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- Pulmonary Vein Isolation for Treatment of Paroxysmal Atrial Fibrillation on Patient with Situs Inversus Totalis
- Excellent symptom rhythm correlation in patients with palpitations using a novel Smartphone based event recorder
- Atrial Fibrillation in Patients with Congenital Heart Disease
- Impact of Radiofrequency Ablation of Atrial Fibrillation on Pulmonary Vein Cross Sectional Area: Implications for the Diagnosis of Pulmonary Vein Stenosis

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Editorial

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Expanding the Horizons of Atrial Fibrillation Management

Dear Colleagues

Welcome to the July issue of the Journal of Atrial Fibrillation. We have a few exciting articles covering a wide array of topics in AF. Angelo Biviano and colleagues have excellent observations that in patients undergoing transaortic valve replacement, the need for permanent pacemaker is significantly higher in those with atrial fibrillation (AF) than those who don't have AF. Resink et al report that acoustic cardiography may be a simple inexpensive and quantitative bedside method to assist in prediction of AF recurrence after an external cardioversion. Another interesting study from the University of Kansas highlights the importance of taking into account the reverse remodeling and associated left atrial shrinking and subsequent impact on the pulmonary vein orifice areas. Often the percentage reduction in the orifice area is taken into account for assessing the PV stenosis.

As medical care moves to more computer based algorithms and artificial intelligence becoming an integral part of patient care, computerized decision support systems are becoming prevalent. Computerized decision support system may decrease decision conflict and increase knowledge of patients with AF about its risk and potential therapies. Sheibani and group studied the effects of computerized decision support system on outcomes such as changing doctor-nurse behavior, anxiety about stroke and bleeding and stroke events. In the California Study of Ablation (CAABL), Srivatsa and colleagues analyzed a large patient database looking at the utilization of ablation therapy in AF patients and potential factors that influenced therapy. Despite two decades of progress in AF ablation, there seems to be a significant lag in time to therapy from diagnosis. The adult congenital heart disease (CHD) population is increasing rapidly, and patients with CHD are more likely to be referred for cardiac electrophysiology procedures. Moe etal have a great review article on the management of in adult CHD patients. AF occurs at a younger age in patients with CHD who are less tolerant of the arrhythmia and whose comorbid conditions make medical arrhythmia therapy more difficult to manage. They highlighted that any time an open-thoracotomy operation is planned, a discussion of concomitant surgical ablation of the arrhythmogenic substrate and excision or exclusion of residual thrombogenic structures should be considered. Patients with complicated CHD and atrial arrhythmias should have the benefit of referral to or collaboration with an adult congenital center of excellence prior to invasive rhythm management therapies.

As we immerse ourselves in the joys of the practice of electrophysiology, the health care bill remains contentious and unresolved. Millions of people in the United States are at risk of losing their health insurance as the ideological battle continues in Washington DC. May common sense prevail and hope the world remains sane until we come back to you in a couple of months.

Have a great summer.
Best wishes

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California Study of Ablation (CAABL):Early Utilization After Index Hospitalization for non-valvular Atrial Fibrillation

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Abstract

Background: Catheter ablation (ABL) for non-valvular AF (NVAF) is recommended for symptomatic patients refractory to medical therapy and its success is related to the duration of the arrhythmia prior to intervention.Our aim was to assess the early utilization and the factors that prompted ABL in patients hospitalized for new onset NVAF.

Methods: Using de-identified administrative discharge records for hospitalizations and emergency department (ED) visits, we determined the patients who had a first-time (since 1991) health record diagnosis of AF between2005 - 2011. We linked ambulatory surgery encounters for ABL based on ICD 9 code occurring within two years of initial hospitalization. After excluding other cardiac arrhythmias, atrio-ventricular nodal ablation or pacemaker/defibrillator placement and cardiac valve disease, bivariate comparisons were made with those who did not undergo ABL.

Results: During the study period,3,440 of 424,592 patients (0.81%) hospitalized for new onset NVAF underwent ABL. Parameters significantly (p<0.001) associated with ABL compared tonon-ABL patientsincluded: principal diagnosis of AF (55% vs 25%), age 35-64 yrs (46.1% vs. 22.4%), male (58.9% vs. 48.2%), private insurance (46.6% vs. 21.1%), Caucasian (81.0% vs.71.6%), lower frequency of ED visit < 6 months before index AF hospitalization (10.7% vs. 15.9%), lower severityofillness at time of AF diagnosis (16.5% vs. 35.6%) anda lower prevalence ofmajor comorbidities (p< 0.001).

Conclusions: Ablation has low utilization for treatment of new onset NVAF within two years of diagnosis. Earlier utilization of ABL may reduce health care burden related to NVAF and requires further evaluation.

Introduction

The current age-adjusted incidence of atrial fibrillation (AF) is13.4 per 1000 person-years[1]and the prevalence ofAF is projected to be over 10 million in the United States by 2050.[2]These patients are at risk for several morbidities requiring recurrent hospitalization, thus contributing to a huge economic burden from direct and indirect costs. [3]-[5]Medical management of non-valvular (NV)AF for rhythm control has moderate success,with median time to recurrence ranging from 74 - 487 days, reflecting frequentrelapses within first two years. [6], [7]The natural history of AF typically progresses fromparoxysmal episodes (PAF) triggered by premature atrial complexes from pulmonary veins or non pulmonary vein locations such as superior vena cava and posterior wall of left atrium, to persistent AF (PeAF) due to rotors, and substrate remodeling.[8]-[13]These patients present frequently with symptoms, however somepatients areasymptomatic with persistent AF of unknown duration. The mean duration of PAF is approximately 1.7 yrs before progressing to PeAF as noted in data from tertiary care centers.[14]

Key Words

Ablation, Atrial fibrillation, Frequency, Epidemiology.

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Clinical trials have shown superiority of ABL over medical therapy when used as second line intervention, and equivalent as first line treatment.[15]-[19] The reported frequency of maintaining sinus rhythm after ABL at one year varies approximately from 60-80%,[16], [17], [19], [20]with PAF requiring less extensive ablation compared to PeAF, achievinggreater success in maintaining sinus rhythm,[21][22]and resulting in fewer procedure related adverse events. [23]The defined success of ABL (non-recurrence of AF > 30 sec) isdependent on the type of AF prior to intervention[24] and theoverall duration of AF.[14] Evidence reflects superior control of AF when ABL is performed early in the course of the disease and is thereforerecommended for those who are refractory or intolerant to therapy with at least one drug.[25]-[27]

Our aim was to determine the frequency and predictors of early catheter ablation (< 2 years) in Californiaby a case control study of new onset AF. We hypothesized that hospitalization or emergency department visits represent severely symptomatic AF and may reflect a population with increased likelihood of referral for ABL.

Methods And Materials

223 consecutive This case control study was approved by the State of California Committee for the Protection of Human Subjects, and by the UC Davis institutional review board. The database utilized constituted patient discharge information from hospitalizations (PDD), emergency department (ED) and ambulatory surgery (AS) encounters from California non-federal hospitals.After linking the

PDD, ED and AS databases, we identifiedthe patientshospitalized with a diagnosis of AF (427.31)between Jan 1, 2005 to Dec 31, 2011, and then excluded all the cases with any prior discharge diagnosis of AF, back to 1990. Among these cases that had an incident hospitalization with a diagnosis of AF after Jan 1 2005, we identified all those who underwent an endovascular ablation (ICD-9-CM = 37.34) between Jan 1, 2005- Dec 31, 2011. We excluded all patientsthat also had a diagnosis of atrial flutter (427.32), supraventricular tachycardia (427.0), ventricular tachycardia (427.1), underwent an open surgical ablation (only procedure =37.34) and all cases that had pacemaker implant (37.80-37.87) coupled with a diagnosis of sino-atrial node dysfunction (427.81) or atrio-ventricular block (426.0-426.1). Rural and urban hospitals were defined basedon recommendations by Office of Statewide Health Planning and Development (OSHPD) with areas under 250 persons/ square mile considered as rural. Comorbidities were defined using the Elixhauser comorbidity index (Healthcare Cost and Utilization Project V3.7), which identifies 29 major comorbidities based on ICD-9-CM codeslisted as being present at the time the admission of first admission with AF.[28] Patients with valve disease were excluded and the remainder were considered to have NVAF. Patients with dementia, human immunodeficiency disease, alcohol abuse, active cancer or psychosis were also excluded. We reviewed approximately 200 hospitalization records to verify the accuracy of the inclusions and exclusions.

Table 1: Baseline characteristics of patients admitted for first time diagnosis of Non valvular atrial fibrillation (NVAF) 2005-2011 in non federal hospitals in California

Characteristics		Total population	Percent
All Patients with new AF in 2005 though 2011		424,592	100.0
New AF prin DX (427.31)		106,942	25.2
New AF any secondary diagnosis (427.31)		317,650	74.8
Patient Age	18-34	6,335	1.5
	35-49	21,640	5.1
	50-64	74,212	17.5
	65-79	155,568	36.6
	80 or older	166,837	39.3
Patient sex	Male	209,371	49.3
	Female	215,221	50.7
Payer source (index admission)	Medicare	293,791	69.2
	Medicaid	20,782	4.9
	Private, incl. HMO	90,337	21.3
	Self-pay	10,561	2.5
	No charge	8,463	2.0
	Other	658	0.2
Race/ethnicity (index admission)	White	304,451	71.7
	Hispanic	51,114	12.0
	Black	21,000	4.9
	Asian/Pacific Islander	31,500	7.4
	Other	16,527	3.9
Inpatient admission within 6 months preceding new AF admission		56,017	13.2
ED visit within 6 month of new AF admission		67,502	15.9
Outpatient admission within 6 months preceding new AF admission		32,834	7.7
Rural location (index admission hospital)	Urban	400,317	94.3
	Rural	24,275	5.7
Admission year	2005	63,164	14.9
	2006	60,787	14.3
Admission year	2007	58,625	13.8
	2008	59,275	14.0
	2009	59,010	13.9
	2010	61,292	14.4
	2011	62,439	14.7

AF- Atrial fibrillation

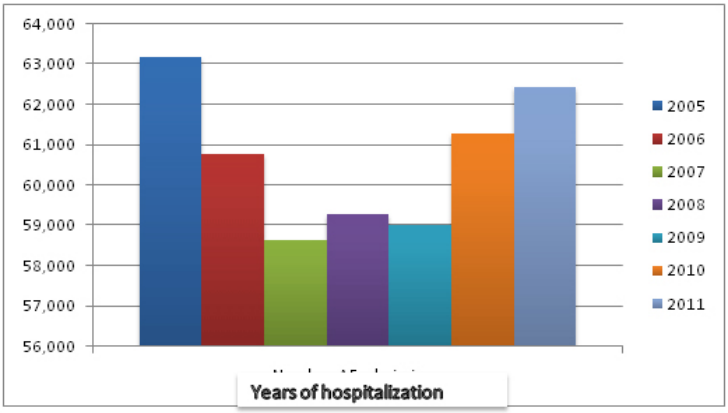

Figure 1A: Number of hospitalizations or emergency department visits for non valvular atrial fibrillation (NVAF) between 2005-2011

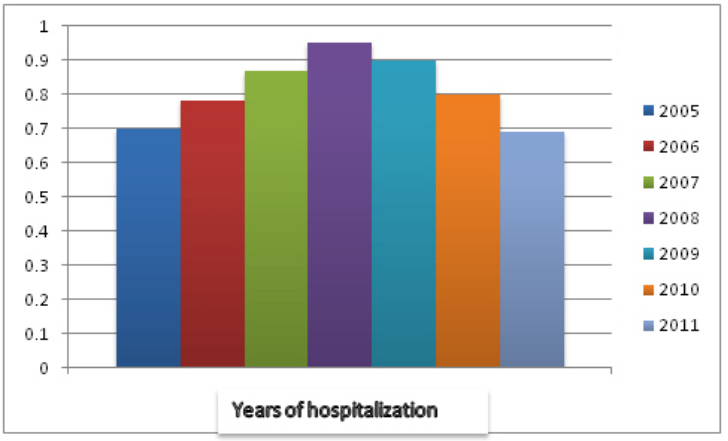

Figure 1B: Percentage of ablations for NVAF every year

All patient refined (APR)-DRGs are measures to assess patient characteristics for resource utilization as an all payer alternative to Medicare system (MS)-DRG and has four levels of severity.We applied this previously described measure called "the severity-of-illness (SOI)" utilizing a software (APR-DRG version 24; 3M) at the time of the hospital admission (minor, moderate, severe and extreme).[29-31]Many of the co-morbidities defined by this algorithm are known risk factors associated with AF.

We compared demographic and clinical characteristics of cases that underwent ABL within two years to controls who never underwent ablation during the study period. Predictors undergoing ABL were analyzed using a proportional hazard model that included demographic variables, clinical variables, SOI, insurance status, and intercurrent hospitalization with a principal diagnosis of AF as a time dependent covariate. SAS version 9.3 was used for all statistical analyses. Continuous variables were expressed as mean + SD. Categorical variables were presented as percentages. Uni-variate analysis was performed with a χ^2 test for nominal variables and

Fisher's exact test was applied for outcomes fewer than 5 events per cell. Analysis was performed using multivariable proportional hazard modeling to predict outcomes. A p-value < 0.05 was considered significant.

Results

Among the total adult population in California (28,068,224), 424,492cases had a first-time hospitalization with a diagnosis of NVAF between 2005-2011, averaging 60,000 admissions per year. [Figure 1]Of these cases, 106,942 patients (25.2%) were admitted for a principal diagnosis of NVAF and 317,650patients (74.8%) had a secondary diagnosis of NVAF. The majority of these patients (75.9%) were >65 yrs old; the number of males (2.39/1000) and females (2.38/ 1000) were comparable.The payer source for the majority of the cases, was medicare (69%)and approximately one fifth had private insurance. [Table 1] There was a slight decrease in the number of cases with a first time admission for NVAF from 60,484 in 2005 to 56,829 in 2009; in 2011, there was an increase to 62,439.[Figure 1A] Most patients were hospitalized in an urban facility (94.3%). Two-thirds of the patients were admitted with moderate or major severity of illness, while a third were either EDadmissions or mild severity of illness.Approximately 60% the patients had hypertension (HTN); diabetes mellitus (DM), heart failure (HF),chronic obstructive pulmonary disease (COPD), obesity were relatively frequent. [Table 2]The prevalence of AFwas higher among Caucasians compared to other races/ethnic groups.[Figure 2]

ABL was performed < 2 years from the first hospitalization/ ED visit in 3440 (0.81%) of the total number of cases admitted during the study period.[Table 3] The number of ablations peaked at 564 (0.95%) in this population in 2008, followed by a decline [Figure 1B] (p<0.0001). ABL wasmorelikely to be performed in cases admitted specifically for NVAF (1.8%) as opposed those that had to a secondary diagnosis of NVAF(0.49%) (p<0001). Males were more likely to undergo ABL (1%) compared to females (0.7%, p<0.001) and Caucasians (0.92%) morethan other ethnicities (p<0.001).There were no differences in rural vs urban ABL.Patients with private insurance (1.8%) were more likely to have ABL than those with Medicare (0.5%, p<0.001) or other insurance, although a majority of the patients were > 65 yrs and had Medicare coverage.[Table 3]

Risk-adjusted predictors included: admission for principal diagnosis of NVAF (HR=2.1), younger age (HR= 3.9); age (50-64 vs >80); male (HR=1.2), private insurance (HR=1.8vs. Medicaid); Caucasian (HR= 2.1 vs. Hispanic), mild severity of illness (HR=1.4). There was less coronary artery disease, peripheral vascular disease, stroke/ neurological disorders, DM, HTN, HF, renal failure, and COPD, but no difference in obesity between ABL and non ABL groups. [Table 4]

Table 2: Comorbidities associated with new diagnosis of Non valvular Atrial Fibrillation

Co morbidities		n	%
Discharge severity	ED Case	98,478	23.2
	Minor	43,355	10.2
	Moderate	132,453	31.2
	Major	115,209	27.1
	Extreme	35,097	8.3
Congestive heart failure		105,645	24.9
Valvular disease		40,071	9.4
Pulmonary circulation disease		20,283	4.8
Peripheral vascular disease		38,312	9.0
Paralysis/Other neurological disorders		45,540	10.7
Chronic pulmonary disease		92,533	21.8
Diabetes		109,886	25.9
Hypertension		254,573	60.0
Renal failure		56,342	13.3
Liver disease		8,629	2.0
Rheumatoid arthritis/collagen vas		11,981	2.8
Coagulopthy		17,387	4.1
Obesity		50,225	11.8
Deficiency Anemias		88,903	20.9
Depression		33,786	8.0
Coronary artery disease		54,968	12.9

ED- Emergency department

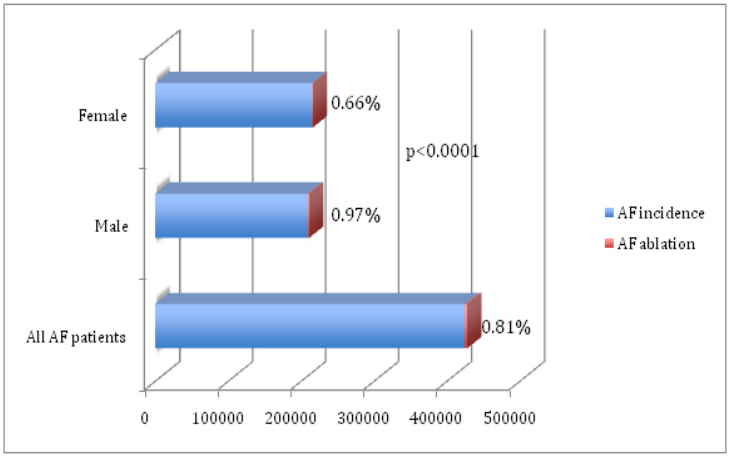

Figure 2A: Gender variation is ablation for non valvular atrial fibrillation (NVAF) among all patients admitted with new onset NVAF

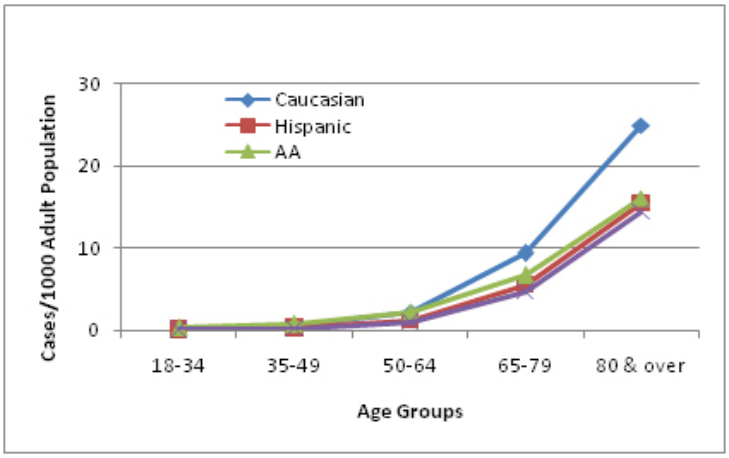

Figure 2B: Racial distribution of hospitalization or emergency department visits for NVAF in non federal hospitals in California (2010)

Discussion

The prevalence of AF is high,[2], [32]primarily attributable to its association with aging, HTN, DM,HF, sleep apnea, pulmonary diseases and obesity.[33]-[37]Worldwideadmissions for AF have increased from 35 to 110/10,000 population between 1996-2006, likely due to the augmented prevalence of these risk factors.[2] However, because of the presence of asymptomatic episodes of AF, the exact prevalence is unknown.[38]-[40]In this study, we attempted

Table 3: Results: Predictors of early ablation for non –valvular atrial fibrillation (NVAF)

	Ablation (n=3440)(%)	No ablation(n=421152(%)	p value
Principal Diagnosis of NVAF	24.9	1.8	<0.0001
Secondary Diagnosis of NVAF	75.1	0.5	<0.0001
Patient age (yrs)			<0.0001
18-34	1.45	1.5	
35-49	1.86	5.0	
50-64	1.69	17.3	
65-79	0.80	36.6	
80 or older	0.27	39.5	
Male	49.2	0.97	<0.0001
Female	50.8	0.66	
Payer source			<0.0001
Medicare	45.3	69.4	
Medicaid	3.4	4.9	
Private	46.6	21.1	
Race			<0.0001
White	71.6	0.92	
Hispanic	12.1	0.54	
Black	5.0	0.38	
Asian/Pacific Islander	7.4	0.51	
Other	3.9	0.83	
Discharge Severity			<0.0001
ED case	23.1	1.1	
Minor	10.1	1.76	
Moderate	31.2	0.77	
Major	27.2	0.42	
Extreme	8.3	0.25	
Co Morbidities:			
Heart failure	15.4	25.0	<0.001
Coronary artery disease	8.8	13.0	<0.001
Peripheral vascular disease	3.4	9.1	<0.001
Prior stroke/neuro disorders	3.7	10.8	<0.001
Pulmonary disease	14.8	21.9	<0.001
Obesity	11.3	11.8	ns
Diabetes	15.8	26.0	<0.001
Hypertension	49.6	60.0	<0.001
Renal Failure	4.8	13.3	<0.001

to determine if these epidemiologic data correlate with an increase in hospitalizations/ ED visitsfor AF in California. We found that the average admissions for AF have been ~ 60,000/ year without a significant change between 2005-2011,[Figure 1A], although this could reflect improved ambulatory care of AF patients.

Similar to previously described associations,in our large study from a California multiethnic population, two-thirds of the patients were over 65 yrs of age, with a third each in the age groups 65-79 yrs and > 80 yrs. AF has been reported to have an increased frequency in males although there are more women with this arrhythmia due to their longer life expectancy.[33],[41] By contrast,in our NVAF population, we found equal prevalence of women and men among those hospitalized for NVAF, which is likely due to a higher association of valvular heart disease among women in the afore mentioned study.[33]As has been previously described, there was also a Caucasian preponderance of NVAF in our cohort.[42]Two- thirds of our patients were admitted with moderate or major illnesses, while a third were either ED admissions or had mild severity of illness, confirming the widely known association of AF to acute ailments.

Due to lack of a specific ICD-9 code, we excluded other arrhythmias and considered ABL as specific for AF when associated in the principal position at the time of hospitalization. We also excluded patients with implantable cardiac devices to avoid those who could have AV node ablation. We decided on an approximate interval of two years as " early" for these patients to have received follow-up care and to have declared themselves in need of invasive management based on natural progression of NVAF and clinical trials of medical management previously described.[7],[14],[43]]

Several studies have shown that the outcomes of ABL are superior with shorter duration of AF. [44]-[48]However, despite these salutary results and advances in ABL technology, this procedure is performed in < 1% of patients within two years after the initial hospitalization in our population and includes racial and gender disparities. The Caucasian preponderance could at least partially reflect income and insurance status, however, these variables were adjusted for in the statistical analysis. The majority of California's population resides in urban areas with medical centers in all major cities providing ABL for NVAF, which is reflected by most of our population. In a study from a national inpatient sample of patients with AF, (NIS) by Patel et al, about 2.9% of patients with underwent ABL, with a significant increase in ABL through a twelve year study period.[49] However this study sample does not represent new onset AF. The results are also weighted, as NIS represents a stratified random sample and does not include all patients, in contrast to our study in which we were able to account for all first time diagnosis of NVAF admissions. Our finding of a low ABL rate is concordant with regional variations in ABL that were noted among the US hospitals by Patel et al. In contrast to their investigation, we found that ABL was more frequent in patients with private insurance than Medicare. Consistent with the study by Bhave et al [43]of Medicare population, male Caucasians were more likely to undergo ABL in our group, even though one third of our patients were <65 yrs. In theirstudy,althoughthe majority wastreated bycardiologists, only about 15% consulted an electrophysiologist and about 1% underwent ABL, which is similar to that of our cohort. Most patients were managed by rate control with about a third also receiving anticoagulation in their study.[43]This finding supported by low ABL rates in our study suggests that rhythm control of AF by intervention is not widely recognized as a potential treatment.

