CLINICAL PROFILE AND OUTCOMES OF PATIENTS UNDERGOING ATRIAL FLUTTER ABLATION AT A TERTIARY CARE CENTER IN INDIA: A RETROSPECTIVE COHORT STUDY

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A THESIS SUBMITTED BY

DR. NAYANI BALBIR SINGH MAKKAR

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR

THE AWARD OF

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No part of this thesis has been submitted for the award of any other degree or diploma before this date.



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Clearance was obtained from Institutional Ethics Committee for conduct of this study.

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Submitted by

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-Nayani Makkar

LIST OF ABBREVIATIONS

AF	Atrial fibrillation
AFl	Atrial Flutter
ASD	Atrial Septal Defect
ARIC	Athesclerotic Risk in Communities
AVR	Aortic Valve Replacement
CTI	Cavo-Tricuspid Isthmus
EF	Ejection Fraction
FHS	Framingham Heart Study
IQR	Inter-Quartile Range
LA	Left Atrium
LV	Left Ventricle
MR	Mitral Regurgitation
ROC	Receiver Operating Characteristics
RF	Radiofrequency
SD	Standard Deviation
TOF	Tetralogy of Fallot
TR	Tricuspid Regurgitation

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1. ABSTRACT

A higher prevalence of operated structural heart disease in Indian patients with atrial flutter (AFl) may impact the clinical demographics and procedural outcomes of radiofrequency (RF) ablation in this population.

We retrospectively analyzed clinical, procedural and outcome data from a cohort of patients who had undergone RF ablation for macro re-entrant atrial tachycardia.

100 patients underwent ablation for a macro re-entrant atrial tachycardia from 2016 to 2023. These patients were predominantly male (66%) with a mean age at procedure of 50.3 ± 28.4 years, 41% patients had undergone cardiac surgery prior to AFl ablation. The patients were followed up for a median of 2 years. Non-cardiac comorbidities were common in these patients with diabetes in 14%, hypertension in 15%, dyslipidemia in 10% and sleep apnea in 4%. 60% of patients had co-morbid structural heart disease, with the commonest being a repaired secundum atrial septal defect (23 patients), 17 patients had co-morbid coronary artery disease, 20 patients had left ventricular systolic dysfunction, 13% patients had atrial fibrillation (AF) prior to ablation and 19% patients developed AF subsequently. 76% of patients had cavo-tricuspid isthmus dependent AFl. Of the remainder, 20 (83%) had macro re-entrant right atrial tachycardia with half of these patients having scar related re-entry from a right atriotomy. Acute success (the presence of bidirectional isthmus block and non-inducibility of tachycardia) was obtained in 95% of patients, with significantly (p=0.08) more acute failures in patients with atypical (4 patients, 12.5%) than those with typical (2 patients, 2.6%) AFl. 8 patients with acute success had a recurrent atrial flutter and 13 patients developed symptomatic bradycardia on follow up.

The presence of atypical flutter is the single most important predictor for procedural failure during AFl ablation. The clinical profile of Indian patients undergoing ablation for AFl differs from data from prior western studies, including a younger age at onset, lower rates of comorbid AF, and a higher propensity for co-morbid structural heart disease.

2. SYNOPSIS

Background & Objectives: Macro-reentrant atrial tachyarrhythmias, more colloquially termed atrial flutter (AFl), represent an important cause of morbidity from arrhythmia with an estimated prevalence of 88 per 100,000 population in western studies. While it is not uncommon to detect 'typical' atrial flutter in the absence of structural heart disease, two conditions notably predispose to AFl influencing epidemiology. The first is the presence of structural heart disease, particularly following surgical repair necessitating atriotomy. Furthermore, the natural history of atrial flutter had been shown to be linked with the development of atrial fibrillation. We hypothesized that the demographic characteristics and predictors of response to therapy with radiofrequency ablation would differ from available global data secondary to a younger age at presentation and a higher prevalence of congenital and structural heart disease. The primary objective of the study was to determine predictors of medium-term freedom from tachyarrhythmia following radiofrequency ablation of atrial flutter. Secondary objectives were to define the clinical, electrocardiographic and echocardiographic characteristics of patients presenting with AFl and to analyze the prevalence of comorbid structural heart disease, atrial fibrillation and sinus node dysfunction in an unselected population of AFl patients.

Methods: Single-centre retrospective study of a historical cohort of patients diagnosed intra-procedurally to have atrial flutter (macro-reentrant atrial tachycardia) who underwent radio-frequency ablation from January 2016 to July 2023. Some of these patients had additional tachyarrhythmias necessitating ablation. Baseline data at initial presentation and procedural details were collected from the electronic medical record system. Statistical analysis was performed to assess association and correlation between predictor variables and outcome and a multivariate logistical regression model was subsequently created to identify predictors of successful AFl ablation over follow up.

Results: 100 patients underwent ablation for a macro re-entrant atrial tachycardia from 2016 to 2023. These patients were predominantly male (66%) with a mean age at procedure of 50.3 ± 28.4 years, 41% patients had undergone cardiac surgery prior to AFl ablation. The patients were followed up for a median of 2 years. Non-cardiac comorbidities were common in these patients with diabetes in 14%, hypertension in 15%, dyslipidemia in 10% and sleep apnea in 4%. 60% of patients had co-morbid structural heart disease, with the commonest being a repaired secundum atrial septal defect (23 patients), 17 patients had co-morbid coronary artery disease, 20 patients had left ventricular systolic dysfunction, 13% patients had atrial fibrillation (AF) prior to ablation and 19% patients developed AF subsequently. 76% of patients had cavo-tricuspid isthmus dependent AFl. Of the remainder, 20 (83%) had macro re-entrant right atrial tachycardia with half of these patients having scar related re-entry from a right atriotomy. Acute success (the presence of bidirectional isthmus block and non-inducibility of tachycardia) was obtained in 95% of patients, with significantly (p=0.008) more acute failures in patients with atypical (4 patients, 12.5%) than those with typical (1 patients, 1.3%) AFl. 8 patients with acute success had a recurrent atrial flutter and 13 patients developed symptomatic bradycardia on follow up.

Conclusions: The presence of atypical flutter is the single most important predictor for procedural failure during AFl ablation. The clinical profile of Indian patients undergoing ablation for AFl differs from data from prior western studies, including a younger age at onset, lower rates of comorbid AF, and a higher propensity for co-morbid structural heart disease.

3. INTRODUCTION

Macro-reentrant atrial tachyarrhythmias, more colloquially termed atrial flutter (AFl), represent an important cause of morbidity from arrhythmia with an estimated prevalence of 88 per 100,000 population in western studies. With a clinical risk profile that mimics that described for incident atrial fibrillation, flutter tends to occur predominantly in older populations, with a significant burden of comorbid risk factors including hypertension, pulmonary disease, obesity and dyslipidaemia. The arrhythmia predisposes to a significant risk of clinical deterioration in patients with and without structural heart disease. It has been shown to herald atrial fibrillation, symptomatic heart failure and stroke.

In contrast to its epidemiology, the management of atrial flutter differs significantly from atrial fibrillation primarily in that a rhythm control strategy with catheter ablation has been demonstrated to have durable, good success rates making this the default strategy for the management of the majority of patients.

We hypothesized that the epidemiology of Indian patients with atrial flutter would differ substantially from their western counterparts driven by a higher prevalence of structural heart disease. Consequently, the acute success and procedural durability of catheter ablation in these patients may also be lower than anticipated. We thus designed a retrospective study to assess the medium term outcomes of unselected patients undergoing catheter ablation for atrial flutter at a tertiary care centre in Southern India.

4. REVIEW OF LITERATURE

4.1 Atrial Flutter: Terms and Definitions

Macro-reentrant atrial tachyarrhythmias, more informally termed atrial flutter (AFl), represent an important cause of morbidity from arrhythmia with an estimated prevalence of 88 per 100,000 population in western studies, representing roughly 15% of the burden of supra-ventricular tachyarrhythmias[1]. Conventionally, a macro-reentrant circuit in the atria is defined as reentry around an anatomical or functional obstacle, confirmed if exact return pauses are recorded from at least two atrial pacing sites separated by at least 2 cm (i.e. two points spatially separated by at least 2 cm are part of the re-entrant circuit)[2]. As is essential for all re-entrant arrhythmias, all atrial flutter circuits are characterized by the presence of an anatomical or functional obstacle to conduction, and usually a zone of altered conduction in the region of an electrically protected isthmus[3,4] .

Broadly, these arrhythmias may be classified based on the dependence of the tachycardia circuit on cavo-tricuspid isthmus (CTI) conduction. CTI-dependent atrial flutter may thus include counterclockwise and counterclockwise AFl, lower loop re-entry and intra-isthmus re-entry[3,4]. By convention, CTI- dependent counterclokwise and clockwise AFl are collectively referred to as ‘Typical Atrial Flutter’ (older literature will frequently establish clockwise CTI-dependent flutter as ‘Reverse Typical’). These typical flutters account for the predominance of paroxysmal atrial flutter and the majority of atrial flutter in structurally normal hearts. All remaining macro-reentrant atrial tachycardias are colloquially grouped as ‘atypical’ atrial flutter.

