmography or by prolonged cardiac monitoring to evaluate a link with the incidence of AF? Can early modification of autonomic nervous system by stellate ganglionic denervation result in the reduction of AF recurrence over long term follow up or be used as an adjunct to catheter ablation?

The primary outcome results from the CASA-AF trial shows TSA to have similar freedom from atrial arrhythmias as CA in managing LSPAF patients with higher rates for adverse events. Therefore, CA could be useful for all types of AF. An interesting theme of the primary outcomes chapter was the improvements in QOL despite high rates of atrial

arrhythmias. There is a need to investigate why patients still felt much better despite AF recurrence. Are improving symptoms a placebo effect of undergoing an ablation procedure, or is there a real change in physiology that can be quantitatively measured by digital plethysmography? Long term outcomes from a randomised control trial in managing LSPAF patients has not been performed, and there is an unmet need to know if these ablation strategies have a role in achieving clinical success along with symptoms improvement over an extended period. The ILRs implanted in the CASA-AF trial will provide this information for three years, and the information derived from this will be invaluable not only for physicians but also for healthcare systems striving to include cost-effective treatments. The CASA-AF trial or another trial of similar design with extended follow up will also allow patients with symptomatic recurrence of AF to be offered a redo CA. Redo CA over longer follow up will allow investigators to understand the mechanism of AF recurrence following CA and TSA. Understanding new mechanisms in promoting AF recurrence will allow for the development of specific technologies that are not available in the current management strategies. Case reports have shown independent epicardial and endocardial LA activations that might be a proposed mechanism of AF recurrence and require to be further investigated in TSA or CA patients.

The rate of pulmonary vein isolation at index procedure was greater than 95% of the patients in both CA and TSA, while linear lesion block was between 70-80% in both CA and TSA. The lack of block was particularly noticeable in the mitral isthmus line and is likely related to anatomical variations in thickness. With the advancement in safe, quick and cheaper imaging techniques it might be worth investigating whether pre-ablation imaging looking at the feasibility of linear lesions can identify regions where ablation is likely to

achieve transmural blocks particularly in mitral isthmus line and roofline and can be predetermined before ablation. Roofline bidirectional block is particularly challenging due to lesions created by catheter orientation pointing straight at the roof and due to significant respiratory movements resulting in large variations of contact force resulting in acute oedema without transmural lesions. Mitral isthmus thickness is very variable depending upon the choice of either anterior, lateral or posterior isthmus line and can be determined by preprocedural CT scan. More research is required in developing catheters that can accommodate respiratory motion and have a maximum limiter in contact force that can be applied by introducing a spring mechanism that might only allow a maximum of 20grams of force when activated.

Cardiac size and function appear to be the strongest predictor for AF recurrence following ablation. LAmax volume has been studied well in the PAF and persistent groups of AF but not in LSPAF. Our data shows a smaller cut-off of LA maximum volume of 42ml/m2 than seen for PAF of >55ml/m^2 in reported literature used as a predictor for AF recurrence. Future research needs to be done based on reviewing ablation strategies to show higher success based on categorised LA size for individual groups of AF categories. For example, the research could recruit patients with PAF and LAmax volume <55ml/m^2, persistent AF with LAmax of <50ml/m^2 and LSPAF with LAmax <40ml/m^2 to see if there is a nonsignificant difference in freedom from AF recurrence following ablation in symptomatic patients.

LA function derived by volume or strain represented by reservoir and contraction function was more sensitive in predicting AF recurrence following ablation. Further investigations are required to improve selection for AF ablation based on stratification by LA function

(reservoir and contraction) instead of LA volume. Patients are convinced to choose rate control strategy based on volume, whereas it might be possible that patients with larger LA size with higher reservoir and contractile function have not yet developed irreversible LA remodelling represented by fibrosis. Measuring LA function instead of volume would potentially change the patient selection criterion in the majority of the heart rhythm programs. Some advanced EP centres are using CMR and CT based scar detection as a mean to select patients and also to inform patient and physician of realistic expectations that might be achieved with UTAH stage IV as opposed to UTAH stage I. However, this is very time and resource consuming. All patients have a TTE as part of cardiac structure and functional assessment in AF management. Therefore, reduced reservoir and contractile function can reflect an underlying fibrotic process, and in these patients, an adequate rate control strategy is likely to be more efficacious in controlling AF related symptoms long-term.

Low reservoir and contractile function are reported in previous studies to be associated with fibrosis or delayed enhancement, as seen in CMR. However, there are no histological validation studies for both delayed enhancement or reservoir and contractile strain function. In our study, there was an increase in scar similar between CA and TSA, without any real differences in scar between AF and SR groups. Increasing LA scar quantified by CMR in our study did not show a relationship to AF recurrence. Moreover, there was a trend of higher LA scar at baseline in the SR group. Therefore, there is a dire need of research to correlate reduced LA function using advanced imaging tools such as strain with delayed enhancement on MRI and to validate the scar parameters with histology. Currently, a lot of infrastructure and resources are being used in deep learning and artificial intelligence to

develop automated methods of delayed enhancement quantification from CMR. However, without histological validation, the delayed enhancement from the manual or automated process has not proven to be very accurate. It might result in the inefficient use of resources and significant variability in the success of ablation.

The effect of ganglionic plexi (GP) ablation was measured for the first time in a randomised control study and raised some important questions regarding the influence of autonomic dysfunction in AF initiation and maintenance. Although there were no differences between TSA and CA from freedom from atrial arrhythmias, there was a clear difference in the impact of GP ablation targeted in TSA measured by HRV. The difference in autonomic function represented by HRV raises the possibility of GP ablation having a role in the rate of AF recurrence without knowing whether the effect to be antiarrhythmic or proarrhythmic. Even though GP ablation alone and in combination with PVI has been studied in the past, the autonomic imbalance was not measured in previous studies, and it is unclear whether autonomic upregulation after a period in follow-up is responsible for AF recurrence in the TSA group or gaps in lesion sets? The use of non-invasive methods such as extended cardiac monitoring or by digital plethysmography over the years in patients with risk of AF due to comorbidities can help in understanding the natural history of the role of the autonomic nervous system in the new onset of AF or with the progression of PAF to persistent AF. Identifying symptomatic patients with a high imbalance of their autonomic nervous system can lead to investigations that aim to determine if interventions such as stellate ganglion block or surgical denervation in addition to PV isolation can improve clinical success.

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