At the present time, failure of AF ABL isdefined as recurrence of >30 sec of monitored AF., which is challenging to identify.[27],[50]Outcomes of clinical significance such as mortality, stroke or hospitalization for AF, have not been clearly documented.The Heart Rhythm Society recommends against ABL as an indication to prevent stroke; it favors using the $CHADS_2VASC$ risk scorefor prophylactic anticoagulation. [51]These factors may contribute to underutilization of ABL in the relatively early phase of the natural history of AF, when ABL is most effective. AF burden demonstrated in our study from California is disproportionately high compared to the number of trained electrophysiologists nationwide during the same period[52] and may indicate lack of access to care. The physician reimbursement for AF ABL is also poor for the complexity and duration of the procedure, compared to simple ablations, which could contribute to diminished interest in this beneficial procedure.

This study is a retrospective investigation with the inherent

Table 4: Predictors of ablation of patients hospitalized for atrial fibrillation

	Ablation (n=3440)	No ablation (n=421152)	p value
Heart failure (%)	15.4	25	<0.001
Coronary artery disease	8.8	13	<0.001
Peripheral vascular disease	3.4	9.1	<0.001
Prior stroke/neuro disorders	3.7	10.8	<0.001
Pulmonary disease	14.8	21.9	<0.001
Obesity	11.3	11.8	Ns
Diabetes	15.8	26	<0.001
Hypertension	49.6	60	<0.001
Renal failure	4.8	13.3	<0.001

limitations of that method. We did not capture outpatient visits that could have led to ABL, and therefore our results reflect only the data pertaining to patients hospitalized with a first time diagnosis of NVAF. Any prior ablation outside California, if not coded at index hospitalization would not be identified from this method. There is also noICD 9 code specific for AF ABL; therefore our method of analysis may have missed capturing this procedure. There also may have been missed diagnoses by the coders, but the validity of the data is supported by periodic audits performed for billing purposes in most of hospitals in this study.We have also reviewed sample charts to ensure accuracy of exclusion and inclusion criteria. Although the purpose of our study was to determine early ablation (within two years of first hospitalization/ ED visit), patients may have undergone ABL later than that interval.

Conclusions

Our investigation suggests limited acceptance of ABL within two years of first hospitalization for NVAF in a multi-ethnic population and may reflect the need for greater awareness, improved education and access to care including ABL, as well as enhanced definition of clinical outcomes of this intervention.

Conflict Of Interests

None.

Disclosures

None.

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Effects of Computerized Decision Support Systems on Management of Atrial Fibrillation: A Scoping Review

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Abstract

Background: Potential role of computerized decision support system on management of atrial fibrillation is not well understood.

Objectives: To systematically review studies that evaluate the effects of computerized decision support systems and decision aids on aspects pertaining to atrial fibrillation.

Data Sources: We searched Medline, Scopus and Cochrane database. Last date of search was 2016, January 10.

Selection criteria: Computerized decision support systems that help manage atrial fibrillation and decision aids that provide useful knowledge for patients with atrial fibrillation and help them to self-care.

Data collection and analysis: Two reviewers extracted data and summarized findings. Due to heterogeneity, meta-analysis was not feasible; mean differences of outcomes and confidence intervals for a difference between two Means were reported.

Results: Seven eligible studies were included in the final review. There were one observational study without controls, three observational studies with controls, one Non-Randomized Controlled Trial and two Randomized Controlled Trials. The interventions were three decision aids that were used by patients and four computerized decision support systems. Main outcomes of studies were: stroke events and major bleeding (one article), Changing doctor-nurse behavior (three articles), Time in therapeutic International Normalized Ratio range (one article), decision conflict scale (two articles), patient knowledge and anxiety about stroke and bleeding (two articles).

Conclusions: A computerized decision support system may decrease decision conflict and increase knowledge of patients with atrial fibrillation (AF) about risks of AF and AF treatments. Effect of computerized decision support system on outcomes such as changing doctor-nurse behavior, anxiety about stroke and bleeding and stroke events could not be shown.We need more studies to evaluate the role of computerized decision support system in patients with atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and its prevalence increases with age[1]. One in five strokes are associated with AF and stroke severity is increased compared to patients with other causes of stroke. Furthermore, AF is associated with increased rates of death, heart failure and hospitalizations[2].

AF is almost a chronic disease and Lifelong treatment is needed. To avoid thromboembolic complications, Patients with AF need anticoagulation therapy and the most used drug is Vitamin K antagonists (like warfarin)[3]. Treatment with anticoagulant warfarin has to be monitored by prothrombin Ratio (PR) and the International Normalized Ratio (INR)test[4]. Range 2 to 3 (therapeutic range) of INR minimize thromboembolic events for patients with AF.

Numerous guidelines exist for the management of AF. CHA_2DS_2-VASc [5] and HAS-BLED [6] scores can help to inform stroke risk and risk of bleeding [7]. However, physicians' adherence to these guidelines has been low [8]. Computerized Decision Support Systems (CDSS) have been postulated as promising tools to improve the quality of decisions [9] in terms of physician adherence [10], [11]. Hence, decision support systems have been designed to implement guidelines also for the management of AF [12].

To investigate the advantages of CDSSs for the management of AF, several studies have been conducted which reported a positive effect [13] or no effect but according to our knowledge no review has been done to integrate these results.

Many reviews have shown effects of CDSS on practitioner performance [14]-[16] by providing patient-specific information and evidence-based recommendations. We therefore aim to systematically review studies that evaluate the effects of CDSS on any aspect that we will encounter in the studies. The specific aims of this scoping review are: 1) To review what outcome types that evaluate effect of CDSS on AF have been studied. 2) To summarize the effect of CDSS on management of AF.

Methods

For the current review CDSS is defined as any intervention that

Key Words

Computerized decision support system, Atrial fibrillation, Medical informatics, Decision aid, Scoping review.

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presents clinical knowledge and patient specific information for providers to enhance health and health care [17]. All aspects of AF (prevention, detection, diagnosis and treatment) were considered. Information sources were: Medline, Scopus and Cochrane database and last date searched was 2016, January 10.

Search strategy and study selection

Our full electronic search strategy for Medline was:

(clinical decision support systems[MESH] OR decision support system*[TITLE/ABSTRACT] OR decision support tool*[TITLE/ABSTRACT] OR reminder system*[TITLE/ABSTRACT] OR reminding system*[TITLE/ABSTRACT] OR alert system*[title/abstract] OR alerting system*[title/abstract] OR computer assisted decision making[MESH] OR computer assisted decision making[TITLE/ABSTRACT] OR diagnosis, computer assisted[MESH] OR computer assisted diagnosis[TITLE/ABSTRACT] OR computer assisted therapy[MESH] OR computer assisted therapy[TITLE/ABSTRACT] OR expert systems[MESH] OR expert system*[TITLE/ABSTRACT] OR *CDS*[TITLE/ABSTRACT] OR medical order entry systems[MESH] OR order entry system*[TITLE/ABSTRACT] OR computerized order entry[TITLE/ABSTRACT] OR computerized prescriber order entry[TITLE/ABSTRACT] OR computerized provider order entry[TITLE/ABSTRACT] OR computerized physician order entry[TITLE/ABSTRACT] OR electronic order entry[TITLE/ABSTRACT] OR automated order entry[TITLE/ABSTRACT] OR CPOE[TITLE/ABSTRACT]OR electronic prescribing[MESH] OR electronic prescribing[TITLE/ABSTRACT] OR electronic prescription[TITLE/ABSTRACT] OR computer assisted therapy[MESH] OR computer assisted therapy[TITLE/ABSTRACT] OR computer assisted drug therapy[TITLE/ABSTRACT]) AND (atrial fibrillation*[TITLE/ABSTRACT] OR Auricular Fibrillation*[TITLE/ABSTRACT] OR Atrial Fibrillation [MESH]).

This search strategy was modified for other databases.

Inclusion criteria were:

1. Studies evaluating effects of a CDSS on all aspects of AF.
2. CDSS provided clinical knowledge to augment clinician decisions or patient specific information to reinforce patient decisions.
3. Real world clinical studies.

Exclusion criteria were:

4. Letters, abstracts, conference proceeding, study protocols, reviews and meta-analysis.
5. Studies that only assessed accuracy and sensitivity.

Searching was complemented by reviewing bibliographies listed in identified articles. Two reviewers screened the titles and abstracts and evaluated the eligibility of studies for detailed evaluation. Disagreements were resolved through consensus or consulting a third reviewer.

Data collection process

Two reviewers extracted, separately, data from the selected studies. Data items were: participants (sample size, audience and characteristics), type of the interventions, primary and secondary outcomes, design of studies (cross sectional, case control, cohort, before-and-after and Randomized Control Trial (RCT)) and results of the studies.

Data collection process

Selected studies were evaluated using a previously published tool in prevention of cardiovascular disease [18]. It provides a maximum of 10 points for quality. The following aspects were considered: Allocation to study groups, data analysis and presentation of results, presence of baseline differences, objective outcomes and percentage of follow-up [Table 1].

Table 1: List of excluded articles and respective reasons.

Quality assessment aspects	score
Allocation to study groups	
Random	2
Quasi-random	1
Selected concurrent control	0
Data analysis and presentation of results	
Appropriate & clear	2
Inappropriate or unclear	1
Inappropriate & unclear	0
Presence of baseline differences between the groups	
No baseline differences present or appropriate statistical adjustment made	2
Baseline differences present & no statistical adjustment made	1
Baseline characteristics not reported	0
Objectivity of the outcomes	
Objective outcomes or subjective outcomes with blinded assessment	2
Subjective outcomes with no blinding but clear criteria	1
Subjective outcomes with no blinding & poorly defined	0
Completeness of follow-up for the appropriate unit of analysis	
90%	2
From 80% to 90%	1
< 80% or not described	0

Each item has a score between 0 to 2.

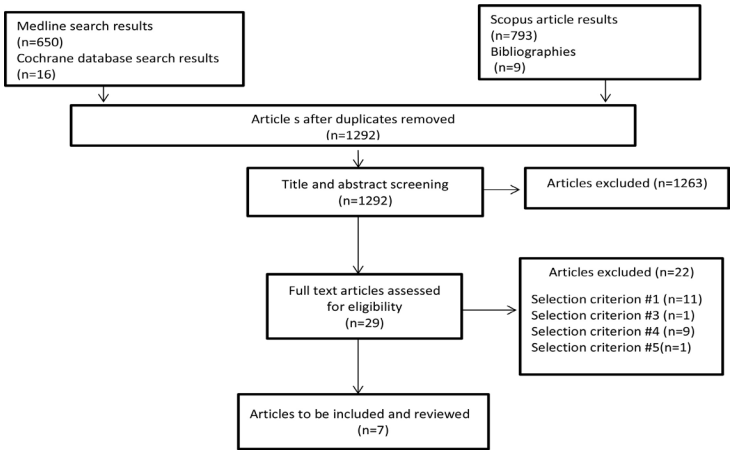

Figure 1: Flow diagram for selecting of studies.

Studies were classified according to type of outcomes. Effects of CDSS on each outcome were extracted and classified as statistically significant positive effects and no effect. Mean differences of outcomes and confidence intervals for a difference between two means are reported. The included studies were heterogeneous and were classified as being one of: Randomized Controlled Trial (RCT), Non-Randomized Controlled Trial (before-after studies), Observational study with controls (cross-sectional studies and cohort studies with controls), Observational study without controls (cohort studies without controls or case series)[19].

Table 2: Characteristics of the included studies

Authors, year of publication	Sample size	Setting	Type of intervention	audience	Design of study
Cook, D. A. et al [24], 2015	Control period No. (n = 226 patients), Notification period No. (n = 268 patients)	inpatient	CDSS(clinical alert system that notify providers of abnormal test results)	Provider (physician)	Observational study with controls
Robson, J. et al [22], 2014	4604 patients	outpatient	Mixed (altering professional beliefs using education, CDSS to facilitate decision making and motivating change using evaluative feedback)	Provider (physician)	Observational study with controls
Simmons, B. J. et al [21], 2012	44 patients	outpatient	Decision aid (patient self-management (PSM) program)	patients	Non-RCT
Fraenkel, L. et al [13], 2012	Control group (n = 66 patients), Intervention group (n = 69 patients)	outpatient	Decision aid (a tool for nonvalvular atrial fibrillation (NVAF) to notify patients of their stroke and bleeding risks, assist in clarifying priorities)	patients	RCT
Hendriks, J. M. L.et al [23], 2010	ICCP group(n=111 patients) control group(n=102 patients)	outpatient	CDSS(stroke risk score was calculated and 2006 guidelines for AF patients were implemented)	Provider (nurse)	Observational study with controls
Wess, M. L. et al [20], 2008	6,123 patients	inpatient	CDSS(a tool to calculate individual stroke and bleeding risk and risk–benefit analysis for anticoagulation is done)	provider	Observational study without controls
Thomson, R. G [25], 2007	109 patients (intervention(n=53) control(n=56))	outpatient	decision aid(applied in shared decision-making clinic)	patients	RCT

Results

Study selection

Our search strategy yielded 1292 distinct articles from all sources. 1263 articles were excluded by assessing the title and abstract. Full text assessment of the 29 articles was done and seven eligible studies were included in the final review [Figure 1].

Study characteristics

All papers were published after 2007. The following study types were present in our final selection: one observational study without controls [20], one non-RCT [21], three observational studies with controls [22]-[24] and two RCTs [13],[25]. The sample size of AF patients, varied from 44 [21] to 6,123 [20] [Table 2]. Two studies were conducted in an inpatient setting and five in an outpatient setting. Patients were excluded if they were ambulatory patients or on a cardiology service [24], receiving warfarin for less than 6 months [21], did not speak English [25], poor hearing or eyesight [13], cognitive impairment [13], [25], contraindication to ASA or warfarin [13], [25], taking warfarin for another indication [13], [25], nursing home residence [13], previous stroke or transient ischemic attack [25] , inpatients [23] and no patients were excluded from one study [22]. Computerized tools were used in six papers and an intervention consisting of a CDSS, education and feedback, was used in one paper [22]. Three of the tools were decision aids and were used by patients [13], [21], [25]. Five papers were of high quality and two papers were of poor quality (on a scale of 10, 5 or less than 5 was their score). Details of quality evaluation are presented in table 3.

Effects of CDSS on outcomes of studies

The included studies differed in study design and/or type of interventions and/or in their control groups. Main outcomes were: stroke events and major bleeding, changing doctor-nurse behavior, time in therapeutic INR range, decision conflict scale, patient knowledge and anxiety about stroke and bleeding [Table 4]. Below we address each outcome separately.

Stroke events and major bleeding

Acute stroke and major bleeding were assessed in a cohort study [20]. A decision support tool that determines patient's risk of bleeding and stroke was proposed. The patients who actually received an anticoagulant when the CDSS was not in practice used but after that decision support tool recommended not to use the anticoagulant, had a high risk of bleeding and for them receiving warfarin was related to increased hazard of bleeding (Hazard ratio=1.54, p=0.03).

Changing doctor-nurse behavior

Two trials reported changing physician behavior [22],[24]. In one cohort study with historical control, an automated system for identifying newly diagnosed AF was proposed [24]. A computerized clinical alert system was developed by decision rules intended to automatically notify physicians. In the control period 94 patients were high risk and 34 of them (36%) received warfarin but in the notification period 125 patients were high risk and 34 of them (27%) received warfarin. (Odds ratio, 0.66 [95% CI, 0.37–1.17]; p = 0.16). The intervention did not change provider behaviors. In [22] was performed a cross sectional analysis with a mixed intervention (guidance, education, software enhancements and evaluative feedback). CHA_2DS_2-VASc and HAS-BLED scores were calculated and Pop-up reminders were used. From April 2011 to April 2013, oral anticoagulant use increase from 52.6% to 59.8% (trend difference P<0.001). One trial reported changing nurse behavior. The cohort study with historical control reported guideline adherence in the treatment of AF as an outcome [23]. Computer-Assisted Decision Support System directed medical therapy according to the patient's profile and clinical guidelines. Guideline adherence was increased significantly to 96% in the ICT-supported integrated chronic care program (ICCP) group compared with 70% in the control group (p<0.001).

Effects of decision aids on outcomes of studies

Time in the therapeutic INR range

One before and after study reported the Percentage of time spent within the therapeutic range (TTR) [21]. Patients received the recommended dose of a decision support tool. No significant difference in TTR occurred between the before and after intervention periods (82.9% vs 81.2%, p=0.65).

Decision conflict

Decision conflict scale [26] was used for reporting the decision

Table 3: Details of quality evaluation

	[24]	[22]	[21]	[13]	[23]	[20]	[25]
Allocation to study groups	0	0	0	1	0	0	2
Data analysis and presentation of results	2	2	2	1	2	2	2
Presence of baseline differences between the groups	2	0	2	2	1	2	2
Objectivity of the outcomes	2	2	2	2	2	2	2
Completeness of follow-up for the appropriate unit of analysis	0	0	1	2	0	0	2
Sum of scores	6	4	7	8	5	6	10

conflict between treatment choices (antiplatelet drugs or warfarin therapy) in two studies [13], [25]. Four subscales of the decision conflict scale are: uncertainty, informed, values clarity, and support.

In a randomized control trial, a decision aid presented advantages and disadvantages of warfarin treatment and an assessment of DCS (Decision Conflict Scale) was done. It was lower in the computerized decision aid group versus the paper guidelines group, mean differences (95% CI) were 0.02 (-0.22 to 0.26), -0.18 (-0.34 to -0.01) and -0.15 (-0.37 to 0.06) at pre-clinic, post-clinic and three month follow-up [25]. In a clustered randomized controlled trial, a decision support tool was developed as an application that runs on a laptop computer and risks of stroke and bleeding for both antiplatelet drug and warfarin were shown. Informed subscale (mean difference = −11.9 , 95% CI =−21.1 to −2.7) and Values Clarity subscales (mean difference = −14.6, 95% CI=−22.6 to −6.6) were lower in the intervention group [13].

Anxiety about stroke and bleeding

Two RCT studies reported anxiety or worry about stroke and bleeding as an outcome [13], [25]. The decision aid was designed for informing patient's stroke and bleeding risks and clarifying priorities but did not affect participants' anxiety (mean difference = −0.38, 95% CI = (−1.4 to .67), p=0.477)in [13]. Furthermore, in [25] the intervention was a computerized decision aid applied in shared decision-making and reduction of anxiety by the decision aid did not differ from the control group (F (1, 95) =0.001; p=0.98).

Patient knowledge

Two trials assessed patient knowledge [13], [25]. Participants in the intervention group knew medications for reducing stroke risk significantly better than the control group (61% vs 31%, p=0.001) [13]. Knowledge scores were improved after the clinic (participants taking warfarin had a higher mean warfarin knowledge score than participants on aspirin (difference=1.79 with 95% CI 1.00 to 2.59)) but after three months were back to the pre-clinic level and there was no significant difference between the decision aid and the guidelines groups [25].

Discussion

The main In this study we assessed the effect of CDSS on all aspects of AF. We systematically reviewed seven studies. Two RCTs that had the highest quality reported positive effect on main outcome [13], [25]. Two of the observational study with controls reported positive effect on all their outcomes [22], [23] but one of them reported no effect on its outcome [24]. Mix of positive, absence of, and negative effects was considered as one class of the measured effects in [27] and was reported in four of selected studies (two RCTs and one non-RCT and one observational study without controls).

We began to do a systematic review study with focus on a well-defined question and assessed the quality of included studies. But as we will explain bellow we had only one or two studies that reported the same results for outcomes and we had different study designs. we could not answer specific review questions so we decided to do the scoping review that had broader topics and is possible with many different study designs [28].

One study reported that a computerized clinical alert system did not change providers' behaviors and reported no effect [24] but another reported improvement in clinical management AF [22]. The quality of the former was higher than the latter and the latter used a mixed intervention. It is difficult to estimate which part of the intervention pertained to the reported improvement. Furthermore, only one low quality study reported the effect of CDSS on guideline adherence[23]

Table 4: Outcomes and effect sizes for the selected studies

reference	outcome	Effect size	effect on outcome	Quality rating
[24]	Prescription of warfarin	In the control period 94 patients were high risk and 34 of them (36%) received warfarin but in the notification period 125 patients were high risk and 34 of them (27%) received warfarin. (Odds ratio, 0.66 [95% CI, 0.37–1.17]; p = 0.16).	No effect	6
[22]	• The proportion of AF patients with a CHA_2DS_2-VASc score ≥1 on anticoagulants • The proportion of AF patients with a CHA_2DS_2-VASc score ≥1 on aspirin	• Oral anticoagulant use increased from 52.6% to 59.8% (trend difference P<0.001) • Aspirin use declined from 37.7% to 30.3% (trend difference P<0.001).	• Positive (statistically significant) • Positive (statistically significant	4
[21]	• Time in the therapeutic INR range(TTR) • number of INR tests	• No significant difference in TTR occurred between the before and after intervention periods (82.9% vs 81.2%, p=0.65). • Intervention increased the mean number of INR tests per patient (2.97 to 4.38, p<0.01).	• No effect • Positive (statistically significant)	7
[13]	• Decision conflict scale • Knowledge • Change in treatment • anxiety	• Informed subscale (mean difference = −11.9, 95% CI =−21.1 to −2.7) and Values Clarity subscales (mean difference = −14.6, 95% CI=−22.6 to −6.6) were lower in the intervention group. • Participants in the intervention group knew medications for reducing stroke risk significantly better than the control group (61% vs 31%, p=0.001).	• Positive (statistically significant) • Positive (statistically significant) • No effect • No effect	8
[23]	Guideline adherence	Guideline adherence was increased significantly to 96% in the ICT-supported integrated chronic care program (ICCP) group compared with 70% in the control group (p<0.001).	Positive (statistically significant)	5
[20]	• major gastrointestinal bleeding • acute stroke	The patients who actually received an anticoagulant but decision support tool recommended not to use the anticoagulant, had a high risk of bleeding and for them receiving warfarin was related to increased hazard of gastrointestinal bleeding (Hazard ratio=1.54, p=0.03).	• Positive (statistically significant) • No effect	6
[25]	• decision conflict scale • anxiety • knowledge	Decision Conflict Scale was lower in the computerized decision aid group versus the paper guidelines group in the post-clinic; mean Difference -0.18 (95% CI -0.34 to -0.01).	• Positive (statistically significant) • No effect • No effect	10

thus we have not enough evidence to determine the effect of CDSS on improving guideline adherence and changing doctor-nurse behavior in the treatment of AF.