4.2 Epidemiology and natural history

In larger epidemiological data including that gathered from the Framingham Heart Study (FHS)[5] and the Atherosclerotic risk in Communities (ARIC Study)[6], atrial flutter is frequently clubbed in estimates with atrial fibrillation. However, both arrhythmias have significant clinical distinctions perhaps most importantly the amenability for atrial flutter to be durably treated with catheter ablation. A post-hoc analysis of the FHS [7] found flutter to occur at a mean age of 72 years with a male preponderance. The study found higher rates of incident flutter in patients with a history of smoking, myocardial infarction and heart failure. Incident flutter was associated with adverse clinical outcomes over follow up including an increased risk of incident atrial fibrillation, myocardial infarction, heart failure, stroke and mortality.

Like atrial fibrillation, atrial flutter appears to be a disease associated with aging and affluence. Analysed data from the Global Burden of Diseases study from 1990-2019[8], demonstrated that the incidence of atrial flutter more than doubled in this period with dominant increments in the lower-middle income and upper middle income countries. Disease prevalence, however, continued to be higher in high income countries reflecting the impact of these factors on the disease. The two most important modifiable risk factors identified in this study included a high systolic blood pressure and a high body mass index.

4.3 Management of the patient with atrial flutter

Acutely, therapeutic options for the management of atrial flutter include a strategy for rate control or one for the restoration of sinus rhythm. When pursuing a strategy for ventricular rate control, it is notable that these arrhythmias are notoriously more difficult to target than atrial fibrillation given a slower, more regular atrial rate[9]. Reversion to sinus rhythm then becomes the default strategy in the majority of cases[10]. In the short term this may be achieved by drugs or direct current cardioversion. When considering a strategy of rhythm reversion meticulous attention to optimal anti-coagulation is essential.

Once acute conversion to sinus rhythm has been attained, the maintenance of sinus rhythm becomes important. The success of drug therapy in initiating and sustaining sinus rhythm is limited. The most effective anti-arrhythmic drug in this subgroup appears to be dofetilide but even that is met with a one-year failure rate of 35%[11]. This is in addition to the systemic toxicity and risk for pro-arrhythmia conferred by the majority of anti-arrhythmic drugs.

Catheter ablation, in contrast, has been shown to have high long-term success rates (92% after a single procedure, 97% after multiple procedures) and a low risk for serious complications. It has been shown to improve quality of life, reduce the risk for thromboembolism and eliminate the need for long-term anticoagulation and anti-arrhythmic drug therapy reducing significantly the morbidity conferred by this arrhythmia[10].

5. STUDY RATIONALE

- Macro re-entrant atrial tachyarrhythmias contribute to a significant burden of morbidity in patients with and without underlying structural heart disease. Radiofrequency ablation has been shown to have a high rate of procedural success in these patients and is the mainstay of therapy in patients with ongoing o recurrent symptomatic arrhythmia.

- There remains a paucity of data on Indian patients presenting with atrial flutter and their clinical and demographic characteristics.

- Furthermore, predictors of acute success and long term durability of atrial flutter ablation remains poorly defined in this context.

- We designed this study to investigate the clinical, epidemiological and demographic characteristics of the Indian patient with atrial flutter and to analyse the predictors of a sustained successful response to therapy with atrial fibrillation ablation.

6. MATERIALS AND METHODS

The study is a retrospective cohort study designed to be conducted at a single tertiary care referral centre in Southern India. The study included all patients who underwent atrial flutter ablation at the Department of Cardiology, Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram during the study period from January 2016 to July 2023.

The primary objective was to define the predictors of acute procedural success and arrhythmia free survival over medium term follow up in patients undergoing radiofrequency catheter ablation for atrial flutter (macro re-entrant atrial tachycardia). Secondary objectives were to define the clinical, demographic, electrocardiographic and echocardiographic characteristics of the Indian patients presenting with atrial flutter, to assess the prevalence and clinical impact of comorbid tachy- (atrial fibrillation, in particular) and brady- (especially sinus node dysfunction) arrhythmias in this population, and to study the anatomical patterns of and techniques for ablation in atypical atrial flutter and those with congenital or structural heart diseases.

We included for analysis all patients older than 10 years of age who had undergo radiofrequency ablation for atrial flutter over the study period. Patients with an unclear or ambiguous electrophysiological diagnosis, with missing baseline clinical data, with less than six months of follow-up post-procedurally and those with non-inducible and non-documented atrial flutter who had undergone cavotricuspid isthmus ablation for a different indication (e.g.: during the pulmonary vein isolation procedure) were excluded from further analysis.

On retrospective review, all available electrophysiological records for patients undergoing electrophysiology study or ablation procedures for atrial tachyarrhythmias over the study period were identified. Electronic medical records were accessed for each of these patients and subsequent details accordingly collected. Analysed clinical data included patient demographic characteristics including age at presentation and gender; presence of non-cardiac comorbid illnesses including but not limited to diabetes, hypertension, dyslipidaemia, pulmonary disease, obstructive sleep apnoea, chronic kidney disease and anaemia; prevalence of coexistent cardiac comorbidities in particular coronary artery disease, ventricular dysfunction, and repaired or unrepaired congenital, valvular or structural heart disease; and baseline electrocardiographic and echocardiographic parameters. In patients with repaired congenital or structural heart disease, the time since surgical intervention and key details of the surgical procedure (prosthesis site and size, access incision) were also gathered for analysis. Data on the pre-ablative management of atrial flutter including prior attempts at direct current cardioversion, the use of anti-arrhythmic drug therapy and prior ablation procedures were also collected. Procedural details collected included the classification of the flutter mechanism (typical and atypical as defined above), anatomical localization of atrial scar and the flutter circuit, anatomical localization of isthmuses and zones of slow conduction, number and sites of lesion sets delivered, details of concomitant pulmonary vein isolation, if undertaken, and details of any procedural complications recorded. Follow up details including details of symptomatic recurrences, incident non-flutter tachyarrhythmias necessitating therapy and incident bradycardia events mandating pacing at 6 months, one year and two years were recorded, as were any adverse patient events (e.g.: heart failure hospitalization, mortality) and echocardiographic data at follow up where available.

The project received institutional ethical clearance as a component of the continuation of a prior established atrial flutter registry. As the study was a retrospective, anonymized review of records, individual patient consent was not sought.

Statistical analysis was performed using an SPSS software package[12]. Associations were assessed between flutter classification and demographic variables using a chi square test for categorical independent variables and an unpaired sample T-test for continuous independent variables. A similar protocol was followed to assess univariate relationships with acute procedural outcome. The data thus collected was utilized to select variables for a multivariate logistic regression model to predict acute procedural outcome. Correlation analysis was used to assess the strength of correlation between electrocardiographic and final electrophysiological diagnosis and receiver operating characteristics (ROC) analysis was used to assess the diagnostic accuracy of this test. Finally Kaplan- Meier analysis was performed to compare tachycardia free survival in patients with typical and those with atypical atrial flutter.

7. RESULTS

Retrospective record review identified 123 patients who underwent atrial flutter ablation during the study period from January 2016 to July 2023. 100 of these patients satisfied the pre-specified inclusion and exclusion criteria. As specified above, electronic medical records for these patients were accessed to ascertain details regarding the clinical presentation, baseline electrocardiographic, echocardiographic and laboratory parameters, details of the ablation procedure, and subsequent clinical follow up details. Following data gathered during electrophysiology study, 76 of our patients (76%) were determined to have typical (CTI dependent clockwise or counterclockwise flutter, with the remainder having atypical flutter. 4 patients of the atypical flutter subgroup had left atrial macro re-entrant atrial tachycardia. The patients were followed up post-procedurally for a median duration of 2 years.

7.1 Clinical characteristics and Demography

The demographic and clinical characteristics of the study population are presented in Figure 7.1-7.2 and Table 7.1.

Our patients had a mean age of 50.3 ± 28.4 years with an age range of 15-76 years. The ages were well matched between patients with typical and those with atypical flutter. There was a slight preponderance of male patients (N=66, 66%), which was not significantly different in both groups.

Coexistent co-morbid diseases including type 2 diabetes (14% patients), hypertension (15% patients), dyslipidemia (10% patients), and coronary artery disease (17% patients) had a lower than anticipated prevalence. The prevalence of non-cardiac comorbid illnesses was not significantly different in the two groups. Significantly more patients in the atypical flutter

group had a diagnosed structural heart disease and had undergone prior cardiac surgery. These results are discussed in greater detail in subsequent sections.

Our findings contrast with available data from western literature[13,14] with a younger age at first diagnosis and a lower prevalence of conventional cardiac risk factors including hypertension, hyperlipidemia and chronic pulmonary disease. A distinct phenotype with a preponderance of patients with repaired and unrepaired congenital and valvular heart disease is likely driving these differences in epidemiological characteristics.