Reporting no effect of the CDSS on changing physician behavior was unsurprising. Other studies of decision support systems showed that these do not perform as expected [29]. Inappropriate timing and need to click to access information[24] and alert fatigue [30] were reported as the main reasons. Improving the human-computer interface, providing recommendations for patients in addition to practitioners [31], prioritizing and filtering recommendations for the user [32] can improve the effectiveness of CDSS interventions.

Due to scarcity of evidence for clinical improvement [33],[34] we had only one study that evaluated stroke events and major bleeding [20]. The rates of bleeding were higher in patients who received warfarin, but the decision support system indicated they should not so a decision support system can be a good predictor of bleeding for who warfarin might be harmful. Furthermore, only one study reported the percentage of time spent within the therapeutic range (TTR) and it did not report on a statistically significant improvement. This lack of evidence is a main limitation of our study.

This study had other limitations. The large heterogeneity in the studies meant that meta-analysis is not meaningful. We also could not perform pooled analysis because the two high quality RCTs that reported on anxiety, the decision conflict scale and patient knowledge [13], [25] had different comparison groups: one study compared the decision aid group to a usual care group [13] ,the other compared the decision aid group with an evidence-based paper guidelines group [25]. Furthermore, randomization methods and blinding differed markedly, resulting in further heterogeneity among studies.

Two RCT studies [13], [25] reported no significant difference in psychological outcomes such as anxiety between groups. This coincides with [35] that reported no difference in anxiety scores between decision aid and usual care groups. So decision aids did not have psychological negative effects.

Two studies [13], [25] reported the decision aids for patients with AF decrease decisional conflict. This result is similar to a review [36] that evaluated effects of educational and behavioral interventions on reducing decision conflict for oral anticoagulation therapy (OAT) in patients with AF. Moreover, these two RCTs showed that the decision aids improve knowledge of patients with AF although one study reported that knowledge returned to the baseline level after three months and there was no significant difference between the decision aid and the guidelines groups [25]. The paper guidelines that were used in control group may limit findings significant effect of decision support systems on patient knowledge.

Clear and intuitive user interface was reported as a feature for evaluation of CDSS [37] but only two of the included studies [24], [25] presented the screen of the computerized intervention. If characteristics of output such as content, channel, timing and format [38] were clearer, we could more accurately interpret the results of interventions and evaluate the effect of these characteristics on success of the intervention.

Strengths of the current review include the fact that we searched Medline, Scopus and Cochrane databases and conducted this review in accordance with the PRISMA statement [39] for reporting on review. As far as we know, this is the first review of studies that evaluate the effect of CDSS on all aspects of AF.

Several trial protocols describe trials that investigate the effect of CDSS on AF management [12], [40], [41] but their results are not published yet. These randomized control trials may provide supplemental evidence.

Conclusions

Although limited by a small number of studies, decision aids seems to have significant benefits in decisional conflict reduction and improve knowledge of patients with AF. Computerized tools that addressed AF patients did not show the psychological negative effect and did not affect participants' feeling of worry about stroke and bleeding. The included studies did not show significant effect of CDSS on stroke event rates, time in the therapeutic INR range and doctor-nurse behavior. We need more studies to evaluate the role of computerized decision support system in patients with atrial fibrillation.

Authors' contributions

RS and EN screened the titles and abstracts and evaluated the eligibility of studies and extracted data. Disagreements were resolved by MS. RS and MS drafted the paper. AH as a clinical expert and SE and AA that are experts in medical informatics, were involved in interpretation and revising the final version.

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Conflicts of interest

None of the authors has any financial and personal relations with relevant people or organizations that could have affected this work.

Disclosures

None.

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Sinus Rhythm Restoration after Radiofrequency Ablation Improves Survival in Patients Undergoing mitral valve Surgery : a Eight Year Single Center Study

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Abstract

Background: The usefulness of radiofrequency (RF) ablation in restoring sinus rhythm in patients with permanent atrial fibrillation (AF) undergoing surgery for mitral valve has been demonstrated. Less clear is whether sinus rhythm recovery affects long-term survival.

Methods: This study included 301 consecutive patients (126 men and 175 women, age 69±6 years) undergoing radiofrequency ablation of persistent atrial fibrillation associated with mitral valve surgery. Radiofrequency ablation was performed using unipolar probe in 55.3%, bipolar probe in the remaining 44.7% of cases.

Results: Four patients died during hospitalization. At follow-up, sinus rhythm was present in 76% of the surviving patients. 71 patients never recovered sinus rhythm after hospital discharge. Mortality and recurrent hospitalization were significantly lower in patients with sinus rhythm at the end of follow-up in comparison to permanent AF. The incidence of stroke was also lower in patients with stable sinus rhythm. Larger atria, pulmonary hypertension and history of rheumatic disease were associated with the persistence of AF despite radiofrequency ablation. Although survival and functional capacity were significantly lower in patients with permanent AF at multivariate analysis only age and pulmonary artery pressure before surgery were independently associated with mortality.

Conclusions: Sinus rhythm restoration by RF ablation in patients undergoing mitral valve surgery is associated with an improved long-term survival. However our results suggest that a more severe hemodynamic impairment, expressed by higher pulmonary artery pressure, and increasing age are the only independent factors related to long-term survival.

Introduction

Less than 20% of patients with permanent atrial fibrillation spontaneously recover from sinus rhythm after mitral valve surgery.[1],[2] The persistence of AF after surgery is associated with a decreased exercise tolerance, an increased risk of systemic embolization[3] and higher long-term mortality.[4]

Original surgical treatment –"cut and saw"-[5] has been progressively substituted by other tissue-ablation technologies (radiofrequency -RF- and cryo ablation are the most common). Several different lesion sets have been proposed, at present most frequently including pulmonary vein isolation and other left-sided ablation lines, while the bi-atrial maze lesion set is less commonly used due to the need for right and atrial atriotomy and longer times of cardiopulmonary by-pass.[6] Radiofrequency probes may be unipolar or bipolar.[7]-[9] The main limitation of monopolar probes is the high probability to not obtain transmural lesions in comparison to bipolar probes: moreover the latter have a reduced risk of damaging adjacent structures such as the esophagus.[10]-[11]

Key Words

Mitral valve surgery, Atrial fibrillation, Monopolar and bipolar radiofrequency ablation, Survival.

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Several studies have reported a high rate of success using both monopolar and bipolar RF on rhythm recovery at short and medium term. Evaluation of long-term effects of these procedures has been hampered by several variables including clinical characteristics of patients (age, concomitant valve surgery, etiology of valve heart disease, left ventricular function, pulmonary artery pressure), follow-up strategies and finally the type of energy used and the set of lesions performed. Few studies however examined the effects of AF RF ablation associated with mitral valve surgery on patients' survival and on their functional capacity and quality of life.[7]

The aim of the present study was to prospectively assess the effects of sinus rhythm maintenance on survival after left-sided RF ablation of AF associated with mitral valve surgery.

Methods

In the study entered, all patients underwent unipolar or bipolar RF ablation associated with mitral valve surgery between 1/1/2003 to 12/31/2011 at the Heart Surgery Department of the Azienda Ospedaliera Universitaria of Careggi Hospital in Florence.

The time of onset of AF and functional capacity expressed as NYHA functional class were recorded at hospital admission. Electrocardiographic examination was performed to confirm the presence of arrhythmia. All patients underwent transthoracic echocardiography with a 2.5 and 3.5 MHz probe (Sequoia C256 Accuson Siemens Mount View, California). Left atrium AP diameter (mm), 2D left and right atrium area (cm2) and left ventricular ejection fraction (LVEF) were measured. End-diastolic and end-

Table 1: Clinical characteristics of patients

Gender (M/F)	126/175
Age (years)	69.1 ± 49.7
Preoperative AF duration (months)	36.9 ± 49.7
LVEF (%)	51.6 ± 9.8
LA (mm)	53.7 ± 8
LA area (cm^2)	32.5 ± 10
RA area (cm^2)	22.3 ± 6.7
Systolic Pulmonary pressure (mmHg)	44.2 ± 14.9
NYHA class	2.9 ± 0.6

AF= atrial fibrillation, LVEF = left ventricular ejection fraction, LA = left atrium, RA = right atrium

systolic images were synchronized on ECG. Since patients were in AF we considered the average value of five measurements. Pulmonary systolic pressure (PAP) was calculated adding right ventricle/right atrium pressure gradient to estimated right atrial pressure assessed by inferior vena cava diameter and response to respiration.

Ablation technique

Medtronic Cardioablate surgical ablation systems (Medtronic, Minneapolis USA) were used for monopolar and bipolar treatment. Detailed description of left sided ablation lines has been previously reported.[12] The extra time for the cardiopulmonary by-pass required for ablation was on average 15±8 min.

Post-operative management

To favor maintenance of sinus rhythm after RF ablations amiodarone bolus of 300 mg was administered i.v. followed by a continuous infusion of 1,200 mg in the first 24 hours; thereafter it was prescribed 200 mg orally every 12 hours until discharge. A maintenance regimen of 200 mg/day was prescribed for 3 months. Patients with persistent AF after RF ablation underwent at least one attempt of external cardioversion by biphasic DC-shock. Oral anticoagulation was given to maintain the International Normalized Ratio between 2.5 and 3.5 for the first 6 months in all patients, and life-long in patients who received mechanical valves or who had persistent AF or both.

Follow-up

Patients were seen at the outpatient clinic 3 months, 6 months, and 12 months after the surgical procedure and annually thereafter. Between visits, their referring physician attended patients on a regular basis and routine ECGs were obtained at each clinic visit regardless of symptoms. Event monitors were prescribed for patients who complained of palpitations or symptoms compatible with AF during follow-up. Between visits, all patients were encouraged to seek 12-lead ECG documentation for any symptom suggestive of AF/atrial flutter recurrence and a physician routinely performed trans-telephonic monitoring of any symptoms and complications.

The follow-up evaluation consisted of a detailed history, physical examination and 24-h Holter monitoring. Success and AF recurrence were defined following the HRS/EHRA/ECAS expert consensus document.[13] Informed consent was obtained by all patients and the study approved by the Ethical Committee of our Institution.

Table 2: Etiology of mitral regurgitation

	%
Mitral valve prolapse	26.3
Rheumatic mitral valve disease	28.7
Rheumatic mitral-aortic valve disease	19
Ischemic mitral regurgitation	12.7
DCMP related mitral regurgitation	2

DCMP – dilated cardiomyopathy

Statistical analysis

Data are presented as means ± SD for continuous variables and as percentages for categorical variables. Continuous variables were compared through the use of Student's 2 tailed unpaired-sample test. Categorical variables were compared using the chi-square test or Fisher's exact test if appropriate. Differences among groups were evaluated using ANOVA test. Multivariate analysis was performed using stepwise Cox regression method. Kaplan-Meier curves were used for the survival analysis. Differences between groups were compared using Log-Rank test. A probability value < 0.05 was considered significant. Statistical analysis was performed using SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA).

Table 3: Type of intervention performed

	%
Mechanical MVR	12.7
Biologic MVR	13.7
Mitral valve repair	30
MVR / mitral valve repair and AVR	18.7
Mitral valve repair and CABG	10.3
MVR and CABG	4.3
DCMP related mitral regurgitation	10.3

MVR – mitral valve replacement , AVR- aortic valve replacement CABG -coronary artery by-pass graft

Results

In the period under investigation 301 patients, 126 men and 175 women, mean age of 69.1 ± 9.7 years underwent RF ablation in association with mitral valve surgery. The clinical and echocardiographic characteristics are reported in [Table 1]. Four patients died in the immediate postoperative period (1.2%). One patient died of a cerebral hemorrhage, one of myocardial infarction, the remaining 2 of septic shock. 297 patients were included in the study. At the time of surgery 80% patients had severe functional impairment (III-IV NYHA class). Rheumatic mitral valve disease, lone or combined with aortic valve disease, (47.7%), and mitral valve prolapse were the more frequent indication to surgery [Table 2]. Details on surgical interventions performed are reported in [Table 3]. Radiofrequency ablation was performed using unipolar probe in 55.3%, bipolar probe in the remaining 44.7% of cases. There were

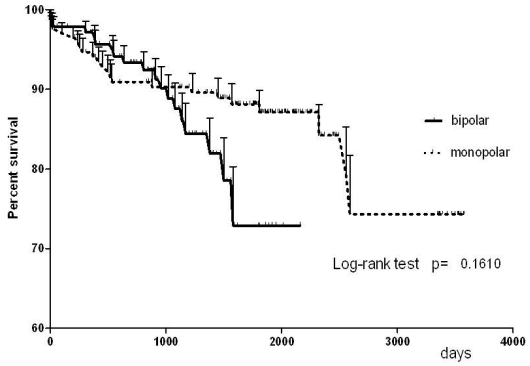

Figure 1: Kaplan Meyer survival curves of patients treated with monopolar and bipolar RF ablation

Table 4: Clinical characteristics of patients treated with monopolar or bipolar RF ablation

	Monopolar	Bipolar	p
	169	132	
Age (years)	67.8+9	70.7+9.0	0.019
Sex M/F	99/70	76/56	0.9
Duration AF	38+43	35+56	0.55
SR at follow-up %	100/69	74/58	0.63
LVEF (%)	52+10	51+9	0.63
LA (mm)	49+6	53+8	0.001
LA area (cm^2)	32+10	32+9	0.8
RA area (cm^2)	22+6	22+6	0.8
Syst Pulmonary pressure (mmHg)	44+15	42+14	0.5
Etiology			
Mitral valve prolapse	48	31	0.06
Rheum MVD	57	29	
Rheum MAVD	25	32	
Ischemic MR	20	18	
Dilated Cardiomiopathy	19	22	
NHYA class			
I	0	1	0.05
II	28	40	
III	117	78	
IV	24	13	

SR- sinus rhythm , LVEF = left ventricular ejection fraction, LA = left atrium, RA = right atrium , MVD= mitral valve disease, MAVD= mitro-aortic valve disease, MR= mitral regurgitation

no significant differences between clinical characteristics of the two groups except for age and LA diameter [Table 4].

Rhythm analysis

At the end of follow-up 69.4% patients were alive. Among them 76% were in sinus rhythm at the last follow-up visit. During follow up (mean duration about 8 years) 40.9% of patients remained in sinus rhythm at periodic clinical examinations and never experienced clinically demonstrated recurrent AF. 9 patients discharged in AF were in sinus rhythm at the end of follow up. One hundred and three patients (35.2%) had at least one symptomatic AF episode during follow-up. Finally 24% had permanent AF despite radiofrequency treatment and electrical CV attempts. Transient arrhythmias different from AF, all lesional atrial tachycardia, were recorded in 6.9%. Twenty-seven patients underwent definitive pacing, 8 during hospitalization, 19 during the follow-up period. The clinical and echocardiographic characteristics before surgery of the three groups of patients (stable sinus rhythm, recurrent AF, persistent AF) are shown in [Table 5]. Patients with persistent AF despite treatment were on average older, on average 3 year, in comparison to those than those with recurrent AF or who remained in stable sinus rhythm (p=0.03).

We did not find any relationship between rhythm at follow-up and respectively with gender, surgical procedure performed, the need for permanent pacing, left ventricular ejection fraction and finally NHYA class before surgery. Left atrium diameter, left and right atrium area were significantly lower in patients with stable sinus rhythm in comparison with the other two groups. Systolic pulmonary artery pressure was higher in patients who persistent AF than in those with stable sinus rhythm. Logistic multivariate analysis showed that duration of the arrhythmia (OR 1.005 95%CI 1.00019 -1.01074 p= 0.04) , preoperative left atrial area (OR 1.03874 95%CI 1.00537-1.07321 p= 0.02) , tricuspid valve repair (OR 2.07273 95%CI 1.07453-3.99821 p=0.03) and finally in hospital attempt of DC cardioversion (OR 1.9163 95%CI 1.00933 -3.63854 p= 0.04) were associated with permanent atrial fibrillation.

Other outcome

Ischemic stroke occurred in 8 of patients (3%) during follow-up. Among the 6 who were in permanent AF, 5 had INR values at stroke occurrence below the therapeutic range. A significant carotid stenosis was found in 1of the 2 patients in SR.

Hospitalization due to cardiac cause during the follow-up period was needed in 31% of patients. The hospitalization rate was almost twofold in patients who never regained sinus rhythm after ablation in comparison with patients in sinus rhythm at the end of follow-up. The high hospitalization rate in patients with recurrent AF was mainly related to attempts of SR restoration. A significant improvement in functional capacity was found after surgery.

Table 5: Clinical characteristics of different groups

	Stable SR	AF recurrence	Permanent AF	P
Age (years)	67.7 + 9.2	67.9 + 10	71.9 + 8.5	0.0494
LA (mm)	50.7 + 7.1	53.9 + 8.7	56.1 + 8.4	<0.0001
LA area (cm^2)	30.7 + 7.8	32.1 + 8.0	37 + 11.4	<0.0001
RA area (cm^2)	20.4 + 4.0	21.9 + 6.0	23.9 + 6.8	0.0159
Systolic PAP (mmHg)	41.0 + 11.9	44.4 + 14.1	46.1 + 15.4	<0.0001
Electric cardiovesion before discharge (%)	9.1	20.1	28.9	0.0092
Hospitalization (%)	17.5	48.8	30.0	<0.0001

AF= atrial fibrillation, LVEF = left ventricular ejection fraction, LA = left atrium, RA = right atrium

Survival analysis

At the end of follow-up period overall survival was of 85.7%. Forty-three patients died during follow-up, 67.4% due to cardiac causes. Patients went to death were older than survivors (mean age 72.9 ± 6,2 vs. 68.6 ± 9.4 years, p 0.026). We did not find gender related differences in mortality. There was no difference in mortality between patients who underwent monopolar or bipolar radiofrequency ablation [Figure 1].

The failure to restore sinus rhythm using RF ablation was related to a worse prognosis. Among surviving patients, 37.2% were in stable sinus rhythm, 42.6% had at least one recurrence of AF in the postoperative period while 20.2% was in permanent AF. In patients went to death relative percentages were respectively 23.3%, 30.2% and 46.5%.

Overall mortality was significantly higher in patients with persistent AF in comparison to those in stable sinus rhythm after discharge (Log Rank test-p=0.009). The survival rate however was not significantly different in patients with stable sinus rhythm during follow-up in comparison to patients who had transient AF recurrences but were in sinus rhythm at the end of follow-up [Figure 2].

Overall long-term mortality was higher in patients with rheumatic mitral valve disease who had a lower probability of sinus rhythm recovery, than in those suffering from mitral valve prolapse. Tricuspid valve repair was associated to a worse prognosis: it was performed in 28.6% patients went to death in comparison to 14.8% survived at the end of follow-up (p=0.041).

Preoperative functional capacity was not related to survival. The

Table 6: Clinical characteristics of survived and died patients

	Survived	Died	p
Preoperative AF duration (months)	36.5 + 50	39.4 + 48.3	0.72
AF recurrence free (days)	759 + 831.5	293 + 575	0.0001
LVEF (%)	59 + 9.5	49.9 + 12.1	0.22
LA (mm)	53.4 + 27	56 + 91	0.06
LA area (cm^2)	31.1 + 7.9	36.3 + 18.7	0.0135
RA area (cm^2)	21.9 + 5.7	24.5 + 10.7	0.0328
Syst Pulmonary pressure (mmHg)	43.3 + 14.3	49.3 + 17.2	0.022

AF= atrial fibrillation, LVEF = left ventricular ejection fraction, LA = left atrium, RA = right atrium

percentage of patients in advanced NYHA class (III-IV) was not significantly different in the two groups (82% of survivors vs. 91% of deceased patients). Atrial size (both right p=0.0023 and left atrial area p=0,0135) and pulmonary artery pressure (43.3 ± 14.3 vs 49.3 ± 17.2 mmHg; p=0.022) were significantly lower in survived patients.

At multivariate analysis, only age (OR= 1.1; 95% CI= 1.02-1.11; p= 0.003) and pulmonary artery pressure (OR=1.03; 95% CI= 1.02-1,12; p= 0.02) were independently associated with survival [Figure 3].

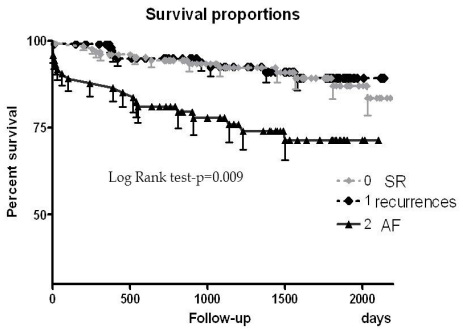

Figure 2: Kaplan Meyer survival curves : comparison among patients with stable sinus rhythm, recurrences of AF and persistent AF

Discussion

Radiofrequency ablation associated with mitral valve surgery has been reported to significantly affect rate of sinus rhythm recovery however the characteristics of the population included in each study and the use of different RF probes (unipolar or bipolar) and ablation line sets may account for the large differences in success percentage observed.[14]-[17] Moreover results may have been influenced by the absence of a uniform AF classification, of an adequate reporting of preoperative cardiac conditions and by the different methods of evaluating AF recurrences.

In our study we followed the HRS/ EHRA/ECAS expert consensus document to evaluate the success of the procedure.[13]

In previous studies preoperative LA size, cardiothoracic ratio over 60%, fine AF wave at preoperative ECG, and no early sinus rhythm restoration, an increasing number of concomitant surgical were reported as independent predictors of ablation failure in the mid-term follow-up period at multivariate analysis.[14]-[16],[18]

An elevated mean-age of patients, the absence of paroxysmal AF and a high percentage of rheumatic valve disease may explain the relative high rate (26%) of persistence of AF at hospital discharge observed in present investigation. Atrial fibrosis[19] may be responsible

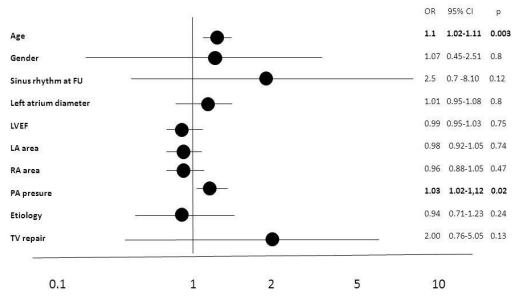

Figure 3: Results of multivariate logistic analysis on survival

for the poor results of RF ablation in rheumatic heart disease. Duration of the arrhythmia, preoperative left atrial area, tricuspid valve repair and finally in hospital attempt of DC cardioversion were independently associated with persistence of AF.

Few studies evaluated the effects on long term survival of sinus rhythm maintenance after radiofrequency (RF) ablation in patients with permanent atrial fibrillation (AF) undergoing surgery for mitral valve disease.

In a retrospective study an improved survival rate was reported in the subgroup of 65 patients treated with maze procedure (SR rate 81% at 5 years) in comparison with patients who underwent isolated mitral valve repair.[20] Ad et al[21] reported a higher four-year survival in patients who underwent Cox-maze procedure versus patients with untreated AF (OR= 2.47; P = 0.048).

Present study is the largest and with a long follow-up evaluating the relationship between the results of RF ablation associated with mitral valve surgery and mortality. Survival rate is significantly lower in patients with permanent AF after surgery, in comparison with patients with stable sinus rhythm and with those in whom at least 1 recurrence of AF was documented during follow-up (70% vs respectively 90 and 91%). Factors associated with mortality were also related to an increased rate of persistent AF at follow-up. Only age and pulmonary artery pressure before surgery were independently associated with survival.

Limitation of the study

The absence of a control group is a limitation of the study. Few clinical studies in literature compared the results of concomitant AF ablation in open heart surgery with those of a concurrent control arm (that is leaving the AF untreated). The absence of a control arm does not allow to assess the absolute effect of the ablative procedure either because it is impossible to know how many of the patients would convert to sinus rhythm spontaneously and more relevant; the effects of confounding variables (e.g. the different degree of hemodynamic impairment).

The results of 7 matched-controlled and 4 randomized trials of Maze procedure associated with concomitant mitral valve surgery showed that freedom from AF was 77% to 95% in the maze group versus 4% to 53% in the control group at 2 and 8 year follow-up.[22] The study by Gillinov et al[23] randomized to surgical ablation or no ablation 260 patients w ith persistent or long standing persistent AF undergoing mitral valve surgery. Sinus rhythm was present in 63.2 % in the ablation group in comparison to 29.4 % (p<0.0001) in the non-ablation group. Ablation was associated with a higher risk of

pace-maker implantation, no significant differences were reported in major cardiovascular or cerebrovascular adverse effects. The effects on survival are not valuable due to brief duration of follow-up (1 year). Another possible limit is related to the lesion set as our study involved only the left atrium. No randomized studies, however, have compared different RF lesion sets. In their study Gillinov et al[23] reported no significant difference after surgical pulmonary vein isolation alone or bi-atrial maze procedure in sinus rhythm rate at 1 year (61 vs 66%).

When we designed the study we did not consider a "blanking period" after RF procedure.

Patients included had long lasting AF before surgery and in patients discharged in AF late recovery of sinus rhythm occurred only in 9. Moreover on average AF recurrence occurred 750 days after surgery, a time significantly longer than "blanking period".

Conclusions

The present study supports the efficacy of RF ablation (unipolar and bipolar) in restoring SR in patients with AF undergoing mitral valve surgery and demonstrates that in patients in whom sinus rhythm is maintained after RF ablation not only the quality of life is improved but mortality is also significantly decreased. However our results suggest that a more severe hemodynamic impairment, expressed by higher pulmonary artery pressure, and increasing age are the only independent factors related to long-term survival.

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Conflict Of Interests

None.

Disclosures

None.

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Impact of Radiofrequency Ablation of Atrial Fibrillation on Pulmonary Vein Cross Sectional Area: Implications for the Diagnosis of Pulmonary Vein Stenosis

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Abstract

Introduction: Restoration of normal sinus rhythm by radiofrequency ablation (RFA) in atrial fibrillation (AF) patients can result in a reduction of left atrial (LA) volume and pulmonary vein (PV) dimensions. It is not clear if this PV size reduction represents a secondary effect of overall LA volume reduction or true PV stenosis. We assessed the relationship between LA volume reduction and PV orifice area pre- and post-RFA.

Methods: A retrospective cohort study was conducted at a tertiary care academic hospital. Pre- and post-RFA cardiac computed tomography (CT) studies of 100 consecutive AF patients were reviewed. Studies identifying obvious segmental PV narrowing were excluded. Left atrial volumes and PV orifice cross-sectional areas (PVOCA) were measured using proprietary software from the CT scanner vendor (GE Healthcare, Waukesha, WI).

Results: The cohort had a mean age of 60 ± 8 years, 73% were male, and 90% were Caucasian. Non-paroxysmal AF was present in 76% of patients with a mean duration from diagnosis to RFA of 55 ± 54 months. Mean procedural time was 244 ± 70 min. AF recurred in 27% at 3 month follow-up. Pre-RFA LA volumes were 132 ± 60 ml and mean PVOCA was 2.89 ± 2.32 cm2. In patients with successful ablation, mean LA volume decreased by 10% and PVOCA decreased by 21%. PVOCA was significantly reduced in patients with successful RFA compared to those who had recurrence (2.18 ± 1.12 vs. 2.8 ± 1.9 cm^2, p = 0.04) but reduction in LA volume between groups was not significant (118 ± 42 vs. 133 ± 54 ml, p=0.15).

Conclusions: The study demonstrates that both PV orifice dimensions and LA volume are reduced after successful AF ablation. These data warrant a reassessment of criteria for diagnosing PV stenosis based on changes in PV caliber alone, ideally incorporating LA volume changes.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, affecting 1-1.5% of the population in the developed world, and is associated with a higher incidence of stroke, coronary heart disease, peripheral artery disease, cognitive impairment, and physical disability [1]. Catheter-based radiofrequency ablation (RFA) of AF by pulmonary vein antral isolation (PVAI) is a standard therapy in selected AF patients with symptoms refractory to drug therapy. Restoration of sinus rhythm by RFA has been shown to reduce left atrial (LA) size while preserving function through reverse remodeling, as measured by two-dimensional (2-D) echocardiography [2]-[4], three-dimensional (3-D) echocardiography [5], [6], cardiac computed tomography (CT), and magnetic resonance imaging (MRI) [7], [8].

Key Words

Atrial fibrillation, Radiofrequency ablation, Pulmonary vein stenosis, Left atrial volume.

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Methods And Materials

Pulmonary vein (PV) stenosis is a known complication of PVAI for AF with a variable incidence ranging from 1.3% - 42.4%, depending on technique and operator experience [9], [10]. Increased operator experience and refinement of the RFA technique by moving lesion sites away from an ostial position to focus more on electrical isolation of the surrounding PV antrum has resulted in a dramatic reduction in the incidence of PV stenosis [11]-[13]. The diagnosis of PV stenosis is made based on percentage reduction in PV caliber by a variety of modalities, such as cardiac CT, which can ascertain the PV orifice cross sectional area (PVOCA) for comparison with pre-procedural measurements [12], [14]-[17]. PV stenosis is usually categorized into mild, moderate, or severe stenosis, corresponding to a < 50%, 50 – 70 %, or > 70% reduction in the PVOCA post-ablation, respectively [15].

Even though reduction in LA dimensions post-ablation has been reported in AF patients [3]-[5], [7], there is a relative paucity of data concerning changes in PV dimensions after AF ablation [7]. A decrease

Table 1: Baseline Characteristics

AF Patients Undergoing PVAI (n = 100)	
Age (years)	60 ± 8
Gender (male)	73 (73%)
Race	Caucasian 92 (92%) Other 8 (8%)
Body Mass Index (kg/m2)	27 ± 7
Past Medical History	
Hypertension	70 (70%)
Diabetes	25 (25%)
Coronary Artery Disease	21 (21%)
Cardiomyopathy	11 (11%)
Thyroid Dysfunction	19 (19%)
Sick Sinus Syndrome	11 (11%)
COPD	12 (12%)
Dyslipidemia	68 (68%)
Sleep Apnea	33 (33%)
Atrial Fibrillation	
Type	
Persistent	67 (67%)
Paroxysmal	24 (24%)
Permanent	9 (9%)
Mean Duration (months)	55 ± 54
Pre-ablation 2-D TTE	
Ejection Fraction (%)	57 ± 8
Left Atrial Size (cm)	4.3 ± 0.6
Atrial Fibrillation Ablation	
Mean Procedural Time (min)	244 ± 70
Fluoroscopy time (min)	95 ± 40
Outcomes	
Recurrence at 3 months	27 (27%)

AF: Atrial fibrillation; PVAI: Pulmonary vein antral isolation; TTE: Transthoracic echocardiogram. All values are expressed as number (percent) or mean ± standard deviation.

in LA volume and improved overall cardiac function can result in decreased pulmonary vascular congestion thereby decreasing the overall PV size [4], [18]. In the absence of a discrete area of stenosis, we attempted to evaluate what percentage of PVs experience a reduction in PVOCA on multi-slice cardiac CT and their relationship to the overall LA volume reduction following restoration of sinus rhythm.

Methods

The first 100 eligible AF patients undergoing pulmonary vein antral isolation were enrolled in a retrospective cohort study at a high volume, tertiary care academic medical center.

Inclusion Criteria

All patients who had a 64-slice CT scan before and 3-9 months after their first radiofrequency ablation for AF.

Exclusion Criteria

All patients with a history of prior radiofrequency ablation and/or Cox-Maze procedure for AF, and those with a known history of constrictive or restrictive pericarditis were excluded. Patients whose cardiac CT studies showed segmental narrowing of pulmonary veins pre-ablation were also excluded from the study [Figure 1]. Common and middle pulmonary veins were excluded from the analysis. Patients who had MRI studies to evaluate the LA/PV anatomy were also excluded to maintain uniformity in imaging modality. Lastly, patients who developed focal stenosis of the one or more PVs

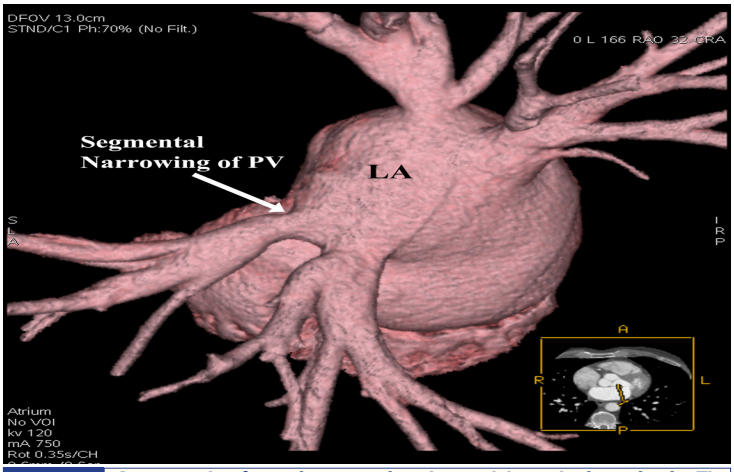

Figure 1: An example of a patient meeting the study's exclusion criteria. The figure shows a cardiac CT image of a patient whose pulmonary veins shows a segmental narrowing near the left superior pulmonary vein ostium. PV: Pulmonary vein; LA: Left atrium.

post-ablation were also excluded to purely assess the impact of sinus rhythm restoration on LA and PV dimensions.

The study protocol was approved by the Human Subjects Committee at the University of Kansas Hospital & Medical Center (Kansas City, KS, USA). Baseline, procedural, and outcome data were obtained from our locally maintained institutional atrial fibrillation ablation registry.

Cardiac CT Studies & Measurements

Patients had cardiac CT images acquired using standard procedure (LightSpeed VCT 64-slice Scanner, GE Healthcare, Waukesha, WI). Heart rate was slowed to about 60 bpm using either oral or intravenous beta-blockers at the time of image acquisition. All patients received iodixanol (Visipaque®, GE Healthcare, Waukesha, WI) using a three-phase protocol. The images were acquired with ECG gating. In patients with AF, images were acquired at 70% of the R-R interval by retrospective gating. In patients who were in sinus rhythm images were acquired before the P wave (at 75% of R-R duration) by prospective ECG gating technology. All cardiac CT scans were manually reviewed by two cardiologists who were blinded to the ablation outcomes.

PVOCA was determined at 0.5 cm from each orifice, defined as the point of departure of the vein tangent to the curvature of the LA [17], to provide a uniform pulmonary vein cross-sectional area and to avoid error from any funnel shaped ostia [Figure 2]. Pulmonary vein bifurcation areas were carefully avoided. Using Volume Viewer (GE Advanced Visualization platform) software, LA volume was measured by 3-D reconstruction after defining the region-of-interest

Table 2: Baseline Cardiac CT Measurements

	Atrial Fibrillation Type			
	Paroxysmal (n = 24)	Persistent (n = 67)	Permanent (n = 9)	p-value
LA Volume (ml)	110.2 ± 29.5	128.5 ± 32.0	214.0 ± 159.5	<0.0001
RIPV (cm^2)	2.6 ± 1.2	3.4 ± 2.5	3.5 ± 2.5	0.3104
LIPV (cm^2)	2.0 ± 1.1	2.3 ± 0.8	2.4 ± 0.8	0.3070
RSPV (cm^2)	3.0 ± 1.2	3.4 ± 2.1	4.9 ± 2.1	0.0439
LSPV (cm^2)	2.4 ± 1.1	2.6 ± 1.8	2.5 ± 1.1	0.8696
Average of all PVs	2.5 ± 1.1	2.9 ± 1.8	3.3 ± 1.6	0.4058

LA: Left atrium; LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; RIPV: Right inferior pulmonary vein; RSPV: Right superior pulmonary vein. All values are expressed as mean ± standard deviation.

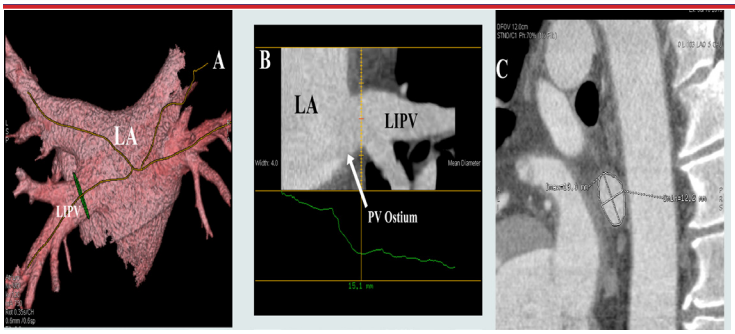

Figure 2: Method demonstrating the measurement of the pulmonary vein orifice cross-sectional area. A. Left atrium and pulmonary veins are reconstructed and the axes of the pulmonary veins are marked as lines. B. In this view, the point where the cross-sectional area is to be measured is determined. Care was taken to avoid the funnel shaped ostia and venous bifurcations. C. Once the measurement point has been determined, the cross-sectional area is calculated after marking the entire pulmonary vein cross-section. The picture shows the marked circumference with both major and minor axes. LA: Left atrium; LIPV: Left inferior pulmonary vein; PV: Pulmonary vein.

by identifying the mitral annulus and pulmonary vein ostia. The left atrial appendage was included in the volume measurements [Figure 2].

Atrial Fibrillation Radiofrequency Ablation Procedure

Pulmonary vein antral isolation has been described in detail elsewhere [11], [13], [19]. Briefly, intracardiac echocardiography (ICE) was used to obtain transseptal access and define the anatomy of the pulmonary veins. A circular mapping catheter (Lasso®, Biosense Webster, Inc. Diamond Bar, CA) was used to map around the pulmonary veins and a 3.5-mm irrigated tip catheter NAVISTAR® THERMOCOOL®, Biosense Webster, Inc. Diamond Bar, CA) was used to ablate the PV antra thus achieving electrical isolation. A 3-D map of the LA was reconstructed with CARTO® 3 (Biosense Webster, Inc. Diamond Bar, CA) or Ensite™ NavX™ (St Jude Medical, St. Paul, MN). The procedural end point for this ablation strategy was elimination of all local pulmonary vein potentials along the antra or inside the veins (entrance and exit block). The procedure was performed in patients regardless of presenting rhythm, and, if necessary, direct current cardioversion was performed at the end of the procedure. All patients had therapeutic INRs at the time of the procedure, and additional unfractionated heparin was used to keep the activated clotting time > 400 seconds during the procedure.

Statistical Analysis

All data variables are presented as absolute and relative frequencies. Quantitative variables are expressed as mean ± standard deviation. Paired t-test and Wilcoxon signed-rank test were used to compare paired groups and one-way ANOVA was used to compare 3 groups. All reported p-values are based on two-tailed tests and compared to a significance level of 0.05. All data were analyzed with PASW Statistics for Windows (Version 18.0. Chicago: SPSS Inc.).

Table 3: Post-procedural Cardiac CT Measurements Grouped by Ablation Outcomes

	Pre-ablation (n = 100)	Post-ablation AF Recurrence (n = 27)	Post-ablation Successful (n = 73)	Percentage Change with Restoration of Sinus Rhythm	p-value
LA Volume (ml)	132 ± 60	133 ± 54	118 ± 42	11%	0.15
Pulmonary Vein Cross Sectional Areas (cm^2)					
Left Superior PV	2.5 ± 1.6	2.4 ± 1.5	1.8 ± 1.0	25%	0.02
Left Inferior PV	2.2 ± 0.9	2.3 ± 0.9	1.8 ± 0.8	21%	0.01
Right Inferior PV	3.2 ± 2.3	3.0 ± 1.3	2.5 ± 1.2	17%	0.07
Right Superior PV	3.4 ± 2.0	3.4 ± 1.5	2.6 ± 1.2	18%	0.01
Average	2.89 ± 2.32	2.80 ± 1.9	2.18 ± 1.12	22%	0.04

LA: Left atrium; PV: Pulmonary vein. All values expressed as mean ± standard deviation

Results

The baseline characteristics are shown in [Table 1]. Patients were predominantly Caucasian (92%) with a mean age of 60 ± 8 years and an average body mass index (BMI) of 27 ± 7 kg/m^2. Men accounted for 73% (n=73) of the cohort. Many had hypertension (70%) and dyslipidemia (68%). Sleep apnea was observed in 33%, diabetes in 25% and corrected thyroid dysfunction in 19%. A majority of the patients had persistent AF (67%), while permanent and paroxysmal AF were noted in 9% and 24%, respectively. The average AF duration was 55 ± 54 months. The baseline 2-D transthoracic echocardiogram showed an average left ventricular ejection fraction of 57 ± 8% with an LA dimension of 4.3 ± 0.6 cm. On average, the ablation procedure took 244 ± 70 min.

Baseline LA volume and PVOCA measurements are shown in [Table 2]. LA volume at baseline differed significantly between paroxysmal and permanent AF ($p < 0.0001$). The average PVOCA for paroxysmal, persistent, and permanent AF was 2.5, 2.9, and 3.3 cm2 (p=0.41), respectively. Differences in PVOCA among the three types of AF did not reach statistical significance (p = 0.31, 0.31, 0.87) in any of the PVs except in RSPV (p = 0.04).

Effect of RF ablation on LA volume & PVOCA

[Table 3] summarizes the baseline and post-procedural cardiac CT measurement data. Successful RF ablation resulted in a dramatic reduction in post-ablation PVOCA compared to the pre-ablation values (2.89 ± 2.32 cm^2 vs. 2.18 ± 1.12 cm^2, p = 0.04). Patients who remained in AF after PVI (n = 27) did not demonstrate a significant change in LA volume or PV ostial cross-sectional area from baseline. When sinus rhythm was restored, the LA volume decreased by 11% (p = 0.15). On average, the PV cross-sectional areas was decreased by 22%.

Table 4: Percentage Reduction of All Individual Pulmonary Veins

	LA Volume (n = 100)	LSPV (n = 97)	LIPV (n = 96)	RIPV (n = 98)	RSPV (n = 99)	All PVs (n = 390)
>25% reduction	13 (13%)	52 (54%)	31 (32%)	30 (31%)	31 (31%)	144 (37%)
0-25% reduction	65 (65%)	25 (26%)	35 (36%)	43 (44%)	37 (37%)	140 (36%)
No reduction or increase in size	22 (22%)	20 (21%)	30 (31%)	25 (26%)	31 (31%)	106 (27%)

LA: Left atrium, LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; RIPV: Right inferior pulmonary vein; RSPV: Right superior pulmonary vein; PV: Pulmonary vein. All values are expressed as number (percentage). The percentage reduction of each vein was calculated compared to preablation CT. They were grouped into 3 groups depending the amount of change noticed (>25%, 0-25% reduction, no reduction or increase). A total of 390 veins were analyzed, common or middle pulmonary were not included in the analysis.

Subgroup Analyses

Data related to subgroup analyses are displayed in [Table 4]-[Table 6]. In the subgroup of patients in whom sinus rhythm was successfully restored, post-ablation follow-up CT scan measurements generally showed a trend towards smaller volumes and cross-sectional areas [Table 4]. In paroxysmal AF patients who successfully maintained sinus rhythm, LA volumes were reduced by 11% (p = 0.30). In the persistent AF group, LA volumes were reduced by 13% (p = 0.02),

Table 5: Subgroup Analysis of Patients with Successful Restoration of Sinus Rhythm

Sinus Rhythm Restored Group (n = 73)									
Baseline AF Type	**Paroxysmal (n = 15)**			**Persistent (n = 52)**			**Permanent (n = 6)**		
	Pre-ablation	**Post-ablation**	**% Change (p-value)**	**Pre-ablation**	**Post-ablation**	**% Change(p-value)**	**Pre-ablation**	**Post-ablation**	**% Change(p-value)**
LA Volume (ml)	114 ± 25	102 ± 36	11% (0.30)	132 ± 37	115 ± 38	13% (0.02)	151 ± 47	137 ± 38	9% (0.58)
LSPV (cm^2)	2.50 ± 1.26	2.39 ± 0.78	4% (0.78)	2.50 ± 1.69	1.72 ± 0.88	31% (0.004)	2.72 ± 1.27	2.38 ± 1.69	13% (0.70)
LIPV (cm^2)	2.24 ± 1.11	1.68 ± 0.42	25% (0.08)	2.25 ± 0.83	1.64 ± 0.71	27% (0.0001)	2.47 ± 1.00	1.82 ± 0.65	55% (0.21)
RIPV (cm^2)	2.65 ± 1.04	2.38 ± 0.96	10% (0.47)	3.46 ± 2.79	2.32 ± 1.30	34% (0.009)	3.84 ± 3.06	3.07 ± 2.03	20% (0.62)
RSPV (cm^2)	2.82 ± 0.85	2.10 ± 1.23	26% (0.07)	3.32 ± 2.31	2.38 ± 1.04	28% (0.009)	5.53 ± 2.08	3.87 ± 0.83	30% (0.10)
Average	2.55 ± 1.07	2.14 ± 0.85	16% (0.26)	2.88 ± 1.91	2.01 ± 0.98	30% (0.004)	3.64 ± 1.85	2.79 ± 1.3	23% (0.38)

AF: Atrial fibrillation; LA: Left atrium; LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; RIPV: Right inferior pulmonary vein; RSPV: Right superior pulmonary vein; PV: Pulmonary vein. All values are expressed as mean ± standard deviation.

and in permanent AF group, the reduction was 9% (p = 0.58). The average PV cross-sectional areas were reduced by 16% (p = 0.26), 30% (p = 0.004), and 23% (p = 0.38) in the paroxysmal, persistent, and permanent AF groups, respectively [Table 5].