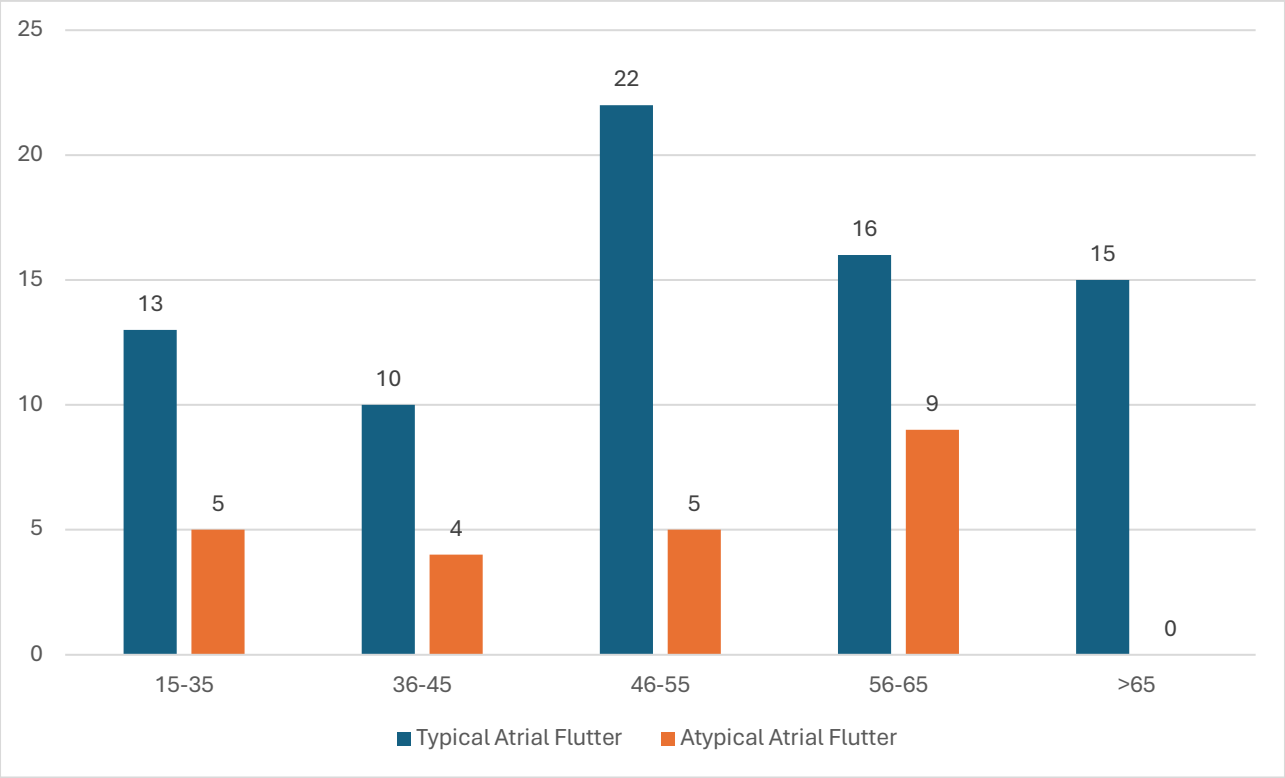


Figure 7.1: Age distribution of our study population

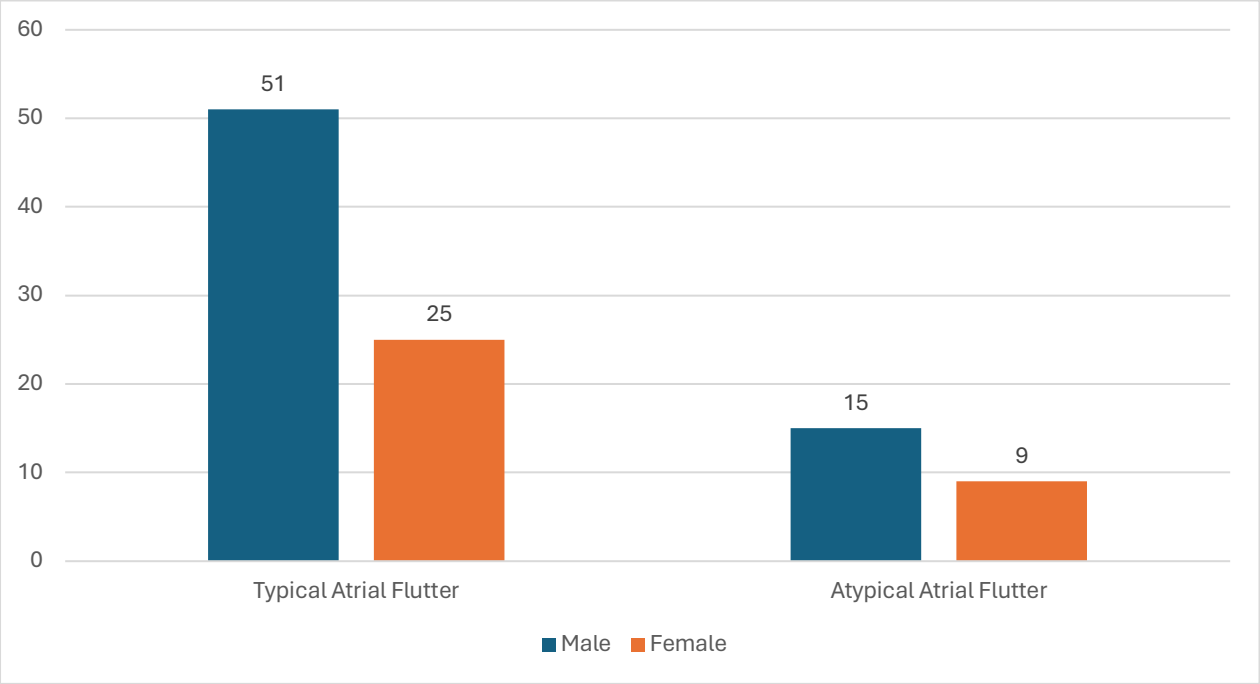


Figure 7.2: Gender distribution of our study population

Variables	All Patients	CTI Dependent Flutter (N=76)	Atypical Flutter (N=24)	P-value
Demographic and Clinical Characteristics				
Age (years) (Mean ± SD)	50.3 ± 28.4	50.8 ± 30.2	49.1 ±21.8	0.316
Male Sex Number (%)	66(66%)	51 (67.1%)	15 (62.5%)	0.596
Comorbid Diseases				
Hypertension	15 (15%)	14 (18.4%)	1 (4.2%)	0.224
Diabetes	14 (14%)	13 (17.1%)	1 (4.2%)	0.146
Dyslipidemia	10 (10%)	8(10.5%)	2 (8.3%)	0.591
Obstructive Sleep Apnea	4 (4%)	4 (5.2%)	0	0.518
Coronary Artery Disease	17 (17%)	14 (18.4%)	3 (12.5%)	0.743
Atrial Fibrillation	13 (13%)	10 (13.2%)	3 (12.5%)	0.121
Prior Cardiac Surgery	41 (41%)	25 (32.8%)	16 (66.7%)	**<0.001**
Structural Heart Disease	60 (60%)	40 (52.6%)	20 (83.3%)	**0.002**
Prior Attempt at Rhythm Version (Cardioversion, Drugs or Ablation)	52 (52%)	37 (50%)	15 (62.5%)	0.562

Table 7.1: Clinical and Demographic Characteristics of the Study Population

7.2 Structural Heart Disease and Prior Cardiac Surgery

60 of our study patients (60%) had established structural heart disease. This group included 40 patients (52.63%) with typical flutter and 20 (83.3%) patients with atypical flutter. 2 of 5 (40%) patients with left atrial flutter had prevalent structural heart disease.

The two commonest co-morbid heart conditions were a repaired secundum atrial septal defect (23 patients, 38.3%) with the majority (20 patients) having undergone surgical repair and coronary artery disease with ventricular dysfunction (17 patients, 28.3%) (three of these patients had undergone prior coronary artery bypass grafting).

41 patients (41%) had undergone cardiac surgery prior to their ablation procedure. The median time to clinical presentation after last cardiac surgical intervention was 18 years (Interquartile range (IQR) 12-32.25 years). The most common of these surgeries was surgical closure of secundum (20 patients, 48.7%) or sinus venosus (10 patients, 24.39%) atrial septal defects (ASD). The earliest post-operative presentation was after one year of atrio-ventricular canal defect (complete, balanced) repair and the latest presentation was 41 years following a sinus venosus ASD repair. As we will discuss subsequently, both right atrial dilatation and surgical atriotomy scars contributed to the flutter circuits in these post-operative patients.