In the subgroup of patients where AF persisted despite ablation, the change in LA volumes and PV cross-sectional areas were relatively unaffected. The mean LA volume was reduced by 3% in paroxysmal AF (p = 0.86), 2% in persistent AF (p = 0.76) and 9% in permanent AF (p = 0.85). The individual PV cross-sectional areas remained relatively unchanged as well [Table 6].

Discussion

Our study confirms that, following RF ablation of atrial fibrillation, restoration of sinus rhythm reduces LA volume and PV orifice cross-sectional areas physiologically. We believe the reduction in LA volume and PV dimensions are a direct consequence of RF ablation and sinus rhythm restoration. Care was taken to avoid including patients whose pulmonary veins showed segmental narrowing, which may indicate a pre-existing anomaly or direct injury to the pulmonary vein from RF energy delivery. In addition, conditions that could potentially limit or restrict changes in LA volume were excluded from the study. Therefore we believe the exclusion criteria resulted in a cohort in whom the effect of sinus rhythm restoration could be studied in relative isolation.

The results confirmed that a reduction in LA volume, in the absence of focal stenosis, is associated with a concomitant reduction in PV caliber, as assessed by ostial cross-sectional area. The diagnosis of PV stenosis is typically made based upon comparison with pre-ablation cardiac CT dimensions [12], [14]-[16], [20]. Our study demonstrates that following successful AF ablation, a reduction in cross-sectional area of up to 25% may be observed in some pulmonary veins. We believe that reduction of this magnitude without any evidence of focal stenosis should be considered physiologic and likely a distinct, compensatory process in comparison to the pronounced pathologic changes of PV stenosis. Asymptomatic patients may therefore be spared additional cardiac CT studies, thereby reducing their radiation exposure in addition to healthcare expenditures.

At baseline, LA volumes were significantly different among the different AF type groups. Previous studies have shown similar changes in LA diameter and volume after AF ablation [2]-[4], [6], [7], [21]-[23]. The precise mechanisms resulting in the observed LA volume and PVOCA reductions could not be established in this study. Multiple etiologies have been postulated to explain the volume reduction, including reverse remodeling of the LA, scar tissue resulting from RF thermal injury, improved LA function, and reduced LA pressures [4], [6], [18].

Our results are consistent with other studies which have shown similar reductions in LA size only in patients seemingly free of AF at follow-up [3], [22], suggesting positive remodeling of LA after successful sinus rhythm restoration. Other studies have shown reduction in LA volume irrespective of sinus rhythm restoration [4], [6], [7]. This could be due to fibrosis from scarring of the LA from RF injury rather than positive remodeling. A more nuanced explanation might involve a correlation between AF burden and pre-ablation LA size, as suggested in the findings of Jayam et al. who found that in a multivariate regression only pre-ablation LA volume predicted the percentage reduction in LA volume post-ablation [7]. Indeed, this seems consistent with our finding of significant LA volume differences among paroxysmal, persistent, and permanent AF patients at baseline (Table 2).

Furthermore there appears to be an important relationship between

Table 6: Subgroup Analysis of Patients Remaining in AF after Radiofrequency Ablation

AF Recurrence Group (n = 27)									
Baseline AF Type	**Paroxysmal (n = 9)**			**Persistent (n = 15)**			**Permanent (n = 3)**		
	Pre-ablation	**Post-ablation**	**% Change (p-value)**	**Pre-ablation**	**Post-ablation**	**% Change(p-value)**	**Pre-ablation**	**Post-ablation**	**% Change(p-value)**
LA Volume (ml)	107 ± 34	104 ± 35	3% (0.86)	121 ± 18	119 ± 17	2% (0.76)	185 ± 104	169 ± 99	9% (0.85)
LSPV (cm^2)	2.14 ± 0.74	1.74 ± 0.73	19% (0.27)	2.74 ± 2.04	2.32 ± 1.29	15% (0.51)	2.09 ± 0.70	1.90 ± 0.65	9% (0.75)
LIPV (cm^2)	1.55 ± 1.03	1.73 ± 0.92	-12% (0.70)	2.29 ± 0.76	2.08 ± 0.99	9% (0.52)	2.17 ± 0.65	2.23 ± 0.85	-3% (0.03)
RIPV (cm^2)	2.57 ± 1.59	2.25 ± 0.89	12% (0.61)	3.23 ± 1.09	2.86 ± 1.3	11% (0.41)	3.04 ± 1.61	3.00 ± 1.17	1% (0.97)
RSPV (cm^2)	3.17 ± 1.71	2.79 ± 0.97	12% (0.52)	3.49 ± 1.31	2.9 ± 1.36	17% (0.24)	3.78 ± 1.91	3.76 ± 0.64	1% (0.99)
Average	2.36 ± 1.27	2.13 ± 0.88	10% (0.66)	2.94 ± 1.3	2.54 ± 1.2	14% (0.39)	2.77 ± 1.22	2.72 ± 0.83	2% (0.96)

AF: Atrial fibrillation; LA: Left atrium; LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; RIPV: Right inferior pulmonary vein; RSPV: Right superior pulmonary vein; PV: Pulmonary vein. All values are expressed as mean ± standard deviation.

the reduction in LA volume and PVOCA post-ablation and AF chronicity, with a significant benefit seen in early persistent AF patients as compared to those with paroxysmal AF. Interestingly, though the improvement in the long standing persistent or permanent AF patients was higher than that seen in the paroxysmal AF group, it was less than pronounced than the early persistent group. This observation highlights the untoward effects of progressive AF and also suggests the possibility of permanent remodeling changes that could result in irreversible scar formation in this subgroup of patients. Further clinical and laboratory investigation promises to help elucidate these mechanisms further.

Limitation

This is a Our study has a number of limitations that merit discussion. The time span from restoration of sinus rhythm to completion of the follow-up CT scan is important, as it can affect the observations related to LA remodeling and fibrosis and affect comparisons between various subgroups. LA pressure changes can alter the LA size and shape, and unfortunately there are no reliable, non-invasive methods to accurately assess LA pressure. The amount of LA fibrosis can affect the the chamber's elasticity and prevent positive or reverse remodeling of the LA after restoration of sinus rhythm. Quantification of post-ablation LA scarring and fibrosis for comparison to pre-ablation findings would have helped us to differentiate the relative contributions of increased LA scarring and/or positive remodeling to the observed changes in LA and PVOCA dimensions. However, due to technical limitations with our institutional MR scanners, we could not assess the LA scar reproducibly, which precluded this endeavor. Lastly, our study is limited by small size, particularly in the paroxysmal and permanent AF subgroups. In these subgroups, although there was a trend of decreased LA volume and PVOCA after restoration of sinus rhythm, it did not reach statistical significance, which may have been circumvented with a larger sample size.

Conclusions

The study demonstrates that both PV orifice cross-sectional area and LA volume are reduced after successful AF ablation. These data warrant a reassessment of criteria for diagnosing PV stenosis based on changes in PV caliber alone, ideally incorporating adjustments to reflect reductions in LA volume post-ablation. Further studies are needed to identify the role of LA pressure, remodeling and fibrosis in predicting LA and PV dimension changes, as they may also enhance our understanding of the pathophysiology of pulmonary vein stenosis and inform techniques to prevent this complication.

Conflict Of Interests

None.

Disclosures

None of the authors have any disclosures relevant to the study.

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Use of Acoustic Cardiography Immediately Following Electrical Cardioversion to Predict Relapse of Atrial Fibrillation

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Abstract

Predicting atrial fibrillation (AF) recurrence after successful electrical cardioversion (ECV) is difficult. The main aim of this study was to investigate whether acoustic cardiography (AUDICOR® 200) immediately post-ECV might provide indices for AF relapse following cardioversion. Acoustic cardiography parameters included Electromechanical Activation Time (EMAT), Left Ventricular Systolic Time (LVST), QRS duration, heart rate and third heart sound intensity (S3 Strength). We analysed data from 140 patients who underwent successful cardioversion and in whom AUDICOR results and echocardiographic measurements immediately after (baseline) ECV were available. Patients were prospectively followed-up at 4-6 weeks, 3 and 12 months post-ECV, and sinus rhythm maintenance was evaluated using acoustic cardiography and Holter electrocardiography. The effect of each baseline AUDICOR parameter on the hazard of AF relapse was investigated using Cox proportional hazards (PH) models. Fifty patients (35.7%) had AF relapse. Of all the AUDICOR parameters, only S3 Strength exhibited consistent predictive value. Increasing S3 Strength increased the hazard of relapse in a univariable Cox PH model (HR=2.52, p=0.003), and in two multivariable Cox PH model constructions (Model 1 excluded heart rate and Model II excluded EMAT/RR, LVST and LVST/RR) both of which included the parameters as continuous variables (Model I: HR=1.15, p=0.042; Model II: HR=1.14, p=0.045) or the parameters dichotomized according to suggested cut-points (Model I: HR=2.5, p=0.007; Model II: HR=2.09, p=0.031). In conclusion, this study suggests that acoustic cardiography may be a simple inexpensive and quantitative bedside method to assist in prediction of AF recurrence after ECV.

Introduction

Atrial fibrillation (AF) is the most common heart rhythm disorder encountered in clinical practice. It is associated with decreased exercise tolerance and substantial mortality and morbidity due to thromboembolic accidents and heart failure.[1] Therapy of AF is primarily aimed at restoration of a regular rhythm so that optimal cardiac output is sustained, risk of stroke reduced and the symptoms are lessened, with the ideal end result being long term maintenance of normal sinus rhythm (SR) to potentially prevent tachycardia-induced myocardial remodelling and heart failure.

In the hospital, external direct current electrical cardioversion (ECV) is the most frequently used and effective method for converting AF to SR. With vigilant attention to cardioversion technique and anti-coagulation, ECV is successful in 80-95% of patients.[2] However, AF recurrence after successful cardioversion is common: around 20-50% of patients suffer from AF recurrences within 2 weeks of cardioversion even if under antiarrhythmic drug therapy, 40-60% of patients relapse into AF within 3 months and 60-80% relapse within 12 months.[2],[3] Reported predisposing factors for AF recurrences include advanced age, AF duration, left atrial enlargement, increased heart rate variability, structural heart disease, hypertension, diabetes and serological biomarkers of inflammation, coagulation activity, cardiovascular stress, myocardial injury, and cardiac and renal dysfunction.[4]-[7] In particular, echocardiographic assessment of left atrial diameter, volume and area have been identified as predictors of AF recurrence.[7] However, all these factors have limited predictive value and are used mainly to direct therapy or advise against the procedure in patients with a high risk of AF recurrence. It remains a matter of debate as to whether and when AF relapses should be treated.

Identification of easy-to-obtain, non-invasive parameters documenting successful cardioversion and potential for AF relapse would facilitate a better management of patients in whom conversion is difficult and/or in whom long-term maintenance of SR is difficult to achieve. This study aimed to identify acoustic cardiography parameters acquired immediately after ECV (i.e. at baseline) that might predict AF recurrence during follow-up and compared their predictive value to echocardiographic measurements. We carried out a 12-month follow-up in patients who were referred for ECV due to AF to examine the association of the acoustic cardiography-and

Key Words

Acoustic cardiography, Atrial fibrillation, Electrical cardioversion, Relapse.

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echocardiographic variables with relapse.

Methods

Study Population

The study was approved by the local Medical Ethics Committee. All patients provided written informed consent. A total of 156 patients were referred for ECV to the Luzerner Kantonsspital (Department of Cardiology) for AF-related symptoms. Patients who experienced episodic AF, self-terminating within 7 days, were said to have paroxysmal AF, while patients whose arrhythmia persisted more than 7 days (or required intervention to terminate) were considered to have persistent AF. One hundred and thirty-eight patients had persistent atrial fibrillation and 18 had paroxysmal atrial fibrillation. Eight patients could be converted on improved medical therapies during work up. The remaining 148 patients were elected for ECV.

Electrical Cardioversion Protocol

ECV was performed under sedation with intravenous midazolam or propofol. A biphasic R-wave synchronized shock (Lifepak12, Physiocontrol Ltd, Redmond, WA, USA) was applied to the patients via self-adhesive skin electrodes (TZ Medical Inc., Portland, OR, USA) in an anterior–posterior position. An initial ECV started out with 300 J, and it was repeated until the patient was either in SR or a maximum of 3 shocks were given. In patients not receiving amiodarone or QT prolonging drugs the repeat ECV was performed after intravenous administration of either ibutlide or vernakalant. Patients in whom AF still persisted (n = 6) were considered to have failed ECV.

Acoustic Cardiography (AUDICOR)

Prior to (between 1 to 7 days), and immediately after (within 5-6 min), ECV patients underwent acoustic cardiography (AUDICOR® 200, Inovise Medical, Inc., Beaverton, Oregon, USA) testing. AUDICOR measurements immediately before ECV are defined as "baseline" measurements. Acoustic cardiography consists of recording and algorithmically interpreting simultaneous digital 12-lead electrocardiographic and acoustic signals using dual-purpose sensors placed in the V3 and V4 positions. The technology produces a variety of hemodynamic relevant measurements including the presence and strength of diastolic heart sounds, such as the third (S3) and fourth (S4) heart sound, and it registers systolic properties through the calculation of systolic time intervals, i.e. its proprietary Electromechanical Activation Time (EMAT, defined as the time from Q-wave onset to the mitral component of the first heart sound), Left Ventricular Systolic Time (LVST, interval from the first heart sound to the second heart sound), as well as a Systolic Dysfunction Index (SDI). Those parameters have been shown to correlate well with established measures of cardiac function,[8]-[15] and have proven to provide prognostic information[16],[17] relevant for the optimization of cardiac treatment.[18]-[21] EMAT reflects the time for the LV to generate enough force to close the mitral valve and when prolonged indicates impaired LV function measured by reduced ejection fraction[8], [11] or decreased maximum LV dP/dt in patients in both normal sinus rhythm[12] and atrial fibrillation.[15] S3 Strength is a continuous parameter that correlates with increased LV end-diastolic pressure and echocardiography determined increased E deceleration rate, E/E' and lower ejection fraction.[11], [13]

Table 1: Demographics and baseline echocardiographic results for the population, overall and split by successful conversion (no CV vs. CV).

	All	no CV	CV	p
N	146	6	140	
Age (years, mean (sd))	67.5 (12.5)	73.9 (4.6)	66.8 (12.9)	0.186
Sex = F (%)	37 (25.0)	2 (33.3)	34 (24.1)	0.635
Persistent AF = persistent (%)	131 (88.5)	6 (100.0)	124 (87.9)	1.000
Device = ICD (%)	71 (48.0)	4 (66.7)	66 (46.8)	0.425
LV ejection fraction (%, mean (sd))	50.7 (12.8)	49.3 (15.3)	50.8 (12.8)	0.829
LA diameter (mm, mean (sd))	43.5 (6.0)	46.8 (11.3)	43.4 (6.7)	0.487
LA area (cm^2, mean (sd))	26.4 (6.5)	29.7 (11.6)	26.1 (6.24)	0.501
Lateral E/e_l (mean (sd))	8.5 (5.0)	8.2 (3.6)	8.5 (5.1)	0.828

Comparisons were done using t-test for continuous variables and Fisher's exact test for categorical variables. AF = atrial fibrillation; ECV = electrical cardioversion; ICD = implantable cardioverter defibrillator; LA = left atrial; LV = left ventricular.

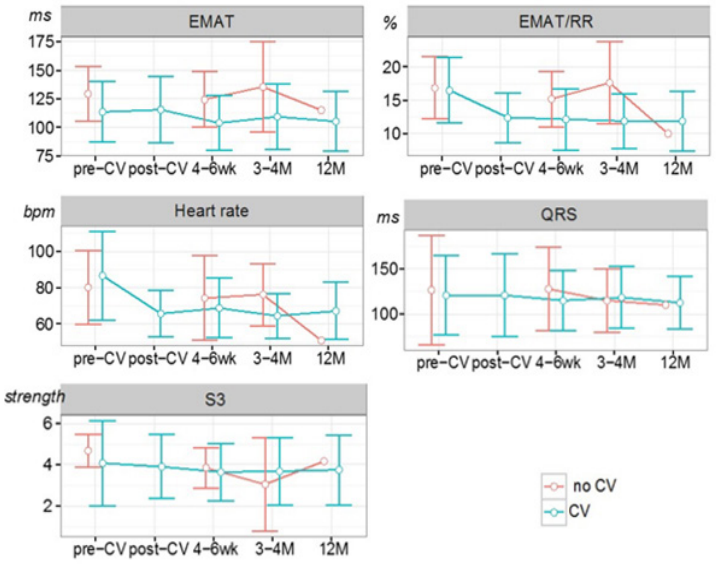

Figure 1: Graphical representation of the descriptive statistics (mean ± standard deviation) of AUDICOR measurements in patient subgroups based on successful (CV) or unsuccessful (no CV) cardioversion. EMAT = electromechanical activation time; RR = R-R interval; S3 = third heart sound.

Echocardiography

Transthoracic Doppler echocardiography was performed according to the guidelines of the American Society of Echocardiography (Philips IE 33, Eindhoven, The Netherlands) before ECV, after ECV and at all follow-up appointments. Measurements included left ventricular ejection fraction, left atrial diameter (long axis view), left atrial area and E/e' ratio.

Follow-up

Table 2: Summary of the association of AUDICOR variables measured at baseline with the hazard of AF relapse. Estimates from univariable Cox proportional models.

Variable	HR	95% CI	p
EMAT (ms)	1.02	[0.91, 1.14]	0.767
EMAT/RR (%)	0.57	[0.32, 1.04]	0.0673
Heart rate (bpm)	0.86	[0.76, 0.97]	0.0178
S3 Strength	1.16	[1.03, 1.32]	0.0179
QRS duration (ms)	1.00	[1.00, 1.01]	0.309

The hazard ratios (HR) represent the relative increase (CI = confidence intervals) in hazard per 10-unit increase in AUDICOR variable measurements EMAT and heart rate, or 1 unit for S3 and QRS. EMAT = electromechanical activation time; RR = R-R interval; S3 = third heart sound.

Patients were prospectively followed-up at 4-6 weeks, 3 months and 12 months after ECV. Acoustic cardiography was performed using AUDICOR® 200 at every visit. In addition, Holter echocardiography (7 days) was evaluated and success of conversion considered if there was complete absence of AF. Anti-arrhythmic therapy was reduced in patients still in SR at 3 months post-ECV, and for patients still in SR at 12 months post-ECV anticoagulation and beta-blocker therapies were terminated. Not all of the patients returned to our clinic for every follow-up examination due to death (n = 3 within 3 months of ECV; n = 3 within 12 months of ECV), refusal of follow-up (n = 2 and n = 5 at 3 and 12 month follow-ups, respectively) and decision by patients to be followed-up by their referring doctors (n = 40 and n = 54 at 3 and 12 month follow-ups, respectively). This latter patient group was included in the analyses since requisite information on clinical status (e.g. AF relapse or not) was provided to our clinic by the referring doctors.

Table 3: Number of patients and relapse events (%) for each AUDICOR parameter and echocardiographic measurement, split by the applied cut-points.

Variable	Cut-point Group	N patients	No relapse	Relapse
EMAT (ms)	< 136	121 (86.4)	79 (65.3)	42 (34.7)
	≥ 136	19 (13.6)	11 (57.9)	8 (42.1)
EMAT/RR (%)	< 13	28 (20.0)	14 (50.0)	14 (50.0)
	≥ 13	112 (80.0)	76 (67.9)	36 (32.1)
Heart rate (bpm)	< 103	108 (77.1)	63 (58.3)	45 (41.7)
	≥ 103	32 (22.9)	27 (84.4)	5 (15.6)
QRS duration (ms)	< 92	29 (26.6)	25 (86.2)	4 (13.8)
	≥ 92	80 (73.4)	46 (57.5)	34 (42.5)
S3 Strength	< 6.24	120 (85.7)	83 (69.2)	37 (30.8)
	≥ 6.24	20 (14.3)	83 (69.2)	13 (65.0)
LA area (cm^2)	< 30	97 (70.8)	64 (66.0)	33 (34.0)
	≥ 30	40 (29.2)	23 (57.5)	17 (42.5)
LA diameter (mm)	< 50	111 (81.6)	73 (65.8)	38 (34.2)
	≥ 50	25 (18.4)	14 (56.0)	11 (44.0)
E/e'ratio	< 11	90 (81.1)	59 (65.5)	31 (34.5)
	≥ 11	21 (18.9)	13 (61.9)	8 (38.1)

EMAT = electromechanical activation time; RR = R-R interval; S3 = third heart sound.

AUDICOR measurements S4 and SDI were not analysed due to incomplete records for a large proportion of the patients at many of the time-points. The strength of the S4 is not generated in AUDICOR measurements when the rhythm is detected to be atrial fibrillation or atrial flutter. The SDI parameter was introduced in the AUDICOR software mid-way through the study and therefore, not available for the acoustic cardiography tests prior to the software update. Comparison between groups was done using t-test for continuous variables and Fisher's exact test for categorical variables. The association of AUDICOR parameters with the odds of successful conversion was examined using univariable logistic regressions. AUDICOR variables were included, each in turn, as single, continuous, predictors. A Kaplan-Meier curve was plotted for the probability of time without relapse, with patients lost to follow-up or dead being censored on their last known time. The effect of each AUDICOR parameter on the hazard of AF relapse was investigated using Cox proportional hazards (PH) models. Best cut-points of AUDICOR parameters were suggested as the values which, when splitting patients accordingly, provided the most significant result in a Cox PH model (i.e. lowest p-value). Multivariable Cox PH regression models once with continuous and once with dichotomized variables were used to examine which variables would remain potential/important predictors of relapse when utilizing the linear combination of all AUDICOR variables. Two multivariable Cox PH models were constructed. Since heart rate correlated strongly with three other AUDICOR parameters (EMAT/RR, LVST and LVST/RR), the first multivariable model included the three variables and excluded heart rate Model I), while the second excluded the three correlated variables but included heart rate (Model II). Since exact time of relapse between follow-up visits was mostly unknown, the data could be seen as interval censored. A sensitivity analysis was performed using methods appropriate for the analysis of interval censored data based on the R package "interval".[22] Results of this analysis did not differ qualitatively from the main results, and thus are not reported. Unless otherwise specified, data are reported as mean values and standard deviations. P< 0.05 was taken as level of statistical significance. Statistical analyses were performed using R version 3.3.2 software.[22]

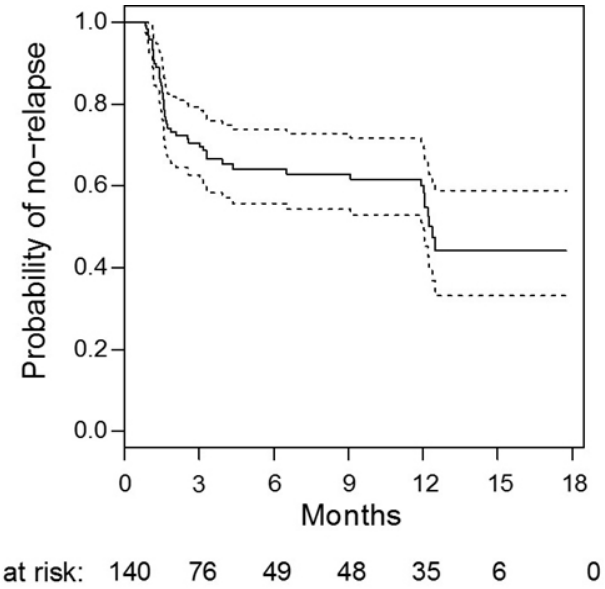

Figure 2: Kaplan-Meier estimates (with 95% confidence intervals) of the probability of no relapse.