Notably absent are patients with established rheumatic heart disease. This represents a likely selection bias and underrepresentation of this population in patients selected for ablation given the historically poor outcomes in this subset. The details of the structural heart diseases are presented in Figure 7.3 and Table 7.2**.**

Variables	All Patients	CTI Dependent Flutter (N=76)	Atypical Flutter (N=24)	P-value
Prevalent Structural Heart Disease (N,%)	60 (60%)	40 (52.63%)	20 (83.3%)	**0.002**
Comorbid Diseases (N,%)				
Repaired Ostium Secundum Atrial Septal Defect	23 (38.3%)	13 (32.5%)	10 (50%)	
Coronary Artery Disease with Left Ventricular Dysfunction	17 (28.3%)	13 (32.5%)	4(20%)	
Repaired Sinus Venous Atrial Septal Defect	10 (25%)	8 (20%)	2 (10%)	
Repaired Total Anomalous Pulmonary Venous Connection	3 (5%)	1 (2.5%)	2 (10%)	
Repaired Tetralogy of Fallot (Or TOF Physiological Variants)	2 (3.3%)	2 (5%)	0	
Corrected Aortic Stenosis (Post-transcatheter or surgical AVR)	2 (3.3%)	2 (5%)	0	
Repaired Atrioventricular Canal Defect	2 (3.3%)	1 (2.5%)	1 (5%)	
Hypertrophic Cardiomyopathy	1 (1.7%)	1 (2.5%)	0	
Cardiac Sarcoidosis	1 (1.7%)	0	1 (5%)	
Prior Cardiac Surgery	41 (41%)	25 (62.5%)	16 (20%)	**<0.001**
Elapsed duration since prior cardiac surgery (Median (IQR)) (years)	18 (12-32.25)	16 (11-24)	29 (17-34.5)	0.697

Table 7.2: Prevalence and Nature of Structural Heart Disease (TOF: Tetralogy of Fallot; AVR: Aortic Valve Replacement)

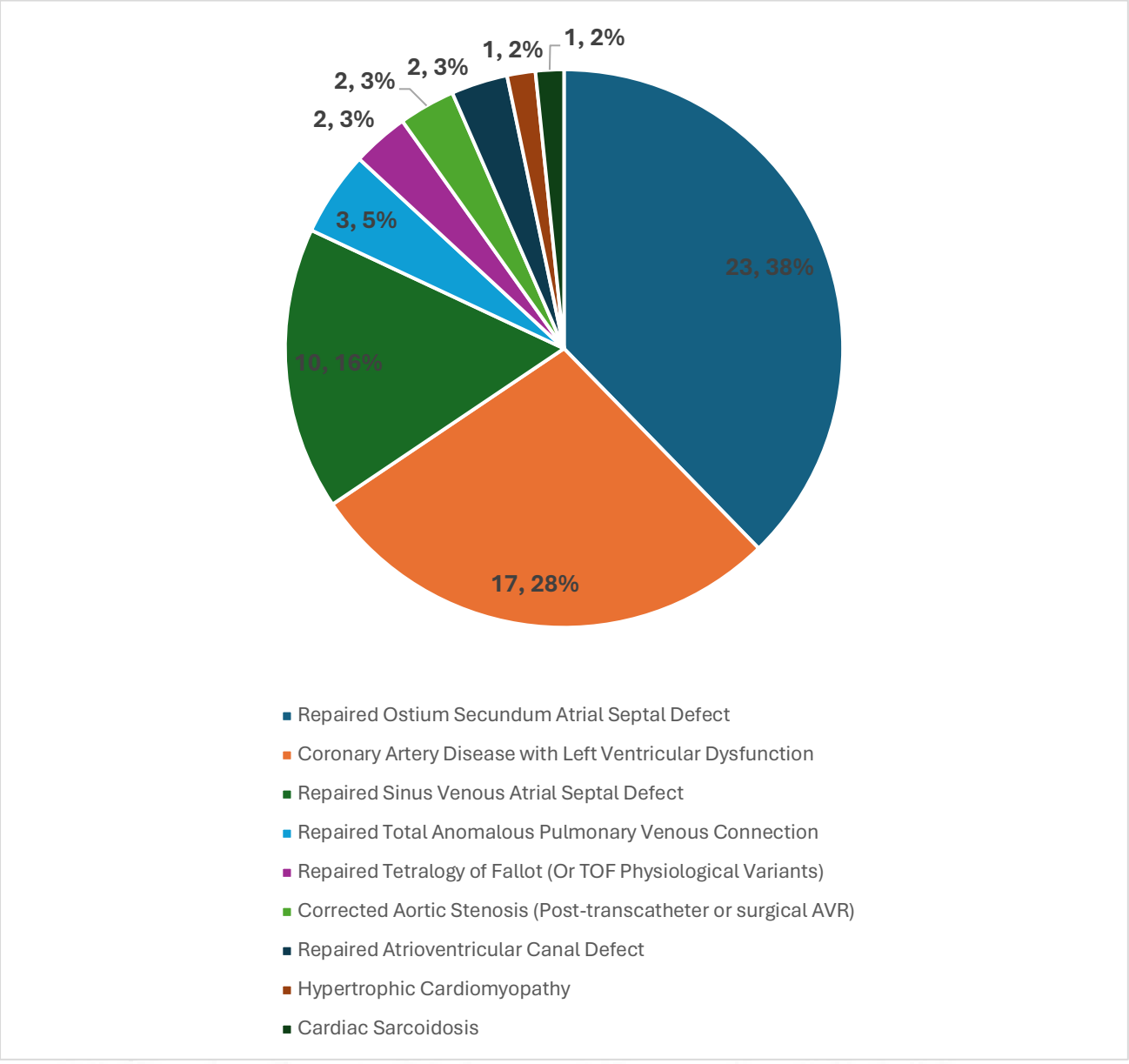


Figure 7.3: Prevalent Structural Heart Diseases in the Flutter Population

7.3 Electrocardiography and Echocardiography

Electrocardiogram during tachycardia was used to classify the atrial flutter into typical (CTI dependent counter-clockwise or clockwise), atypical and left atrial flutter. The electrocardiographic diagnosis correlated well with the final diagnosis following electrophysiology study (r=0.582, p=0.005). 15 electrocardiograms were incorrectly diagnosed, typical flutter electrocardiograms were less frequently mislabelled as atypical or left atrial flutter (N=4, 5.26%) than the inverse (N= 11, 42.3%). Basal electrocardiography was a good diagnostic test with an area under the receiver operating characteristics curve of 0.757 (95% Confidence Interval: 0.625-0.885)(P-value < 0.001)(Figure 7.4). The overall sensitivity of the test was 94.7% and specificity was 79.2%.

The mean left ventricular ejection fraction was 59.9 ± 22.11%, which was not significantly different in the groups with typical and atypical flutter. 21 patients (21%) had left ventricular systolic function at baseline assessment (Defined as a an ejection fraction <= 50%). Follow up echocardiographic data is available for 14 of these patients. Left ventricular systolic function improved to >=50% in all but 3 patients (i.e. recovered ejection fraction in 11 (78.6%) patients. This likely represents a subgroup of patients with tachycardia induced cardiomyopathy. Other echocardiographic parameters including left atrial and ventricular dimensions, prevalence of valvular abnormalities and prevalent diastolic dysfunction was well matched within the two subgroups.

The echocardiographic data is presented in Table 7.3.

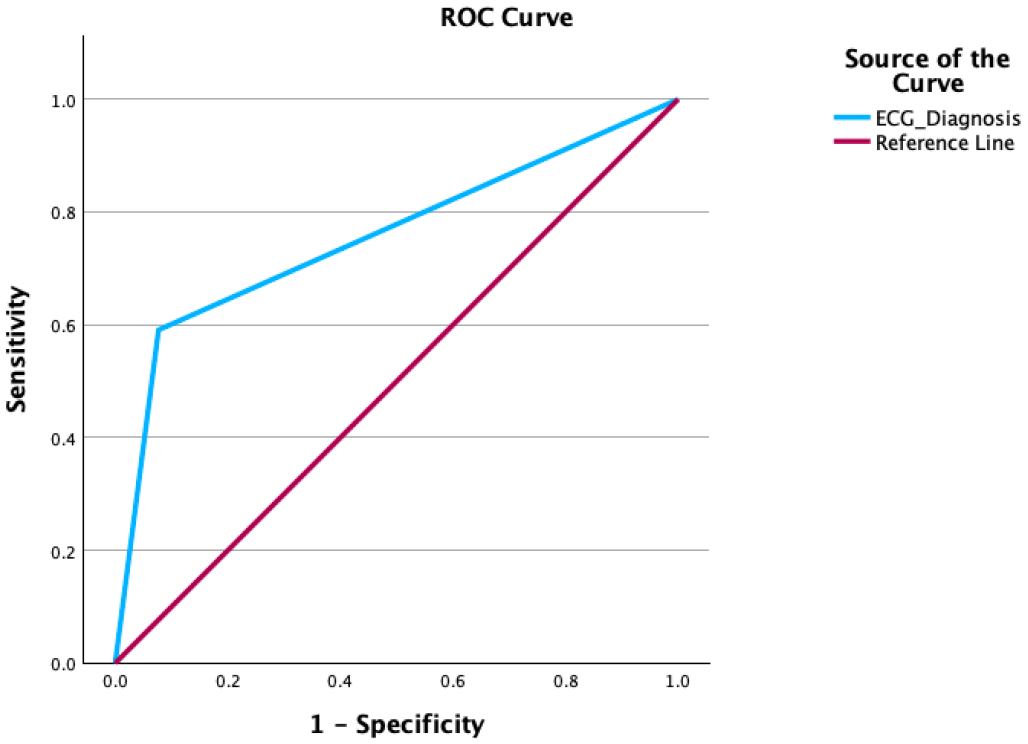


Figure 7.4: Receiver Operating Characteristics Curve for the Diagnostic Suitability of Baseline Electrocardiographic predicting the Final Electrocardiographic Diagnosis

Variables	All Patients	CTI Dependent Flutter (N=76)	Atypical Flutter (N=24)	P-value
Echocardiographic Variables				
Left Ventricular Ejection Fraction (%) (Mean ± SD)	59.9 ± 22.1	61.1 ± 22.4	57.1 ± 20.5	0.349
Left Atrial Size (mm)	37.4 ± 13.7	36.9 ± 13.4	38.8 ± 14.5	0.510
Left Ventricular Internal Diastolic Dimension (mm) (Mean ± SD)	45.6 ± 13.5	45.3 ± 12.8	46.3 ± 16.1	0.687
Left Ventricular Internal Systolic Dimension (mm) (Mean ± SD)	30.4 ± 13.5	29.8 ± 12.8	31.7 ± 15.4	0.741
Left Ventricular Hypertrophy (N)(%)	7(7%)	7(17.5%)	0	0.155
Left Ventricular Diastolic Dysfunction (N) (%)	5 (5%)	5 (12.5%)	0	0.268
Mitral Valve Abnormality (Structurally abnormal or prosthetic valve/Moderate to Severe Regurgitation) (N) (%)	7 (7%)	4 (10%)	3 (15%)	0.177
Tricuspid Valve Abnormality (Structurally abnormal or prosthetic valve/Moderate to Severe Regurgitation) (N) (%)	4 (4%)	3 (7.5%)	1 (5%)	0.636

Table 7.3: Echocardiographic characteristics of the study population

7.4 Pre-Ablative Management of Atrial Flutter

A strategy of upfront ablation at first clinical presentation to our centre was preferred for most patients with a median duration from first assessment to ablation of 3 months (IQR 1 month -1 year). However, alternate rhythm reversion strategies were attempted in half of the study population (50 patients; 50%) prior to selection for ablation. This included Direct Current (DC) cardioversion in 28 patients (the median number of undertaken DC cardioversions was 1 (Range 1-3)), drug therapy in all 50 patients (The most commonly used drug was amiodarone in 43 (86%) patients) and prior radiofrequency ablation in 10 patients. All patients had symptomatic recurrences after one or more of the above therapies and were hence considered candidates for radiofrequency ablation.

At the time of diagnosis, 13 patients (13%) had documented atrial fibrillation in addition to atrial flutter. This included 10 patients (13.2%) in the typical atrial flutter subgroup and 3 patients (15%) in the atypical flutter subgroup. 8 of these patients underwent radiofrequency (5 patients) or cryoballoon (3 patients) pulmonary vein isolation in the same session as atrial flutter ablation.

The utilized rhythm control strategies prior to ablation are depicted in Figure 7.5.

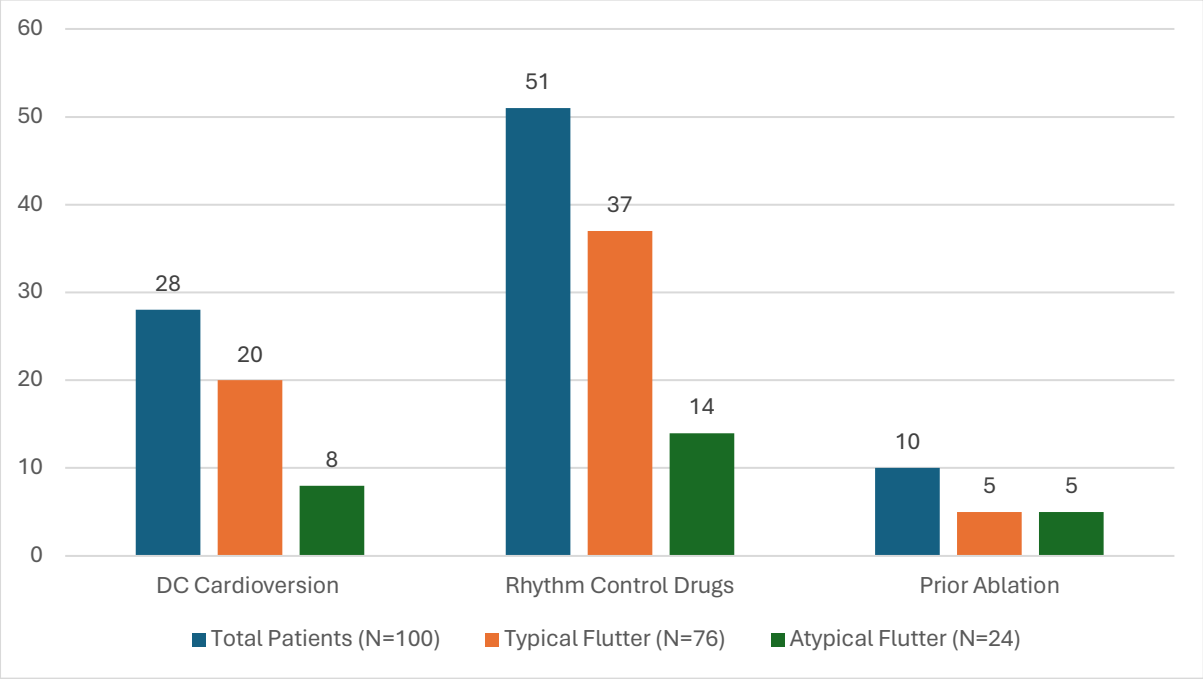


Figure 7.5: Strategies for Rhythm Reversion Prior to Ablation

7.5 Procedural Course and Acute Procedural Outcomes

All procedures were performed under three-dimensional electroanatomical impedance-based mapping using an Ensite Precision™ (Abbott, St. Paul, Minnesota) mapping system. In patients whom tachycardia could be induced at baseline, voltage and activation mapping was performed during ongoing tachycardia (in addition to voltage mapping in sinus rhythm, if feasible) to determine the tachycardia circuitry and atrial scar burden. Subsequently, entrainment mapping was performed for all patients to validate the mechanism suggested by the activation map during tachycardia.

Radiofrequency ablation was performed using a 4 mm-tip deflectable ablation catheter with standard power settings and irrigation flow rates[15]. Additional hardware including deflectable sheaths, intracardiac echocardiography catheters and multipolar mapping catheters were selected per the choice of the operator. Acute procedural success will henceforth be defined as the non-inducibility of tachycardia and the demonstration of bidirectional isthmus block. Across the cavo-tricuspid isthmus, complete bidirectional block was demonstrated if there was a transisthmus conduction time of >130 ms or an increase of >50% over the baseline (if available). Additional activation mapping across the line of block following ablation and the presence of split double potentials separated by more than 110 ms was sought in nearly all patients to confirm bidirectional CTI block. Representative three-dimensional maps are presented in Figure 7.6.

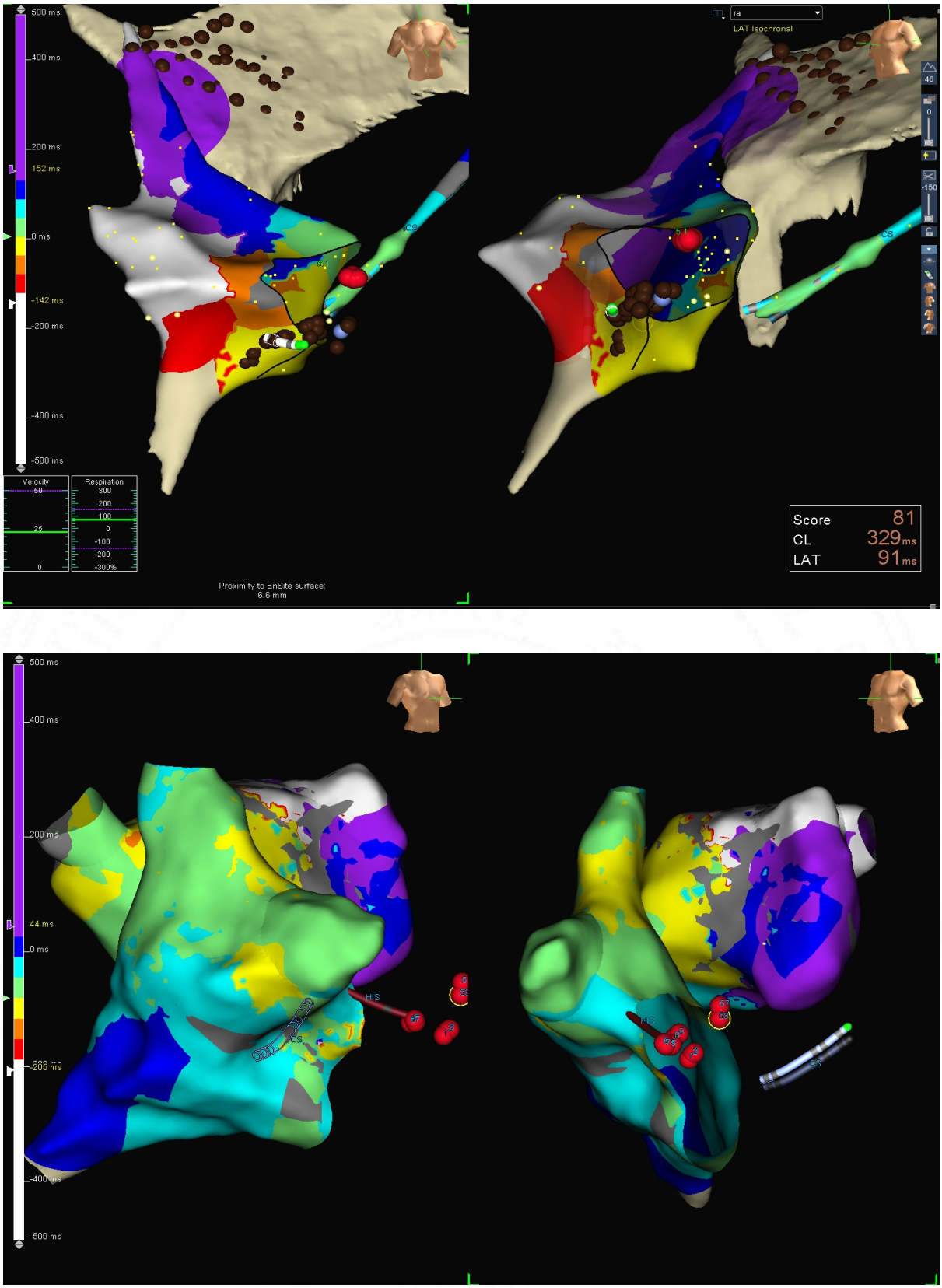


Figure 7.6: Representative three-dimensional electroanatomical map of (A) Typical Counterclockwise Atrial Flutter (B) Denovo scar related left atrial roof dependent flutter.