Results

Of the 148 patients who underwent ECV, cardioversion was documented as successful in 141 (95.2%). In 1 patient ECV outcome was not documented: this patient was excluded from the study analysis. One of the successfully converted patients was also excluded from the study due to missing baseline AUDICOR measurements. Population demographics and baseline echocardiographic

Table 4: Suggested cut-points for AUDICOR parameters and the related hazard ratios (HR) for relapse. Echocardiographic parameters with previously reported cut-points and the related HR for relapse.

Variable	Cut-point	HR	95% CI	p
EMAT (ms)	136.00	1.30	[0.57, 2.97]	0.498
EMAT/RR (%)	13.00	0.55	[0.27, 1.14]	0.052
Heart rate (bpm)	103.00	0.30	[0.16, 0.56]	0.007
QRS duration (ms)	92.00	4.31	[2.20, 8.45]	0.002
S3 Strength	6.24	2.54	[1.09, 5.94]	0.003
LA area (cm^2)	30.00	1.60	[0.33, 1.19]	0.105
LA diameter (mm)	50.00	1.40	[0.67, 2.95]	0.317
E/e' ratio	11.00	1.08	[0.49, 2.39]	0.847

The hazard ratios (HR) represent the relative increase (CI = confidence intervals) in hazard per 10-unit increase in AUDICOR variable measurements EMAT and heart rate, or 1 unit for S3 and QRS. EMAT = electromechanical activation time; RR = R-R interval; S3 = third heart sound.

measurements for the analysed patient population (n = 146) split by ECV success at baseline are summarized in [Table 1]. Of the 121 patients followed-up at 4-6 weeks 82 (67.7%) were in SR, of the 103 patients followed-up at 3 months 81 (78.6%) were in SR, and of the 82 patients followed-up at 12 months 61 (74.3%) were in SR.

Graphical representations of the descriptive statistics of AUDICOR measurements collected at each time point in the patient subgroups are given in [Figure 1].

The effect of each AUDICOR parameter on the hazard of AF relapse was investigated using Cox proportional hazards (PH) models. Only patients who originally had successful ECV and in whom AUDICOR data was collected at baseline (n = 140) were included in the analysis and of these, 50 (35.7%) had AF relapse. [Table 2] summarizes the results of univariable Cox models of the time until first relapse. The effects of increasing 10 units of EMAT/RR equals an approximately 40% decrease in the hazard of relapse, although this trend is not quite statistically significant. The effect of increasing S3 levels was also significant, indicating a significant 16% increase in hazard per S3 unit increase.

A Kaplan-Meier curve was plotted for the probability of no-relapse [Figure 2]. Based on Cox PH models fit to each observed value of AUDICOR parameter, best cut-points were suggested. [Table 3] shows the distribution of patients, and the number of relapse events in each group, when split according to the suggested cut-point for each AUDICOR parameter as well as echocardiographic measurements at published cut-points (E/e' at 11,[23] LA diameter at 50 mm,[24] LA area

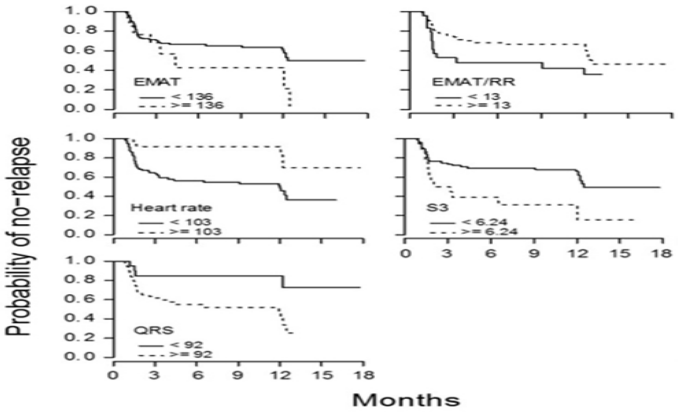

Figure 3: Probability of relapse when grouping patients based on suggested cut-points using Regular Kaplan-Meier estimates. EMAT = electromechanical activation time; RR = R-R interval; S3 = third heart sound.

at 30 cm²[25]). The suggested cut-points for AUDICOR parameters LVST and LVST/RR were unrealistic and impracticable; therefore, those results are not presented. This limitation notwithstanding, for the parameters EMAT/RR, QRS duration and S3 Strength there were significant differences in the hazard of relapse when splitting the patients according to the suggested cut-points [Table 4]. Hazard ratios for echocardiographic measurements of LA area, LA diameter and lateral E/e' are also provided in [Table 4] for comparison with AUDICOR results. [Figure 3] shows the Kaplan-Meier curves for probability of no-relapse when patients are grouped based each time on an AUDICOR parameter's suggested cut-point.

We further used multivariable Cox PH regression models to examine which variables would remain potential/important predictors of relapse when utilizing the linear combination of all AUDICOR variables. Results of the multivariable Cox PH model

Table 5: Results of the multivariable Cox proportional hazards model I including continuous or dichotomized AUDICOR parameters measured at baseline. (Model I excludes heart rate measurements.)

Variable	HR	95% CI	p
Continuous			
EMAT (ms)	1.09	[0.79, 1.49]	0.607
EMAT/RR (%)	0.34	[0.03, 4.51]	0.416
LVST (ms)	0.98	[0.83, 1.16]	0.837
LVST/RR (%)	1.24	[0.51, 3.06]	0.635
QRS duration (ms) (.imp)	1.01	[1.00, 1.01]	0.307
S3 Strength	1.15	[1.01, 1.31]	0.042
Dichotomized			
(cut.) EMAT (ms)	2.11	[0.95, 4.69]	0.066
(cut.) EMAT/RR (%)	0.54	[0.25, 1.13]	0.100
(cut.) LVST/RR (%)	0.74	[0.24, 2.23]	0.588
(cut.) QRS duration (ms) (.imp)	2.21	[0.77, 6.36]	0.142
(cut.) S3 Strength	2.50	[1.29, 4.84]	0.007

Missing QRS duration measurements were imputed (.imp) by the median before dichotomization (cut.). Hazard ratios (HR) and 95% confidence intervals (CI) in hazard per 10-unit increase in AUDICOR variable measurements EMAT, LVST and heart rate, or 1 unit for S3 and QRS. p-values determined by Wald test. EMAT = electromechanical activation time; RR = R-R interval; LVST = left ventricular systolic time; S3 = third heart sound.

I with either continuous or dichotomized variables are shown in [Table 5]. A consistent and significant association with hazard of relapse was found only for S3 Strength. Results of the multivariable Cox PH model II with either continuous or dichotomized variables are reported in [Table 6]. This model also yielded a consistent and significant increase in hazard of relapse for increasing S3 Strength. Heart rate showed a significant association with the hazard of relapse only when dichotomized.

Discussion

Introducing simple, objective, and reproducible predictors of ECV success and SR maintenance during follow-up may facilitate the decision-making process concerning the choice of strategy of rhythm or rate control. Duration of AF prior to intervention has been shown to be a predictor of AF recurrence in patients with left-atrial (LA) dilation after ECV[23] and after LA ablation.[24] Echocardiographic measurement of LA diameter >50 mm has also been shown to predict recurrence of AF after LA ablation.[24] These findings are consistent with the expert consensus statement of the European Cardiac Arrhythmia Society which recommends patient selection for atrial ablation including severity of symptoms, age, duration of AF and LA diameter.[26] Other LA properties determined by various imaging modalities have shown promise as predictors of AF recurrence. Fornengo et al found echocardiographic septal E/e' ratio ≥11 predicted AF recurrence after ECV at 3 months in patients with LA dilation.[23] Also, Hussien et al found pre-procedural BNP, LA area and LV ejection fraction were independently associated with AF recurrence within 24 months in patients who underwent successful radiofrequency catheter ablation.[27] With more advanced imaging, multi-detector computed tomography, Abecasis found LA volume to be a predictor of patients in whom successful AF ablation can be achieved with simpler pulmonary vein ablation procedures.[28] Based on invasive LA pressure measurements, Park et al found low LA compliance was independently associated with a 2-fold higher risk of clinical AF recurrence.[29] Aside from AF duration, these predictors depend upon echocardiography, computed tomography or invasive cardiac catheterization which are expensive and/or invasive

Table 6: Results of the multivariable Cox proportional hazards model II including continuous and dichotomized AUDICOR parameters measured at baseline. (Model II excludes EMAT/RR, LVST and LVST/RR measurements.)

Variable	HR	95% CI	p
Continuous			
EMAT (ms)	0.95	[0.83, 1.09]	0.461
Heart rate (bpm)	0.88	[0.77, 1.00]	0.054
QRS duration (ms) (.imp)	1.01	[1.00, 1.01]	0.221
S3 Strength	1.14	[1.00, 1.30]	0.045
Dichotomized			
(cut.) EMAT (ms)	1.72	[0.78, 3.79]	0.177
(cut.) Heart rate (bpm)	0.34	[0.13, 0.88]	0.027
(cut.) QRS duration (ms) (.imp)	2.09	[0.73, 6.04]	0.171
(cut.) S3 Strength	2.09	[1.07, 4.09]	0.031

Missing QRS duration measurements were imputed (.imp) by the median before dichotomization (cut.). Hazard ratios (HR) and 95% confidence intervals (CI) in hazard per 10-unit increase in AUDICOR variable measurements EMAT, LVST and heart rate, or 1 unit for S3 and QRS. p-values determined by Wald test. EMAT = electromechanical activation time; S3 = third heart sound.

procedures thus accentuating the need for noninvasive predictive parameters that can be easily collected and repeated, if necessary.

Diastolic dysfunction can cause LA remodeling that affects LA diameter, volume, pressure and underlying electrical substrate. LA remodeling due to volume overload in exercise training does not appear to increase the occurrence of AF[30] but diastolic dysfunction increases atrial pressure and reduces atrial compliance leading to atrial stretch, myolysis and fibrosis.[31] One theory related to the increased atrial pressure with diastolic dysfunction and resultant pulmonary vein dilation suggests activation of stretch-sensitive signaling pathways near the pulmonary vein may induce ectopic firing and contribute to the occurrence and maintenance of AF.[31] In a study of AF patients with diastolic dysfunction, Hu et al found lower LA voltages possibly due to atrial fibrosis and hypothesize that lower LA voltage might aggravate an interatrial conduction delay resulting in formation of circuits for re-entry.[32] Alternatively, it has been argued that the elevated atrial wall stress with diastolic dysfunction increases atrial fibrosis that electrophysiologically impairs intermyocyte coupling via gap junctions producing fragmented conduction and thus arrhythmia.[33]

Thus, evidence of diastolic dysfunction can be useful to predict those patients who will develop AF as well as those who may have recurrence of AF after ECV or ablation. For example, in a longitudinal study, Tiwari et al found an enlarged LA via echocardiography as a measure of diastolic dysfunction was a significant risk factor of development of AF (moderately enlarged LA 60% higher risk; severely enlarged LA 4.2 times higher risk).[34] Additionally, in a one-year follow-up study of 124 patients undergoing catheter ablation, significant LV diastolic dysfunction (grade 2 or 3) was an independent predictor of recurrence (hazard ratio 2.6, p=0.009) after adjusting for persistent vs. paroxysmal AF and left atrial volume.[35]

The present study found a similar hazard ratio of 2.50, p=0.007, for the acoustic cardiography S3 Strength parameter based on multivariable Cox PH models including AUDICOR parameters dichotomized according to the suggested cut-points. S3 Strength determined by AUDICOR acoustic cardiogaphy has been shown using multivariate analysis to be associated with echocardiographic E/e'[36] a marker for elevated LV filling pressure and therefore atrial pressure. Using invasive measurements of ventricular function, S3 Strength was found to have a positive linear relationship with LV end-diastolic pressure.[37] Thus, abnormally high S3 Strength may be a marker for increased LA pressure, atrial wall stress and resultant atrial remodeling. In addition, in a study of 474 heart failure patients over a mean of 484 days, S3 Strength was found to be an independent predictor of all-cause mortality and significantly lower mortality.[17] In contrast, in a study by Roos et al, EMAT was found to be superior to LV ejection fraction in detecting LV systolic dysfunction defined as reduced LV dP/dt.[12] Therefore, since recurrence of AF is associated with diastolic dysfunction and atrial remodeling due to elevated atrial pressure, it is not surprising that S3 Strength performed better than EMAT or EMAT/RR in this study.

The limitations of the current study include the relatively small size and the use of a referral-based population. The AUDICOR parameters cut-points defined in this study are data-driven and specific to our current population, such that generalization to "all" patients should be done cautiously. On the other hand, the advantage is that all our cut-points for AUDICOR parameters are actually based on data and not on assumptions, which is often the case with some "commonly used" cut-points". There were no acoustic cardiography measurements after ECV in the patients with unsuccessful ECV. We used Holter monitoring data for the assessment of heart rhythm results. Therefore, asymptomatic AF episodes occurring outside of the Holter recording may have been missed. As time to first recurrence of AF was the central outcome, we used Cox proportional hazards regression to identify risk factors. However, factors influencing the time until AF recurrence may not be constant in time, and thus using "baseline" values does not directly reflect the mechanistic/direct association of these variables and relapse. Another limitation relates to interval censoring. A summary analysis of the follow up times for patients with relapse, without relapse and combined suggested that use of univariate Cox PH models and its results may have been a simplification, as the data could be seen as interval censored. This may explain the observation of sharp drops in probability at around 12 months, likely stemming from the fact that patients returning for follow-up then could not precisely report the time of the relapse. This issue would be compounded by the limited number of follow-ups, so that estimates of HR should be taken cautiously. Nevertheless, a sensitivity analysis (not reported) using current methods for analyzing interval censored data yielded similar results.

Conclusions

Recurrence of AF after ECV or atrial ablation is, unfortunately, quite common and the ability to predict those patients with a high likelihood of AF recurrence is important. Studies using echocardiography, tomography and invasive pressure measurement have documented the relationship between AF recurrence and diastolic dysfunction with resultant atrial remodeling. The current study suggests that acoustic cardiography, a simple, bedside method that does not require specialized technicians, provides a useful marker for AF recurrence in the S3 Strength parameter.

Conflict Of Interests

None.

Disclosures

Drs. Bauer and Arand work for Inovise Medical, Inc., the company that provided the acoustic cardiography technology. All other authors have no conflicts of interest to declare.

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Excellent Symptom Rhythm Correlation in Patients with Palpitations Using A Novel Smartphone Based Event Recorder

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Abstract

Background: Definitive diagnosis of arrhythmia relies on "symptom-rhythm correlation" when electrocardiographic (ECG) evidence of the patient's cardiac rhythm is obtained at the time of symptoms. The AliveCor smartphone App and device (AliveCor Inc, California, USA) has recently been introduced as an easy to use cardiac event recorder. The aim of this study was to investigate whether the smartphone based event recorder could be effectively used to achieve symptom rhythm correlation in unselected patients with palpitations.

Methods: 20 patients (13 female, mean age 35±16 years) underwent evaluation of their palpitations for 12 weeks using 2nd generation AliveCor monitors.

Results: Symptom rhythm correlation was achieved in 85% of patients with 45% detecting an arrhythmia. Of a total of 966 ECGs available for review 96% were interpretable.

Conclusions: The novel smartphone based event recorder is an efficient tool for achieving symptom rhythm correlation in patients with palpitations. By utilising their Smartphone, ECG recording is easily and readily accessible to patients when palpitations occur.

Introduction

The definition of palpitations is subjective and patients frequently complain of this symptom in normal sinus rhythm. Furthermore, patients often report symptoms that are transient or short lived in nature and therefore difficult to diagnose. In such patients, ambulatory ECG (AECG) monitors are commonly utilized.[1]-[3]

Recently a new AECG device has been developed which allows the user to record a single lead ECG on their smartphone. The AliveCor monitor incorporates two electrodes and attaches directly to the back of the user's smartphone or its case. A 30 second real-time ECG equivalent to Lead I on a 12-Lead ECG is recorded by activating the App and placing at least one finger from each hand across the electrodes. The user then has the opportunity to annotate the recorded ECG with symptoms. Patients' personal data and recorded ECGs are stored on a secure server and accessed online by patient or healthcare professional via AliveCor's website.

Use of the AliveCor monitor in the ambulatory setting for patients with a primary complaint of palpitations has been evidenced in selected groups only; such as those with atrial fibrillation post ablation and in paediatric patients with documented paroxysmal arrhythmias.[4],[5] Although complementary of the device, further reports of its utility as an AECG device for patients with palpitations are largely anecdotal; reporting case studies and identifying potential benefits of the new technology in the larger population.[6-10] Given this potential we investigated whether the AliveCor monitor could be effectively used to achieve symptom rhythm correlation in an unselected group of patients with a primary complaint of palpitations.

Key Words

Palpitations, Arrhythmia, Smartphone ECG, AliveCor.

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Methods

Over a 3 week period, 23 patients with palpitations were referred from cardiology outpatient clinics for AliveCor monitoring. Patients were excluded if their palpitations were associated with syncope, they had an implantable cardiac device already in-situ, did not own a compatible smartphone, were unable to consent to us accessing their recorded ECGs, or were unable to use the monitor effectively.

Patients attended an outpatient AECG appointment where they received their monitor. Informed consent of the subjects for monitoring was obtained. Under instruction from the cardiac physiologist patients downloaded the 'AliveECG' App to their Smartphone and set up a 'personal account'. All patients agreed to AliveCor's data protection policy, with personal data stored on AliveCor's secure server. The patient was required to grant us access to their account in order to view recorded ECGs. This was done by accepting an invitation email sent from the department's 'healthcare provider account' accessed via the AliveCor website. The monitor was then attached to the patient's smartphone and the process of recording an ECG and annotating with symptoms explained to the patient, who was then required to record a test ECG confirming they were able to use the monitor effectively. Patients were instructed to record a 30 second ECG when symptomatic, annotate with 'palpitations' and or any other symptoms. Patients were instructed to annotate any ECGs made when asymptomatic as 'test ECG' and only use the device themselves. Patients were invited to fill in two short questionnaires, one at set-up and one when they returned the

monitor, with questions structured to gain insight into ease of use of the monitor and App.

Monitoring was conducted over 12 weeks with uploads reviewed once a week by a cardiac physiologist. Each ECG recording was categorised as one of the following: sinus rhythm, sinus bradycardia, sinus tachycardia, ventricular ectopics, supraventricular ectopics, ventricular bigeminy/trigeminy, broad complex tachycardia, narrow complex tachycardia, atrial fibrillation, atrial flutter, high grade AV block, unusable ECG or test ECG.

Symptom rhythm correlation was expressed as a percentage of patients reporting palpitations during a recording with successful capture of ECG rhythm. Detection of arrhythmia was expressed as a percentage of patients reporting palpitations during a recording with successful capture of ECG rhythm with findings other than sinus rhythm, bradycardia or tachycardia only. ECG quality was expressed as a percentage of total recorded ECGs where the cardiac rhythm could be identified. Recorded ECGs were classed as 'unusable' simply when the rhythm could not be identified due to poor quality baseline and or presence of artifact. Variables are expressed as mean±standard deviation and data was stored on a password-protected trust computer using Microsoft Excel. The study complied with the Declaration of Helsinki and the research protocol was approved by the local Research and Innovation Department as a service evaluation project.

Results

Twenty patients [Table 1]received an AliveCor monitor. During the 12 weeks, 19 patients (95%) recorded at least 1 ECG, 1 patient (5%) did not record any ECGs. 6 patients (30%) were fully compliant with the instructions given at set-up. Three patients (15%) deleted uploads, 13 patients (65%) uploaded a proportion of their ECGs without annotating with symptoms; these accounted for 66% (n=639) of the total ECGs available to review. At follow-up 11 of these patients reported that they were in fact symptomatic and had failed to consistently annotate with symptoms as instructed at set-up (203 (32%) of the blank uploads). These ECGs were re-classified as symptomatic with palpitations. The remaining 68% of blank ECGs (n=436) were uploaded by 2 patients whilst asymptomatic. These uploads were subsequently re-classified as test ECGs.

Table 1: Patient baseline clinical characteristics

Characteristic	Values
Number of patients	20
Age (years)	35±16 (range12-64)
Female	13 (65%)
Male	7 (35%
Baseline symptoms	
Palpitations	20 (100%)
Pre-syncope	6 (30%)
Fatigue	5 (25%)
Breathlessness	4 (20%)
Chest Pain	1 (5%)
Hypertension	1 (5%)
CAD	1 (5%)
WPW	1 (5%)
Previous EPS	6 (30%)
History of palpitations (years)	2.6±3.5 (range 0.25-13)
Frequency of palpitations	
Daily	3 (15%)
Weekly	8 (40%)
>Weekly	6 (30%)
Monthly	1 (5%)
>Monthly	2 (10%)

CAD - Coronary artery disease, WPW - Wolf Parkinson White, EPS - Electrophysiology study
*Continuous data presented as mean ± SD and range (in parenthesis), Categorical data as number of patients (percentage of sample in parenthesis).

A total of 1145 uploads were made during the 12 week monitoring period. 179 uploads did not have stored ECGs, as patients (n=3) had deleted them from their personal account. 42 (4%) were deemed unusable as the ECG was of poor quality, 462 (48%) were test ECGs and 157 (16%) were recorded with symptoms not including, or other than palpitations. 7 (<1%) were uploads where patients (n=4) documented their palpitations had subsided before recording the ECG. 340 uploads were recorded by patients when symptomatic with palpitations of which 37 (11%) were unusable. A sample of recorded ECGs uploaded with the AliveCor monitor is shown in [Figure 1].

Patients achieving symptom rhythm correlation was found to be 85% with 17 patients recording at least 1 ECG whilst reporting palpitations. For detection of arrhythmia 9 patients (45%) recorded at least 1 ECG while reporting palpitations with findings other than sinus rhythm, bradycardia or tachycardia only. Identification of cardiac rhythm was possible in 96% of the total ECGs uploaded (922/966) and in 89% of symptomatic uploads (303/340). ECG recordings deemed unusable were through poor quality baseline and interference, examples of which are displayed in [Figure 1] (ECGs i and j). The irregular 'spiked' interference shown in [Figure 1] (ECG - j) was present in 3 patients' recordings.

20 patients (100%) completed the questionnaire at set-up and 17 (85%) at follow-up. 18 patients (90%) reported the process of finding and downloading the AliveCor App as very easy/easy, while 2 patients (10%) found it difficult. 20 patients (100%) found the instructions given at set-up very easy/easy to follow. 16 (94%) found using the monitor very easy/easy. 3 patients (18%) reported problems using the monitor (n=1 encountered the unknown interference displayed in [Figure 1] (ECG - j) on a number of their ECGs causing distress as the interference resulted in an inaccurate very high heart rate reading, n=2 felt they were unable to activate device in time to record ECG during short lived palpitations).