In describing the site of flutter circuit in patients with atrial flutter, it was noted that 20 patients had atypical flutter from a right atrial site. This included 10 patients with a circuit in the right atrial free wall (18 of these, 90% related to a right atriotomy scar), 7 with right atrial posterior wall related flutter, 2 with lower loop re-entry[16] and one patient with upper loop re-entry[17]. The procedure succeeded in abolishing the arrhythmia acutely in 17 of these patients. The site origin of right atrial flutter was not significantly associated with acute procedural outcome (p= 0.059). 4 patients had macro re-entrant atrial tachycardias with origin in the left atrium. Two of these had left atrial roof dependent atrial flutter, one had a flutter circuit in the left atrial anterior wall (related to an old surgical incision in the Waterston's groove) and 1 had multiple circuits in the left atrium (including a mitral isthmus dependent circuit and a re-entry circuit around the right superior pulmonary vein; this was a patient with cardiac sarcoidosis, infiltrative myocardial disease, left ventricular systolic dysfunction, severe mitral regurgitation and left atrial dilatation). The procedure was acutely successful in all but the last patient with left atrial flutter. The sites of atypical flutter origin are depicted in Figure 7.7.

All lesions delivered were drag lesions delivered along the defined isthmuses. The median number of lesion sets delivered was 1 (IQR 1-3). The maximum number of lesion sets delivered intra-procedurally was three. All 76 patients with typical atrial flutter, received a single lesion set along the cavotricuspid isthmus. 6 of these patients additionally underwent pulmonary vein isolation. In contrast, the median number of lesion sets delivered to patients with atypical flutter was 2 (IQR 1.75-3). 18 of these patients (75%) received lesions to ablate the CTI in addition to the primary isthmus, and 18 patients (75%) received two or more than

two lesion sets. Two patients with atypical flutter additionally underwent pulmonary vein isolation.

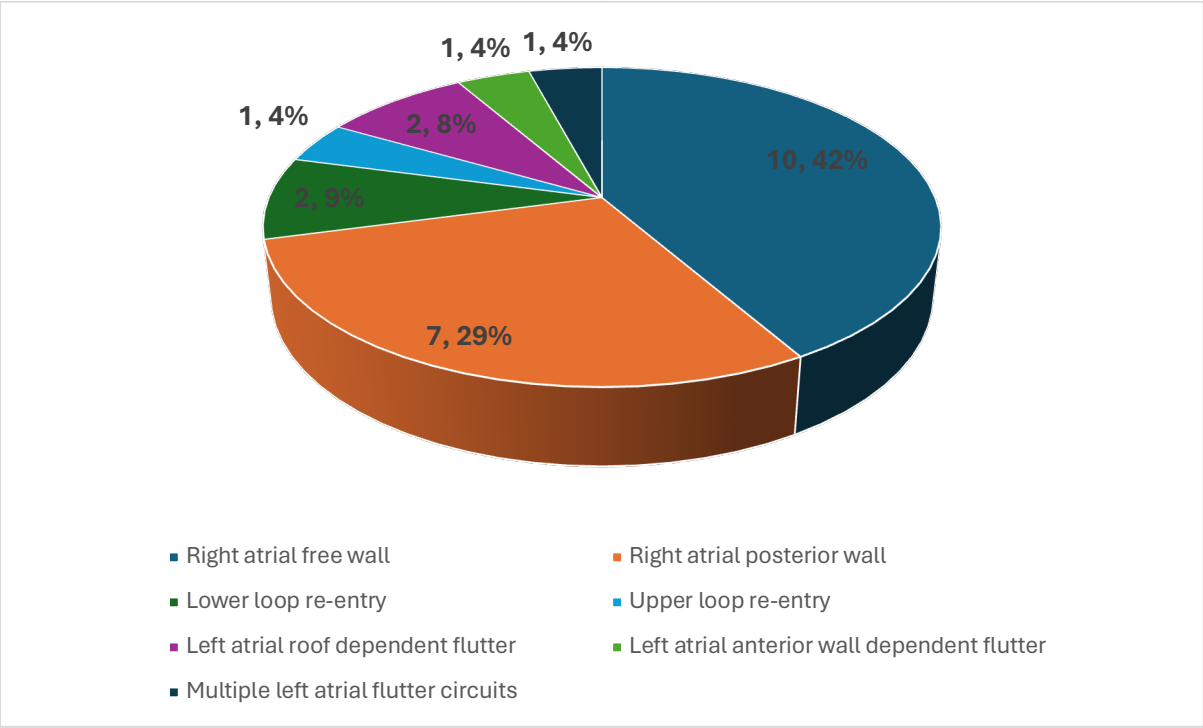


Figure 7.7: Anatomic distribution of atypical atrial flutter circuits

Acute procedural success, as defined above, was recorded in 95% of patients undergoing ablation. Significantly more patients with atypical flutter (4 patients, 12.5%) than patients with typical flutter (1 patient, 1.3%) (p=0.008) had an unfavourable ablation outcome. On univariate analysis, no other variable including age at diagnosis, the presence of comorbid structural heart disease, the history of prior cardiac surgery, echocardiographic parameters, the receipt of prior rhythm control therapy and the presence of additional tachycardia was significantly associated with acute procedural outcome. No major peri-procedural adverse events were noted.

A multivariate logistic regression model with the independent variables of age, atrial flutter classification (i.e. typical or atypical flutter), and the presence of additional tachycardia was generated. The model was a good fit (p=0.010) with a modest predictive accuracy (Nagelkerke R^2: 0.328). The final atrial flutter classification diagnosis was the only significant coefficient (p=0.010) with an odds ratio of 22.68. The inference from the analysis are presented in Table 7.4.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Age	.036	.049	.542	1	.462	1.036
	Final_Diagnosis	3.122	1.219	6.556	1	.010	22.684
	Additional_Tachy	-1.757	1.129	2.419	1	.120	.173
	Constant	-6.394	4.075	2.462	1	.117	.002

a. Variable(s) entered on step 1: Age, Final_Diagnosis, Additional_Tachy.

Table 7.4: Multivariate logistic rejection model for the outcome of acute procedural success

7.6 Medium-term clinical outcomes and predictors

Over a median follow up duration of 2 years (IQR 1-4 years), 13 patients (13%) had recurrent atrial flutter. This set included 7 patients (17.5%) with typical atrial flutter and 6 patients (30%) with atypical flutter(p=0.320). 3 of 5 patients (60%) who were recorded to have acute procedural failure had recurrent tachycardia on subsequent follow up as compared to 10 patients of the remaining 95 (10.5%) (p=0.016). 3 additional patients (3%), all with typical atrial flutter had a late recurrence beyond two completed years of follow up. Five patients with symptomatic recurrences had a second successful ablation procedure. A single patient with ablated typical atrial flutter and symptomatic recurrences (for which he underwent successful repeat ablation) succumbed to refractory pump failure over the follow up duration. Tachycardia free survival over two years was not significantly different in the subgroups with typical and atypical atrial flutter as demonstrated in Figure 7.8. Note that the follow up data is incomplete beyond two years for a significant proportion of patients, so these estimates may likely change with a longer duration of follow up.

Incident atrial fibrillation over the follow up period was noted in 19 patients (19%). This included 16 patients (40%) in the typical atrial flutter subset and 3 patients (15%) in the subset of patients with atypical atrial flutter. Furthermore, 14 patients (14%) developed symptomatic bradycardia requiring pacing secondary to underlying sinus node dysfunction over the follow up period. This included 11 (27.5%) of patients with typical flutter and 3 patients (15%) with atypical atrial flutter.