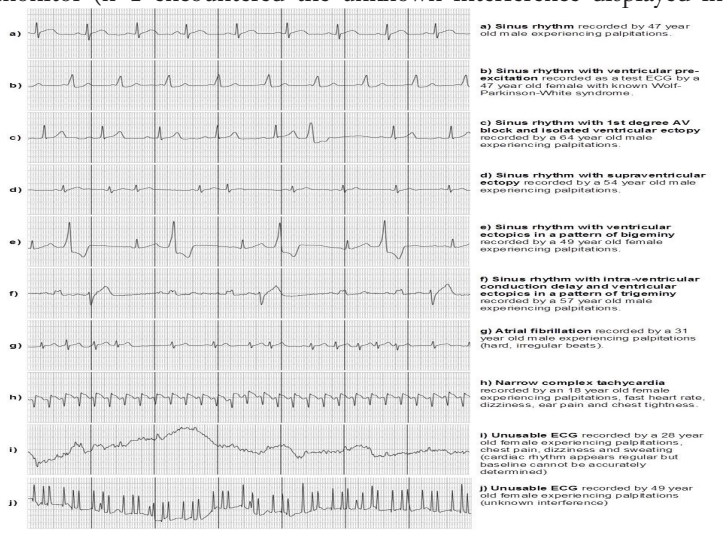

Figure 1: Example ECG rhythms uploaded with the AliveCor heart monitor

Discussions

This study demonstrated that the smartphone based event recorder

used under medical supervision can be effectively used to record good quality ECG and achieve symptom rhythm correlation in patients with palpitations. In contrast with the historically reported poor quality ECG recordings of conventional event recorders,[1] in this study the overall quality of ECG recordings was good and consistent with other studies in the ambulatory setting reporting between 87% and 99% of ECGs recorded with the AHM as being interpretable.[5],[6] Other studies where the AliveCor monitor was used as a screening tool have reported similar high quality ECG recordings.[12]-[15]

Patient training by the cardiac physiologist is likely to have increased the overall quality of recorded ECGs than if patients had purchased and used the device independently. Even under these circumstances, complete adherence was modest with many patients not consistently annotating the ECGs with symptoms. Furthermore, some patients elected to record multiple recordings without symptoms. This can in future be dealt with by better patient education when prescribing the device. In addition, short lived palpitations may not be recorded as the arrhythmia may terminate before activation. This is a commonly reported limitation of non-looping event recorders.[3]

At £74.99 unit cost of the 2nd generation AliveCor monitor (2015) is cheaper than most other conventional forms of AECG monitoring, especially implantable loop recorders and could even be a single use device. Another potential cost saving is the online ECG reviewing system which is free to use. Conventional forms of AECG monitoring often require costly analysis systems with associated maintenance costs.[10] Furthermore, current conventional patient activated devices are often limited to 3-4 weeks of monitoring as well as requiring continued maintenance and battery changes.[1] In contrast maintenance of the AliveCor monitor is not required and battery life is reported at 12 months with typical use. This could allow for external (non-invasive) monitoring over long periods of time free of continued device up-keep, previously unavailable without use of implantable loop recorders which are both costly and have associated risks of an invasive procedure.[3]

With conventional patient activated devices there is evidence that if symptom rhythm correlation is not achieved within the first 2 weeks of monitoring, then further diagnostic yield will be low.[11] A potential reason is that patients lose interest and do not carry their monitor.[8] This problem is obviated with the AliveCor monitor as it is attached to the patient's smartphone. Interestingly, Ofcom (The independent regulator and competition authority for the UK communications industries) recently branded the UK a "smartphone society" with an estimated 66% of adults owning a smartphone in 2015.[16] Together with the fact that the 3rd generation monitor has extended compatibility, this monitor is likely to be suitable for a large number of people.

Conclusions

The novel smartphone based event recorder is an efficient tool for achieving symptom rhythm correlation in patients with palpitations. By utilizing their Smartphone, ECG recording is easily and readily accessible to patients when palpitations occur. In order to ensure appropriate use and quality of recorded ECGs, use of these devices under the supervision of a healthcare professional is advised.

Conflict Of Interests

Biosense Webster (research grant and travel grant), St Jude Medical (research grant and travel grant), Medtronic (research grant, travel grant and proctorship), Boehringer Ingelheim (research grant).

Disclosures

None.

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Atrial Fibrillation is Associated with Increased Pacemaker Implantation Rates in the Placement of AoRTic Transcatheter Valve (PARTNER) Trial

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Abstract

Atrial fibrillation (AF) is associated with worse outcomes in many cardiovascular diseases. There are few data examining pacemaker implantation rates and indications in patients with AF who undergo transcatheter aortic valve replacement (TAVR). To examine the impact of AF on the incidence of and indications for pacemakers in patients undergoing TAVR, we evaluated data of 1723 patients without pre-existing pacemakers who underwent TAVR in the Placement of AoRTic TraNscathetER Valve (PARTNER) trial. Permanent pacemaker implantation rates and indications were compared in groups based on baseline and discharge heart rhythm: sinus rhythm (SR) vs. AF. 1211 patients manifested SR at baseline/SR at discharge (SR/SR), 105 SR baseline/AF discharge (SR/AF), and 407 AF baseline/AF discharge (AF/AF). Patients who developed and were discharged with AF (SR/AF) had the highest rates of pacemaker implantation at 30 days (13.7% SR/AF vs. 5.4% SR/SR, p=0.0008 and 5.9% AF/AF, p=0.008) and 1 year (17.7% SR/AF vs. 7.1% SR/SR, p=0.0002 and 8.1% AF/AF, p=0.0034). Conversion from SR to AF by discharge was an independent predictor of increased pacemaker implantation at 30 days (HR 2.19 vs. SR/SR, 95% CI 1.23-3.93, p=0.008) and 1 year (HR 1.91 vs. SR/SR, 95% CI 1.33-3.80). Pacemaker indications differed between groups, with relatively more implanted in the AF groups for sick sinus syndrome (SSS) versus AV block. In conclusion, conversion to AF is an independent predictor of permanent pacemaker implantation in TAVR patients. Indications differ depending on heart rhythm, with patients in AF manifesting clinically significant tachy-brady syndrome versus AV block.

Introduction

Prior reports have documented an increased incidence of conduction abnormalities and other arrhythmias after aortic valve replacement, whether via a surgical or catheter-based approach.[1]-[4] As the clinical adoption of transcatheter aortic valve replacement (TAVR) has increased, there has been particular interest in the clinical implications of post-TAVR arrhythmias and conduction abnormalities.

Atrial fibrillation (AF) has been reported to occur in up to 35% of TAVR recipients overall, with rates as high as 53% using the transapical approach,[5]-[8] as compared to a prevalence in the general population of 1.1-9.1%, depending on age and presence of other cardiovascular disease.[9]-[11] Studies have shown that new onset AF post-TAVR increases not only the risk of stroke and systemic embolism but also overall mortality.[5],[12] Furthermore, the interaction between atrial fibrillation and other conduction abnormalities, including those requiring permanent pacemaker implantation (PPM), has not been well investigated. Recent studies have shown that rates of PPM after TAVR range from approximately 6 to 11.5% with the Edwards SAPIEN Valve (Edwards LifeSciences, Irvine, CA)[13]-[15] and 15 to 33.3% with the Medtronic CoreValve (Medtronic, Minneapolis, MN).[16]-[20] In a recent meta-analysis, the overall PPM rate after TAVR was 17%, but atrial fibrillation was not a predictor of PPM.[21] The indication for PPM, especially for the Medtronic CoreValve, was most often cited as complete AV block.[21],[22] It remains unclear whether incident atrial fibrillation is a predictor of need for PPM, especially in the subgroup of patients receiving the Edwards SAPIEN Valve.

Given the paucity of evidence regarding the implications of post-TAVR atrial fibrillation on pacemaker implantation, the goals

Key Words

Atrial fibrillation, Pacemaker, Transcatheter aortic valve replacement (TAVR).

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of this study are two-fold: 1) to analyze the relationship between atrial fibrillation and pacemaker implantation at both 30 days and 1 year post-TAVR in the Placement of Aortic Transcatheter Valve (PARTNER) study; and 2) to assess whether the indication for PPM post-TAVR is due to AV block versus sick sinus syndrome in patients with as well as without atrial fibrillation.

Methods

The PARTNER trial methods have been previously described.[7],[23] The current study included 1723 patients from the PARTNER trial and continued access registry who did not have a pre-existing permanent pacemaker. All patients were either high-risk surgical candidates or non-surgical candidates for aortic valve replacement. All patients underwent TAVR with the Edwards SAPIEN transcatheter heart valve. Per study protocol, electrocardiograms (ECG) were obtained before TAVR and at hospital discharge. Atrial Fibrillation was defined as either atrial fibrillation or atrial flutter as diagnosed on the baseline or discharge ECG. Patients were stratified based on the presence of sinus rhythm (SR) or AF on the pre-procedure ECG (baseline) and the discharge ECG (discharge). For analysis, the following three subgroups were compared: SR baseline/SR discharge (SR/SR); SR baseline/AF discharge (SR/AF); and AF baseline/AF discharge (AF/AF). The baseline AF/discharge SR group was not analyzed due to low representation from that group (31 patients). The study was approved by the Institutional Review Boards of each participating site and all patients provided written informed consent.

The primary endpoint for the study was pacemaker implantation rate, which was compared among groups at both 30 days and 1 year. A secondary endpoint was indication for pacemaker implantation at 30 days. Sick sinus syndrome (SSS) was defined as symptomatic sinus bradycardia or pauses (either at baseline if in SR or due to therapy if in AF with need to reduce rapid ventricular response). Atrioventricular (AV) block was defined as symptomatic slow ventricular response or heart block during AF, or symptomatic 2nd degree or 3rd degree AV block during sinus rhythm. Baseline, 30-day, and 1 year ECGs were interpreted in an independent core laboratory. Indications for all pacemaker implantations except one (data not available for one patient in SR/SR group) were reviewed and adjudicated by a cardiologist and an electrophysiologist (TN and JD, respectively). Source documentation for pacemaker implantation indication included operative notes, progress notes, and discharge summaries. All other adverse clinical events were adjudicated by an independent clinical events committee.

All analysis was conducted on the as-treated population. The Wilcox Rank Sum test was used to compare continuous variables while either the X^2 or Fisher's exact test was used for categorical variables, as appropriate. Multivariable predictors of outcomes were identified using univariate analysis with those of clinical interest and/or those with p<0.10 being selected. Multivariable predictors of clinical outcomes at 1 year were identified by selecting those candidate variables with p< 0.10 in univariate analysis. Statistical analysis was performed using SAS, version 9.2 (SAS Institute, Cary, North Carolina). A two-sided alpha level of <0.05 was used to determine statistical significance.

Results

Of the 1723 patients who underwent TAVR in the PARTNER trial and continued access registry and did not have a pre-existing pacemaker, 1211 patients had SR at baseline and discharge, 105 had SR at baseline and AF at discharge, and 407 had AF at baseline and at discharge. [Figure 1]

Patient characteristics are included in [table 1]. When comparing the groups of incident AF (SR/AF) and continuous SR (SR/SR) for abnormal baseline conduction, there were no statistically significant

Table 1: Baseline Patient Characteristics

Variable Description	SR/SR (a)	SR/AF (b)	AF/AF (c)	P-Value All Groups	P-Value (a) vs (b)	P-Value (a) vs (c)	P-Value (b) vs (c)
Age							
median (IQR)	85.41 [80.30,89.18]	86.49 [80.50,90.00]	85.82 [81.69,89.19]	0.22	0.17	0.08	0.65
Male	45.9% (556/1211)	47.6% (50/105)	57.5% (234/407)	0.0002	0.74	<0.0001	0.07
BMI							
mean ± SD (n)	27.10 ± 6.76 (1208)	27.38 ± 8.02 (105)	26.53 ± 5.87 (404)	N/A	0.6894	0.1380	0.2504
STS Score							
mean ± SD (n)	11.07 ± 4.40 (1206)	11.62 ± 3.60 (104)	11.91 ± 3.83 (407)	N/A	0.2113	0.0006	0.5212
Any Diabetes	38.3% (441/1151)	38.8% (38/98)	35.7% (135/378)	0.83	0.93	0.37	0.57
Hyperlipidemia	84.3% (970/1151)	83.7% (82/98)	81.2% (307/378)	0.46	0.88	0.16	0.57
Smoking	47.3% (544/1151)	53.1% (52/98)	49.7% (188/378)	0.39	0.27	0.40	0.56
Hypertension	91.5% (1053/1151)	91.8% (90/98)	92.0% (347/377)	0.94	0.90	0.73	0.95
Angina	23.3% (268/1151)	21.4% (21/98)	15.6% (59/378)	0.007	0.68	0.002	0.17
CHF	97.9% (1125/1149)	96.9% (95/98)	98.1% (371/378)	0.77	0.53	0.78	0.46
NYHA class 1	0.1% (1/1150)	0.0% (0/98)	0.0% (0/378)	0.93	0.77	0.57	N/A
NYHA class 2	5.6% (64/1150)	3.1% (3/98)	5.0% (19/378)	0.44	0.29	0.69	0.41
NYHA class 3	50.8% (584/1150)	46.9% (46/98)	46.3% (175/378)	0.15	0.47	0.13	0.91
NYHA class 4	43.6% (501/1150)	50.0% (49/98)	48.7% (184/378)	0.03	0.22	0.08	0.82
CAD	77.1% (887/1151)	75.5% (74/98)	75.1% (284/378)	0.34	0.73	0.44	0.94
Prior MI	25.9% (296/1145)	23.7% (23/97)	23.9% (90/376)	0.45	0.64	0.46	0.96
Prior CABG	40.6% (467/1151)	33.7% (33/98)	42.6% (161/378)	0.44	0.18	0.49	0.11
Renal disease (CR ≥ 2)	16.0% (184/1151)	20.4% (20/98)	17.2% (65/378)	0.68	0.26	0.58	0.46
Liver disease	2.4% (28/1151)	2.1% (2/97)	3.4% (13/377)	0.32	0.82	0.29	0.49
COPD	42.9% (494/1151)	48.0% (47/98)	47.1% (178/378)	0.46	0.33	0.16	0.88

differences in baseline prevalence of 1st degree AV block, type 1 2nd degree AV block, non-specific interventricular conduction delay, incomplete RBBB, RBBB, or LBBB [table 2].

For the endpoint of PPM at 30 days, patients with new AF (SR/AF) had the highest rates of implantation at 13.7%. This was significantly different when compared to both the SR/SR group (5.4%, p=0.0008) and the AF/AF group (5.9%, p=0.008). Similar results were found at 1 year, with 17.7% of patients undergoing pacemaker implantation in the SR/AF group, compared to 7.1% of those in the SR/SR group (p=0.0002) and 8.1% of those in the AF/AF group (p=0.0034).

Multivariable regression demonstrated that conversion from SR to AF by hospital discharge was an independent predictor of pacemaker implantation at 30 days compared to SR/SR patients. Patients in the SR/AF group were over twice as likely to require a permanent pacemaker by 30 days (HR=2.19, 95% CI 1.23-3.93; p=0.008). At 1 year, the hazard ratio was still significant (HR=2.25, 95% CI 1.33-3.80; p=0.0025). Compared to the baseline AF/discharge AF group, patients in the SR/AF group were also more likely to require a permanent pacemaker at 1 year (HR=1.91, 95% CI 1.03-3.53; p=0.0388). The presence of baseline RBBB was also an independent predictor of pacemaker implantation at 30 days (HR=4.98, 95% CI 3.37-7.38; p<0.0001) as well as at 1 year (HR=4.03, 95% CI 2.82-5.74; p<0.0001).

Table 2: Baseline Conduction Abnormalities

Baseline Characteristic	SR/SR (a)	SR/AF (b)	AF/AF (c)	P-Value All Groups	P-Value (a) vs (b)	P-Value (a) vs (c)	P-Value (b) vs (c)
Abnormal Conduction Present	44.7% (541/1210)	49.5% (52/105)	34.6% (139/402)	0.001	0.34	0.0004	0.005
1st degree AVB	19.2% (232/1210)	26.7% (28/105)	N/A	N/A	0.06	N/A	N/A
2nd degree AVB Type I	0.2% (3/1210)	1.0% (1/105)	N/A	N/A	0.21	N/A	N/A
2nd degree AVB Type II	0.0% (0/669)	0.0% (0/53)	N/A	N/A	N/A	N/A	N/A
3rd degree AVB	0.0% (0/1210)	0.0% (0/105)	N/A	N/A	N/A	N/A	N/A
IVCD	5.1% (62/1209)	5.7% (6/105)	5.7% (23/402)	0.71	0.79	0.64	1
Inc. RBBB	1.3% (16/1210)	1.0% (1/105)	2.0% (8/402)	0.66	0.75	0.34	0.47
RBBB	14.5% (175/1210)	21.0% (22/105)	16.4% (66/402)	0.29	0.07	0.34	0.27
LBBB	9.8% (118/1210)	7.6% (8/105)	6.2% (25/402)	0.11	0.48	0.03	0.6

Type of AV block was documented during sinus rhythm for SR/AF patients.

For the endpoint of pacemaker implantation at 30 days post-TAVR, AV block was the most common indication in all three groups [3]. However, SSS was relatively more common as an indication in both AF groups versus the SR/SR group. In the SR/SR group, 11% required a pacemaker for SSS (vs. 89% for AV block); in the SR/AF group, 21% required a pacemaker for SSS (p=NS vs. SR/SR); and in the AF/AF group, 33% of pacemakers were implanted for SSS (p=0.01 vs. SR/SR).

Discussion

This analysis constitutes what we believe to be the first report of the relationship between atrial fibrillation and need for permanent pacemaker implantation in patients undergoing TAVR. The principle findings of the analysis include: 1) Patients in the PARTNER database and continued registry who develop AF after TAVR have an over 2-fold higher rate of pacemaker implantation at both 30 days and 1 year compared to those who remain in their baseline rhythm of either SR or AF; 2) The presence of AF at baseline and discharge is also associated with increased pacemaker implantation rates at 1 year; 3) When compared to SR patients who require pacemakers after TAVR, patients with AF after TAVR require pacemakers relatively more because of SSS (vs. AV block).

It is well established in the surgical literature that atrial fibrillation is a common post-operative complication of cardiac surgery, including after aortic valve replacement (AVR). Furthermore, post-operative atrial fibrillation has been shown to be associated with worse outcomes and longer hospitalizations.[24]-[29] Studies have shown that new AF occurred less often with TAVR than with surgical AVR (6-42% versus 34-60%, respectively), with transfemoral TAVR having the lowest incidence of new AF (14%).[6],[8] Similarly, the SAVR and TAVR literature has shown that post-operative heart block is a common occurrence and a frequent indication for pacemaker implantation.[1]-[3],[21],[22],[30] Thus, both AF and pacemaker implantation have been independently associated as complications after AVR, with pacemaker implantation rates ranging from about 6-53% post-TAVR overall depending on the valve type and approach used.

However, the relationship between AF and the need for permanent pacemaker implantation in TAVR patients has not been previously established.[5]-[8],[13]-[19]

The current study results show that, regardless of risk factors or etiology, TAVR patients who develop AF by discharge are more than twice as likely to require a pacemaker compared to those patients who remain in sinus rhythm. This finding adds to other previously reported risk factors for permanent pacemaker implantation in TAVR patients, including, for example, the presence of baseline RBBB, which was also noted to be an independent predictor in our results.[21] The clinical implications of this finding are noteworthy with regard to TAVR and patient care. Prior studies showed that the transfemoral rather than the transapical approach in performing TAVR affects rates of postprocedural AF (13.6% vs. 86.4%, respectively).[5] The differential occurrence of AF may in part explain the documented superiority of the femoral approach. Further study to identify differences between the various alternative access approach (i.e.,

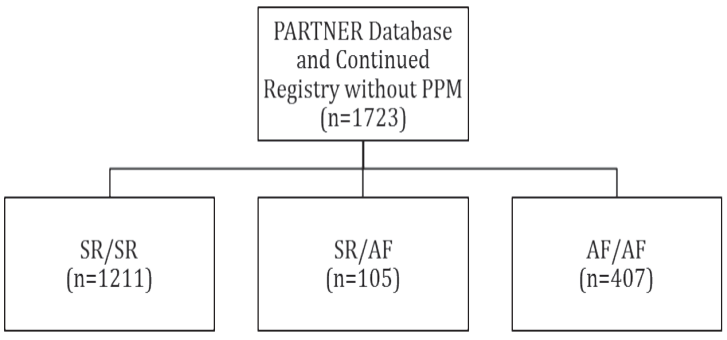

Figure 1: Baseline and Discharge Rhythm

Table 3: Indication for Pacemaker Implantation

Rhythm Classification	SSS (%)	AV Block (%)	p-Value
SR/SR	7/64(11%)	57/64(89%)	vs SR/AF=0.37
SR/AF	3/14(21%)	11/14(79%)	vs AF/AF=0.49
AF/AF	8/24(33%)	16/24(67%)	vs SR/SR=0.01

transapical, transaortic, subclavian, or carotid) may help to refine the understanding of the relative merits of these approaches. Therefore, prevention of AF by controlling for other known risk factors for AF development, including approach and valve type, should be taken into consideration.

In this analysis, categorization of patients was based solely on admission and discharge ECGs, which does not take into account whether patients experienced cross-over in heart rhythm between SR and AF prior to and/or after hospital discharge. As such, these results may be a conservative estimate of the true effect. Thus, patients who do not require a pacemaker prior to hospital discharge, but are discharged in atrial fibrillation should be viewed as a higher risk follow-up group that is more likely to require pacemaker implantation. It remains unclear for how long this increased risk lasts post-TAVR, but the downward trend in pacemaker implantation at 1 year compared to 30 days is representative of a decreased rate of need for pacemakers as time passes. Further analysis of the potential merits of more intensive monitoring of patients in the AF groups are warranted.

As a corollary to our finding that the development of atrial fibrillation is an independent predictor of pacemaker implantation in general, we discovered that AF also affects the indication for pacemaker implantation. For those with AF both before and after TAVR in our study, there was a statistically significant difference in the pacemaker implantation rate related to SSS (versus AV block) when compared to those patients who remained in sinus rhythm throughout. There was also a trend toward more SSS-related implantation in the SR group that developed AF after TAVR. One explanation may be that either the presence or development of AF with RVR leads to the need for treatment with medications that lead to symptomatic bradycardia, an indication for pacemaker implantation due to SSS. These medications also impact upon AV nodal function, which was likely a reason for at least some portion of patients to manifest AV node block. It is not yet clear whether, and the extent to which, the TAVR procedure and/or post-TAVR period itself exacerbates underlying arrhythmia pathophysiology contributing to an increase in SSS. Furthermore,

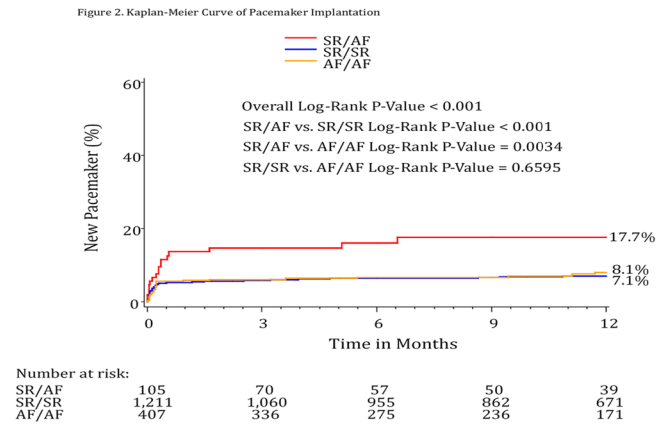

Figure 2: Kaplan-Meier curve of pacemaker implantation rate

it is unclear how treating AF with anticoagulation, antiarrhythmic medications, and/or cardioversion would alter the clinical course for patients undergoing TAVR. Further studies exploring these therapeutic approaches are required.