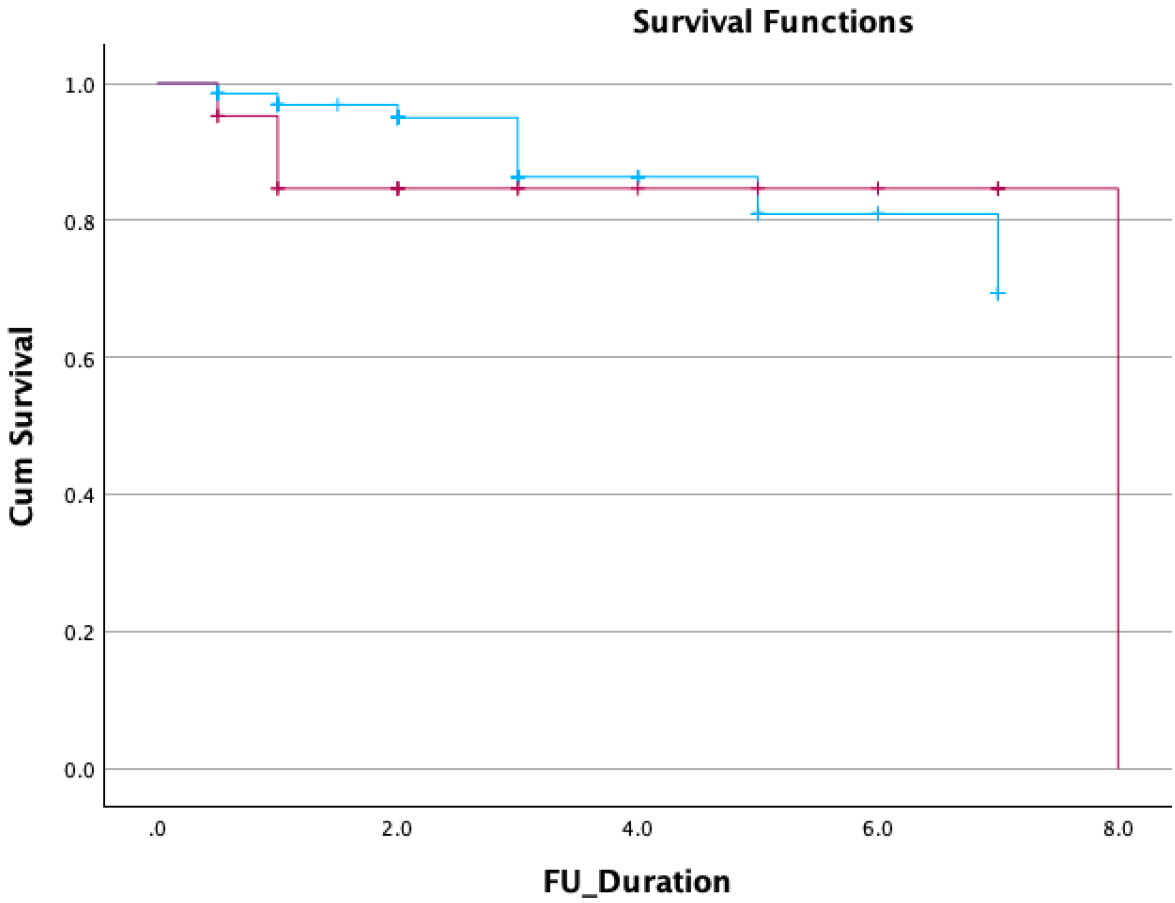


Figure 7.8: Kaplan-Meier survival analysis for the outcome of tachycardia free survival over the follow up period. Blue line: Typical Atrial Flutter; Red line: Atypical atrial flutter (p=0.887)

8. DISCUSSION

As discussed previously, western studies have shown atrial flutter to have a prevalence of 88/100,000 population with a relatively late onset (Mean age of 72 years) and a high prevalence of hypertension, dyslipidaemia and chronic pulmonary disease. We found our population to be epidemiologically distinct from these estimates, a finding driven by three primary factors. Firstly, while the prevalence of congenital heart disease at an estimated 9/1000 live births is congruent with available global data (8-12/1000 live births[18]), a large population at risk makes the overall number of cases quite large at an estimated 240,000 incident cases each year in the country[19]. Furthermore, a multitude of factors including a lack of awareness, limited access to healthcare and financial constraints drive the delay in seeking healthcare for congenital heart disease surgical intervention in the country, with a large proportion of patients undergoing reparative surgeries at older ages and in adulthood[20]. Finally, as the study centre population represented that from a referral paediatric cardiac centre, there appears to be a selection bias for patients with repaired congenital and structural heart disease. Our study population, thus, has a younger age at first atrial flutter diagnosis and a lower prevalence of conventional cardiac risk factors including hypertension and hyperlipidaemia.

It is well established that atrial fibrillation and atrial flutter coexist [21] with nearly a fifth of AF patients having documented flutter, and 80% of patients with atrial flutter having documented atrial fibrillation. Patients with co-existent atrial arrhythmias have a worse quality of life than those with atrial fibrillation alone[22], and patients with prior corrective cardiac surgery had a higher incidence of comorbid atrial flutter than AF alone[23]. Atrial fibrillation at baseline was noted in 13% of our patients and 19% patients developed incident AF over the follow up duration, amounting to a lower than anticipated disease prevalence. A combination of distinct

epidemiology as discussed above and a less rigorous screening procedure for AF detection likely contributes to this anomalous finding.

It is established that nearly 5% of patients surviving to adulthood with unrepaired or repaired congenital heart disease will develop atrial tachyarrhythmias[24]. The risk is higher in patients with complex congenital heart disease[25] and increases with advancing age[26]. Atrial arrhythmias in this population are harbingers of abnormal cardiac hemodynamics and adverse clinical events[26]. It becomes imperative thus to discuss the mechanisms of macro re-entrant atrial tachycardias in these patients. In prior studies, as in our study, the commonest mechanism of atrial flutter was a cavotricuspid isthmus flutter[27]. In this subgroup right atrial enlargement secondary to volume overload, pressure overload or both simultaneously could plausibly lead to an increase in circuit length and conduction time with any reduction in conduction velocity (i.e. in the absence of scar or zone of slow conduction). A second plausible mechanism would be subclinical fibrosis and atrial dilation mediating a non-uniform pattern of anisotropic conduction across the CTI[28]. Scar-related re-entry, secondary in particular to right anterolateral atriotomy (10 patients), was the second most common mechanism of re-entrant arrhythmia in this population. A substantial number of patients who developed atypical flutter in this subset (18 patients, 75%) had either a CTI dependent flutter in addition to their dominant tachycardia or had a dual-loop figure-of-8 re-entry incorporating conduction across the CTI thus necessitating CTI ablation in addition to ablation of their dominant tachycardia mechanism.

Radiofrequency ablation of cavotricsupid isthmus dependent flutter has been shown to have good efficacy acutely with reasonable durability in the medium, conferring a significant improvement in quality of patient life and event-free survival compared to drug therapy [29,30] . In patients with atypical flutter, there is a higher reported rate of recurrence in the medium

term, although outcomes have improved in conjunction with improvements in technology and intracardiac mapping techniques[31]. In both subsets, radiofrequency ablation is presently the therapy of choice to alleviate symptomatic patients. Our study observed an acute procedural success rate of 95% (which was significantly worse in patients with atypical flutter (87.5%)). Over the median two year follow up, we recorded 87% tachycardia free survival (this was proportionately more in the atypical flutter group (6 patients; 30%)).

In addition to symptomatic atrial flutter, a substantial number of flutter patients developed atrial fibrillation and symptomatic bradycardia requiring pacing over the duration of clinical follow up.

The single most important predictor for acute procedural success in our patients was found to be the mechanism of atrial flutter (i.e. atypical rather than typical atrial flutter) with an odds ratio of 22.68. However, in spite of these differences in acute procedural success, over our follow up period, survival free from tachycardia did not differ in patients with atypical and those with typical flutter. This discrepancy may be ascribed to a higher rate of prescription of anti-arrhythmic drugs to patients with atypical atrial flutter following ablation.

9. CONCLUSIONS

To conclude from this study,

1. Indian patients with atrial flutter undergoing radiofrequency ablation are younger at first presentation. This may be attributed to a higher proportion of disease secondary to repaired structural and congenital heart disease.

2. Patients with established structural heart disease ($p=0.002$) and a history of prior surgical intervention ($p<0.001$) (a median of 18 years prior to surgical onset) had a significantly higher prevalence of atypical than typical flutter as compared to patients with a structurally normal heart. Nearly half of these cases were related to scar-related re-entry.

3. 12-lead electrocardiography during tachycardia represents a diagnostic test with good accuracy and an area under the receiver operating characteristics curve of 0.757 (95% CI: 0.625-0.885)($P < 0.001$). The overall sensitivity of the test is 94.7% and specificity is 79.2%. More atypical flutters are misclassified at the time of electrocardiographic diagnosis than typical flutters.

4. The majority of patients undergoing radiofrequency ablation for flutter performed well acutely with a 95% rate of acute procedural success and no reported major complications. An electrocardiographic diagnosis of atypical atrial flutter is the single

most important predictor for procedural failure during AFl ablation (p=0.010) (OR: 22.68).

5. Over the median follow up period of 2 years, radiofrequency ablation for atrial flutter succeeded in sustaining robust responses with an 87% freedom from recurrent atrial tachycardia. However, 19% of patients developed incident atrial fibrillation and 14% developed symptomatic sinus bradycardia necessitating pacing over this period.

6. Tachycardia free survival over the follow up period did not significantly differ in patients with atypical and typical flutter. Thus, while patients with atypical flutter had a lower rate of acutely successful ablation procedures, their tachycardia-free survival following the ablation procedure is comparable to their counterparts with typical flutter over the medium term.

10.STUDY LIMITATIONS

While the study succeeds in bringing forth several important conclusions as discussed above, it has some drawbacks. Firstly, this study population represents retrospective data from a single Indian centre, and is hence intrinsically subject to a selection bias based on institution-specific patient selection processes and to a potential information bias driven by the dependence on the electronic medical record system. Furthermore, in spite of a high population prevalence of rheumatic heart disease with atrial tachycardia, this group was underrepresented in this study, a finding ascribed to an inherent selection bias in a cohort of patients undergoing atrial flutter ablation. Additionally, the follow up duration was modest at a median of 2 years, and, as is evidenced by the recurrence of symptomatic tachycardia beyond the two year mark in 3 of our patients, a longer term follow up is likely to yield critical information regarding the safety and efficacy of atrial flutter ablation. Finally, being a retrospective study, our sample size was limited by the available patient data over the duration of the study period and some populations (e.g.: patients with left atrial flutter) have too small a representation to support robust statistical analysis.

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APPENDIX: STUDY PROFORMA

Subject ID No: Age: Sex:

Age at diagnosis:

Weight: Height: BSA: BMI:

Primary Diagnosis:

I. CLINICAL DETAILS

A. Non-cardiac comorbidities:

1. Type 2 Diabetes: Y/N
2. Hypertension: Y/N
3. Obstructive Sleep Apnoea: Y/N
4. Dyslipidaemia: Y/N
5. Chronic Pulmonary Disease: Y/N
6. Chronic Kidney Disease:Y/N
7. Alcohol use: Y/N; If yes: Duration: Quantification:
8. Smoking: Y/N; If yes: Duration: Quantification:

B. Cardiac comorbidities:

1. Coronary Artery Disease: Y/N

   If yes, a. Anatomical description:

   b. History of coronary intervention: Time since intervention:

   c. History of CABG: Time since surgery:

2. Congenital or Structural Heart Disease: Y/N

If yes, a. Anatomical description:

b. History of surgical intervention: Time since surgery:

c. History of percutaneous intervention: Time since intervention:

3. Documented Atrial Fibrillation: Y/N

   If yes, Nature of therapeutic intervention:

C. Baseline Investigatios:

ECG at assessment

Rate		Rhythm	
QRSd,		PR	
ST segment		T waves	
QRS axis		QTc	
Impression			

Echo at assessment

LVIDD/LVIDS		SW/PW	
LA/Ao		RWMA	
LVEF		MR	
TR		AR	
Estimated PASP		Impression	

Clinical status at assessment

SBP/DBP/PR		Hb/TLC	
Temperature		OT/PT/T.Bil	
SpO2		BU/s.Cr	
GCS		TnI/pro-BNP	
FND		pH/pCO2/pO2/HCO3/Lactate	

D. Pre-ablation Medical Care:

1. Anticoagulation: Y/N

2. Rate-Control Therapy: Y/N

3. Rhythm Control Drugs: Y/ N

   If yes, Drug: Dose: Duration:

4. Direct current cardioversion: Y/N

   If yes, Number of attempts: Dose: Acute success:

5. Prior ablation: Y/N

   If yes, Number of attempts: Site: Acute success:

6. Time from diagnosis/first clinical presentation to ablation:

II. ABLATION PROCEDURE

A. ELECTROPHYSIOLOGICAL DIAGNOSIS:

A. Flutter Classification: Typical/Atypical

B. For atypical flutter:

a. Chamber of Localization for Dominant tachycardia:

b. Site of Localization:

c. Dual Loop Re-entry:

d. Additional flutter circuits:

e. Site of isthmus:

f. Bystander sites: Number: Anatomical localization:

g. Scar territory anatomical localization:

B. RADIOFREQUENCY ABLATION:

1. Primary lesion site:

2. Primary lesion outcome:

3. Secondary lesion site:

4. Secondary lesion outcome:

5. Tertiary lesion site:

6. Tertiary lesion outcome:

C. ADDITIONAL TACHYCARDIAS:

1. Atrial Fibrillation:

If yes, PVI Done: PVI Type: Additional LA lesions:

2. Additional SVT:

3. Additional VT:

D. PROCEDURAL OUTCOME

1. Acute Procedural Success

2. Procedural Complications:

III. FOLLOW UP DETAILS

A.6- MONTH FOLLOW UP:

1. Symptomatic Flutter Recurrence
2. Anti-Arrhythmic drug therapy
3. Repeat DC cardioversion:
4. Repeat Ablation:

B. ONE-YEAR FOLLOW UP:

1. Symptomatic Flutter Recurrence
2. Anti-Arrhythmic drug therapy
3. Repeat DC cardioversion:
4. Repeat Ablation:

C.TWO-YEAR FOLLOW UP:

1. Symptomatic Flutter Recurrence
2. Anti-Arrhythmic drug therapy
3. Repeat DC cardioversion:
4. Repeat Ablation:

D.LATE RECURRENCES:

1. Symptomatic Flutter Recurrence
2. Anti-Arrhythmic drug therapy
3. Repeat DC cardioversion:
4. Repeat Ablation:

E. INCIDENT ATRIAL FIBRILLATION:

1. Time to Occurrence:
2. Anti-Arrhythmic drug therapy

3. Repeat DC cardioversion:
4. Repeat Ablation:

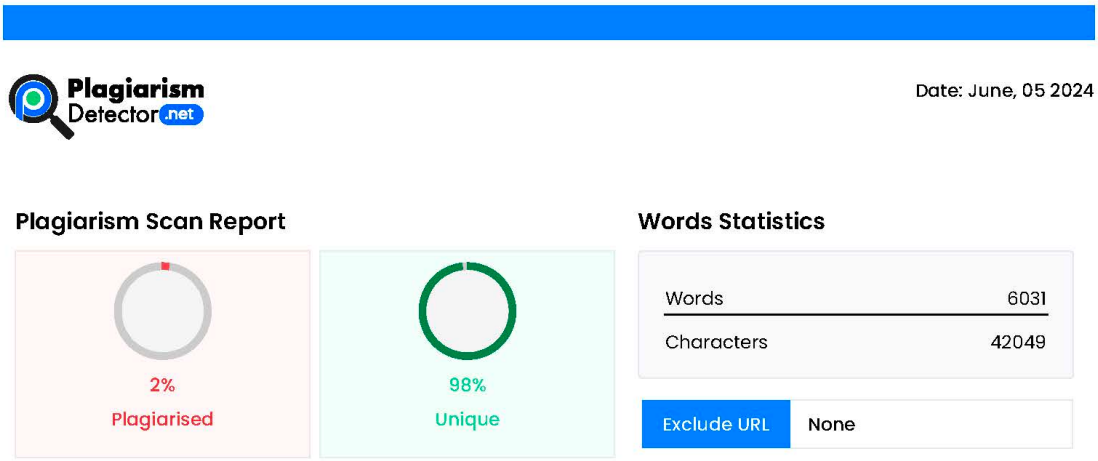
F. INCIDENT SYMPTOMATIC BRADYARRHYTHMIA:

1. Time to Occurrence:
2. Pacing indication:

G. FOLLOW-UP ECHOCARDIOGRAPHY:

LVIDD/LVIDS		SW/PW	
LA/Ao		RWMA	
LVEF		MR	
TR		AR	
Estimated PASP		Impression	

APPENDIX: PLAGIARISM REPORT



Plagiarism Detector .net

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Plagiarism Scan Report

2%
Plagiarised

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Words Statistics

Words	6031
Characters	42049

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CLINICAL PROFILE AND OUTCOMES OF PATIENTS UNDERGOING ATRIAL FLUTTER ABLATION AT A TERTIARY CARE CENTER IN INDIA: A RETROSPECTIVE COHORT STUDY DR. NAYANI BALBIR SINGH MAKKAR POST-DOCTORAL FELLOWSHIP THESIS Year: 2023-2024 SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM An Institution of National Importance established by an Act of the Indian Parliament (Act No.52 of 1980) Dept. of Science and Technology, Govt. of India www.sctimst.ac.in CLINICAL PROFILE AND OUTCOMES OF PATIENTS UNDERGOING ATRIAL FLUTTER ABLATION AT A TERTIARY CARE CENTER IN INDIA: A RETROSPECTIVE COHORT STUDY A THESIS SUBMITTED BY DR. NAYANI BALBIR SINGH MAKKAR TO SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM. IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF Post-Doctoral Fellowship, Cardiac Electrophysiology Year: 2023-2024 1. ABSTRACT A higher prevalence of operated structural heart disease in Indian patients with atrial flutter (AFl) may impact the clinical demographics and procedural outcomes of radiofrequency (RF) ablation in this population. We retrospectively analyzed clinical, procedural and outcome data from a cohort of patients who had undergone RF ablation for macro re-entrant atrial tachycardia. 100 patients underwent ablation for a macro re-entrant atrial tachycardia from 2016 to 2023. These patients were predominantly male (66%) with a mean age at procedure of 50.3 28.4 years, 41% patients had undergone cardiac surgery prior to AFl ablation. The patients were followed up for a median of 2 years. Non-cardiac comorbidities were common in these patients with diabetes in 14%, hypertension in 15%, dyslipidemia in 10% and sleep apnea in 4%. 60% of patients had co-morbid structural heart disease, with the commonest being a repaired secundum atrial septal defect (23 patients), 17 patients had co-morbid coronary artery disease, 20 patients had left ventricular systolic dysfunction, 13% patients had atrial fibrillation (AF) prior to ablation and 19% patients developed AF subsequently. 76% of patients had cavo-tricuspid isthmus dependent AFl. Of the remainder, 20 (83%) had macro re-entrant right atrial tachycardia with half of these patients having scar related re-entry from a right atriotomy. Acute success (the presence of bidirectional isthmus block and non-inducibility of tachycardia) was obtained in 95% of

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