There are several potential limitations to our study that may affect interpretation of the results. First, this is a post-hoc analysis of patients who were categorized solely based on pre-procedure and hospital discharge ECGs, which does not take into account: i) history of AF; ii) patients who had intermittent crossover between groups (i.e. those with paroxysmal AF that was not documented); or iii) patients who may have developed AF after discharge. Second, because of the limits of data available for analysis, this study does not examine the direct effects of more intensive diagnostic monitoring or therapeutic use of anticoagulants, antiarrhythmic medications, or cardioversion on clinical endpoints. Finally, the effect of AF in patients in lower risk groups undergoing TAVR, or being treated with other types of transcatheter heart valves, may not be identical.

Conclusions

In conclusion, this study demonstrates that conversion to atrial fibrillation is an independent predictor of pacemaker implantation in a large population of TAVR patients from the PARTNER trial at both short and long term follow-up. Furthermore, this study shows that SSS is more often an indication for pacemaker implantation in those patients with AF than in those who maintain SR. Further studies should be conducted to assess optimal treatment strategies for patients undergoing TAVR based on baseline or incident arrhythmias.

Conflict Of Interests

None.

Disclosures

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Pulmonary Vein Isolation for Treatment of Paroxysmal Atrial Fibrillation on Patient with Situs Inversus Totalis

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Abstract

A 56-year-old male with paroxysmal atrial fibrillation refractory to class IC and class III antiarrhythmic drugs was admitted to our hospital for radiofrequency catheter ablation of atrial fibrillation. During preoperative examination situs inversus totalis was revealed. Pulmonary vein (PV) isolation was successfully performed with atrial fibrillation termination and elimination of all PV potentials. The procedure was performed without any complications. Our report shows that PV isolation for treatment of drug-refractory atrial fibrillation can be safely performed in patients with dextrocardia and situs inversus totalis.

Introduction

Recently, pulmonary vein isolation (PVI) has become a common procedure for the treatment of drug-refractory paroxysmal atrial fibrillation (AFIB). The presence of abnormal anatomy can make the procedure more complex. There are limited data about the feasibility and safety of PVI in patients with situs inversus totalis.

Case Report

A 56-year-old male with 10-year anamnesis of paroxysmal AFib was admitted to our hospital. Episodes of atrial fibrillation were highly symptomatic, appeared two to four times per month, lasted for two to three hours and were terminated by beta blockers or amiodarone. Chronic antiarrhythmic therapy with class IC and class III drugs was ineffective for AFib prevention. During preoperative examination dextrocardia and situs inversus totalis were revealed.

According to current guidelines[1] radiofrequency ablation (RFA) targeting PV was considered. The procedure was performed using intracardiac echocardiography (ICE) and the CARTO 3 (Biosense Webster) navigation system. Two Swarz SR0 introducers and an 11Fr introducer for ICE were inserted via the left femoral vein. A double transseptal puncture was performed under ICE control. Angiography [Figure 1] and 3D reconstruction [Figure 2] of the left atrium were performed. When a Lasso catheter was positioned in the anatomical right superior PV, prominent left atrial appendage potentials were registered. Atrial fibrillation was induced during manipulations near the left superior PV.

Point-by-point antral isolation of all pulmonary veins was performed using a bi-directional SmartTouch catheter (Biosense Webster), with termination of AFib during anatomical left superior PV isolation and elimination of all PV potentials, confirmed by Lasso catheter. The procedure duration was 85 minutes; fluoroscopy time – 4 minutes 35 seconds. There were no complications during the procedure.

Discussion

There are few case reports of successful PVI in patients with situs inversus totalis using RF energy[2],[3], cryoenergy[4] or robotic navigation.[5] In our case report, because of ICE-assisted transseptal puncture and the use of an electroanatomical mapping system, short procedure duration and low X-ray exposure were achieved. Catheter and long sheath manipulations are complex in cases of heart inversion since the positions of the tools are opposite to those for the case of common anatomy. The use of the SmartTouch catheter can facilitate the procedure performance, especially in the left atrial ridge area.

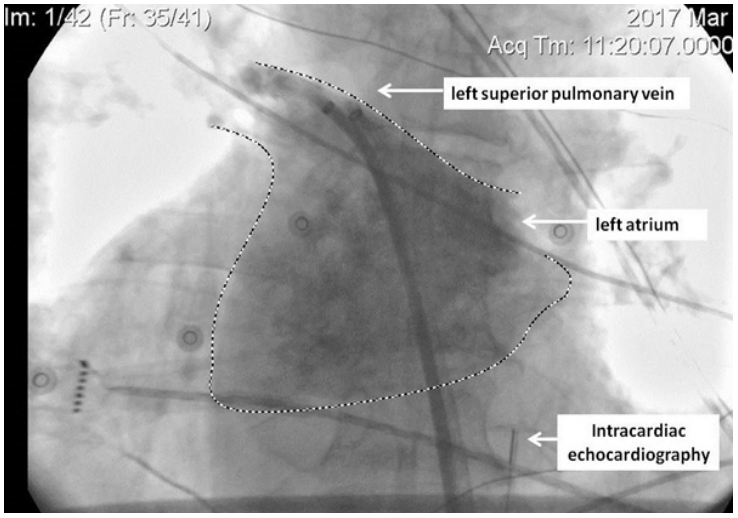

Figure 1: Angiography of left atrium from long sheath, positioned in left superior (anatomical right) pulmonary vein

Key Words

Atrial fibrillation, Pulmonary veins isolation, Dextrocordia.

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The right-sided position of the left atrial appendage makes it more difficult to achieve good catheter-to-tissue contact in the left atrial ridge area.

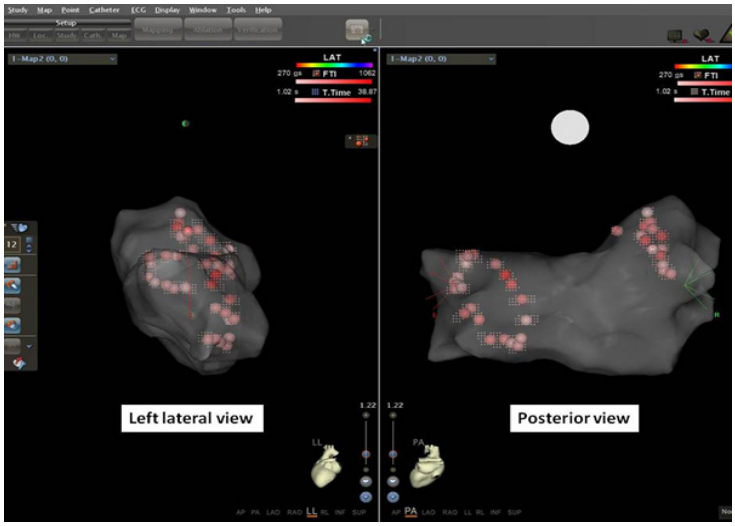

Figure 2: **Reconstruction of left atrium from electroanatomical mapping system with ablation points**

Conclusions

Pulmonary vein isolation for the treatment of drug-refractory paroxysmal atrial fibrillation can be safely performed in patients with situs inversus totalis.

Conflict Of Interests

None.

Disclosures

None.

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Atrial Fibrillation in Patients with Congenital Heart Disease

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Abstract

Advances in surgical techniques have led to the survival of most patients with congenital heart disease (CHD) up to their adulthood. During their lifetime, many of them develop atrial tachyarrhythmias due to atrial dilatation and scarring from surgical procedures. More complex defects and palliative repairs are linked to a higher incidence and earlier occurrence of arrhythmias. Atrial fibrillation (AF) is common in patients who have atrial septal defects repaired after age 55 and in patients with tetralogy of Fallot repaired after age 45. Patients with dextrotransposition of the great arteries who undergo Mustard or Senning atrial switch procedures have an increased risk of atrial flutter due to atrial baffle suture lines. Patients with Ebstein's anomaly are also prone to supraventricular tachycardias caused by accessory bypass tracts. Patients with a single ventricle who undergo Fontan palliation are at risk of developing persistent or permanent AF due to extreme atrial enlargement and hypertrophy. In addition, obtaining vascular access to the pulmonary venous atrium can present unique challenges during radiofrequency ablation for patients with a Fontan palliation. Patients with cyanotic CHD who develop AF have substantial morbidity because of limited hemodynamic reserve and a high viscosity state. Amiodarone is an effective therapy for patients with arrhythmias from CHD, but its use carries long-term risks for toxicity. Dofetilide and sotalol have good short-term effectiveness and are reasonable alternatives to amiodarone. Pulmonary vein isolation is associated with better outcomes in patients taking antiarrhythmic medications. Anticoagulants are challenging to prescribe for patients with CHD because of a lack of data that can be extrapolated to this patient population. Surgical ablation is the gold standard for invasive rhythm control in patients with CHD and should be considered at the time of surgical repair or revision of congenital heart defects. When possible, patients with complex CHD should be referred for care to an adult congenital heart disease center of excellence.

Introduction

Congenital heart defects occur in approximately 9 per 1,000 newborns and are responsible for nearly 30% of all major congenital birth defects.[1] In the modern era of advanced surgical techniques and postoperative care and management, more than 90% of children with congenital heart disease (CHD) will reach adulthood.[2],[3] The successful outcomes of the earlier surgical era have resulted in an ever-increasing number of adults with CHD. As of 2011, more adults than children are alive with CHD. Estimates suggest that there may be as many as 3 million adult survivors of CHD throughout North America and Europe. As this population has aged and the time from surgical palliation lengthened, new comorbidities have been increasingly recognized.[4] Repaired and unrepaired CHD is commonly associated with atrial tachyarrhythmias as a consequence of atrial dilatation, atrial scar, sinus nodal dysfunction, and congenital conduction system abnormalities.[5] Atrial tachyarrhythmias, including atrial fibrillation (AF), and atrial flutter, are associated with thromboembolic phenomena and hemodynamic compromise and are, thus, a major cause of morbidity and mortality in patients with and without CHD.[1]-[5] The higher incidence of AF is also linked to increasing rates of hospitalization and longer hospital stays, leading to higher use of health care resources. As the number of CHD patients continues to increase, a pressing need exists for effective and novel strategies to manage the care of these patients and yet minimize the impact on their otherwise complex pathophysiology. Our aim is to review the most recent literature for epidemiology, pathophysiology, and outcomes of available treatment modalities for AF and other atrial arrhythmias for patients with CHD.

Key Words

Atrial Fibrillation, Fontan, Congenital Heart Disease.

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Epidemiology

The incidence of AF in patients with CHD has been reported primarily for adults with simple, palliated CHD. The more complicated the congenital heart defect and the palliation required, the higher and earlier the incidence of atrial arrhythmias. Patients who underwent surgical closure of an atrial septal defect (ASD) before 15 years of age had a 0% incidence of AF and a 2% incidence of atrial flutter, confirmed by 24-hour Holter monitoring, at 33-year and 35-year follow-up in 2 studies.[6],[7] In contrast, the incidence of atrial arrhythmias was higher when ASD repair occurred during adulthood.[6],[7] In a study of 213 patients who underwent surgical closure of the ASD after age 40 years, 23% had AF or atrial flutter preoperatively.[8] Of these patients, only 60% continued to have these atrial arrhythmias during follow-up. Of the total patient cohort, an additional 2.9% developed new onset AF or atrial flutter. Predictors of late postoperative AF or atrial flutter were age greater than 40 years at the time of surgery, preoperative atrial flutter or fibrillation, and early postoperative atrial flutter or fibrillation or junctional rhythm. Similarly, patients who underwent percutaneous ASD

closure after age 55 had an increased incidence of new onset atrial tachyarrhythmias.[9]

Tetralogy of Fallot is the most common cyanotic congenital heart defect, affecting 0.02% of live births. Tetralogy of Fallot is most commonly associated with ventricular tachycardia, although AF is also frequently observed. Khairy et al[10] reported a 7% overall prevalence of AF in 556 patients with tetralogy of Fallot. AF occurred more frequently in patients over age 45, with a prevalence of more than 30% by the age of 55. Similar to patients without CHD, AF in these patients is associated with increased left atrial volumes and may lead to a decrease in left ventricular systolic ejection fraction.

Before the arterial switch procedure for palliation of dextrotransposition of the great arteries (D-TGA) became common practice in the 1980s, the atrial switch procedure (Mustard or Senning) was the standard of care since the mid-1960s. As a result, there is a large, albeit finite, cohort of patients with this type of palliation moving through adulthood. After a Mustard procedure, sinus rhythm progressively deteriorates at a rate of 2.4% per year.[11] Patients often present with a junctional rhythm and are at increased risk of atrial flutter.[12] In a single-center study of patients with D-TGA who had undergone Mustard repair, 24% of patients had developed atrial flutter and 11% of patients had undergone pacemaker implantation at 20-year follow-up.[13]

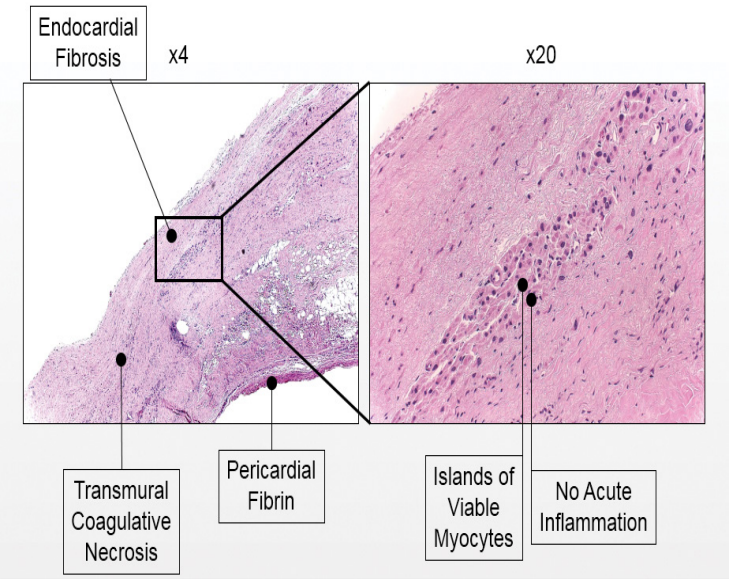

Figure 1: AP Fontan atrium obtained at time of transplant 2 weeks after 8mm high power RF ablation.

Panel A shows a low (4x) power cross section of right atrial tissue in an AP Fontan patient 2 weeks after RF ablation. Notice the extreme atrial hypertrophy with alternating areas of myocytes and fibrous connective tissue.Panel B shows a higher (20x) magnification image showing residual areas of viable myocytes following extensive high power endocardial RF ablation.

Ebstein's anomaly is a rare condition characterized by atrialization of the right ventricle and is frequently associated with additional structural defects, including persistent atrioventricular canal defects and accessory bypass tracts. Supraventricular tachycardias from rapid conduction through these accessory bypass tracts can result in profound hemodynamic compromise and even death. Chauvaud et al[14] evaluated 98 patients with Ebstein's anomaly; 45 of the patients had preoperative arrhythmias, including 12 with AF or atrial flutter. Increasing age was a significant risk factor for the development of arrhythmia. Interestingly, preoperative tricuspid regurgitation, ASD, and severity of Ebstein's anomaly were not associated with AF. Early postoperative AF developed in 8 patients, 6 of whom had preoperative AF. On follow-up, 5 patients with preoperative or early postoperative AF had recurrence, and 2 patients died suddenly.

Single ventricle disease, which encompasses tricuspid atresia, double-inlet left ventricle, double-outlet right ventricle, heterotaxy, and hypoplastic left heart syndrome, are the most complex CHD diagnoses. The final stage in palliation, the Fontan procedure, first performed in 1968, was established as a standard of care in the early 1970s. Peters et al[15] reported that 6 out of 60 patients (10%) who underwent a Fontan palliation had early postoperative AF. This was more frequently seen in patients with double-inlet left ventricle than in patients with tricuspid atresia. One patient had preoperative AF, with recurrence in the early postoperative period. All 6 patients in the study with early postoperative AF died because of progressive hemodynamic instability. During the follow-up period, another 3 patients developed AF. Fujita et al[16] reported on the incidence of postoperative AF in 199 patients with a single ventricle. After a follow-up period of 20 years, 16 patients (8%) had developed AF, 10 of whom had either persistent or permanent AF.

In CHD populations, AF develops with increasing age, increasing complexity of CHD, and increasing numbers of surgical interventions [Figure 1]. Acquired cardiovascular comorbidities, such as hypertension, obesity, sleep apnea, and coronary disease, will continue to occur in patients with CHD as they grow older, which will result in an increase in the incidence and burden of AF.

Pathophysiology

In patient populations without cardiac structural abnormalities, there are well-established risk factors for the development of AF, including increasing age, hypertension, congestive heart failure, diabetes mellitus, obesity, obstructive sleep apnea, myocardial infarction, valvular heart disease, alcohol use, hyperthyroidism, cardiothoracic surgery, and left atrial enlargement on echocardiography.[17] In addition to these risk factors, patients with CHD have a unique set of risk factors specific to those with corrected and uncorrected lesions. These include atrial enlargement caused by ASD (primum, secundum, and sinus venosus), increased atrial volume after operative intervention, and Fontan palliation. Atrial scarring leading to arrhythmogenic foci may develop after surgical repair of an ASD or patent foramen ovale, unifocalization of anomalous pulmonary venous return, repair of coronary fistulae, or construction of an interatrial baffle during an atrial switch procedure (ie, Mustard or Senning).[18] [Figure 2] The scars created by atrial baffles also provide an ideal environment for isthmus-dependent atrial flutter although the isthmus is located on the pulmonary venous side of the baffle. After a Mustard procedure, atrial flutter is associated with an increased risk of sudden death, which may be related to rapid ventricular response from 1:1 atrioventricular conduction or from further impairment of ventricular filling, reducing cardiac output.[19]

Fontan surgical procedures create multiple right atrial scars and Fontan hemodynamics create atrial enlargement and hypertrophy which also increase the risk of atypical atrial flutters (incisional reentry or IART) as well as AF. Specific sequelae of the Fontan procedure that further increase this risk include right atrial gigantism with subsequent right upper pulmonary vein compression, as well as right atrial substrate changes, such as hypertrophy of the right atrial wall. Approximately 50% of patients with right atrial–right ventricular or atriopulmonary Fontan procedures develop atrial tachycardia within 10 years of their palliative procedure. Risk factors include older age

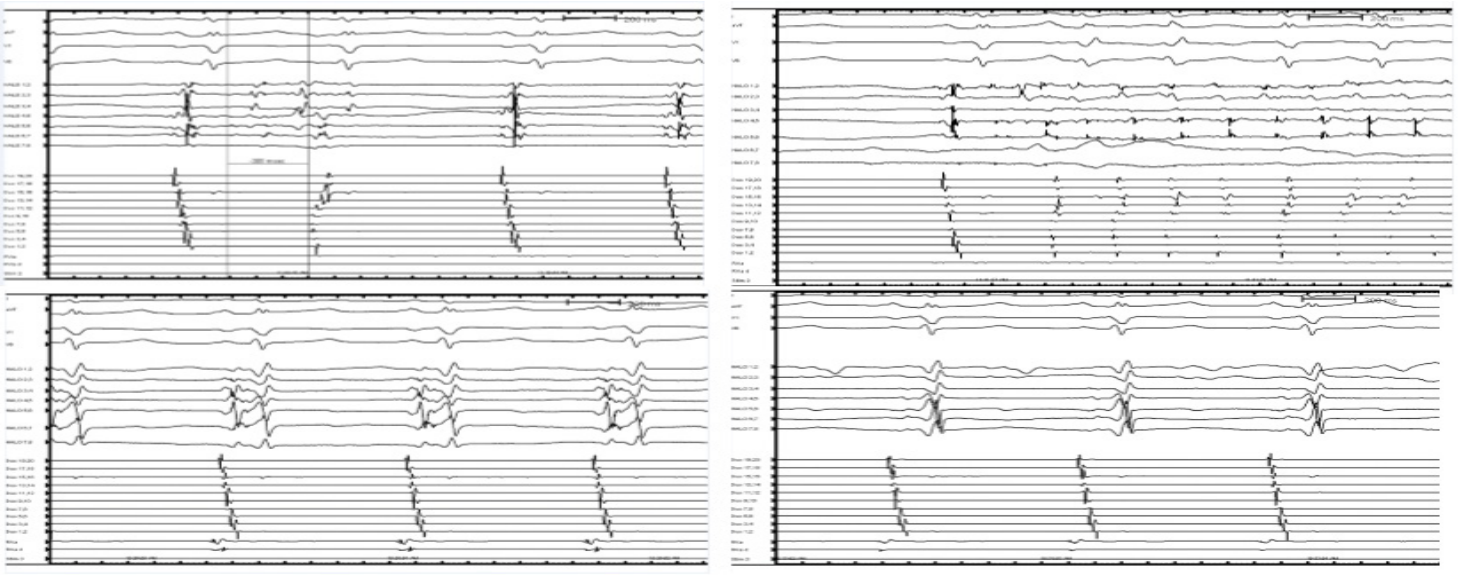

Figure 2: A and B. Pulmonary Vein focus driving coarse atrial fibrillation in a patient with complex atrioventricular septal defect repair. C. pulmonary vein pre-ablation D. pulmonary vein post-ablation

at palliation and increased time to follow-up.[20] Improved surgical techniques have begun to improve risks, which will benefit future patients.

Congenital structural abnormalities allow for the development of AF attributable to effects on the conduction system. One such example is Ebstein's anomaly, which is associated with the presence of accessory bypass tracts, as well as a fractured conduction system.[13] Surgical palliation of CHD places patients at risk for the development of postoperative AF, which is similar to that of adult patients without CHD who undergo other cardiac surgical procedures. Many CHD patients have had multiple cardiac and non-cardiac operations before the age of 18, and each episode of postoperative AF has a cumulative risk for the further development of AF that is not related to surgery. With each such episode, the underlying atrial substrate undergoes fundamental changes.[21],[22]

Patients with CHD are more likely to have comorbid conditions that contribute to the risk of developing AF, including scoliosis with pulmonary restriction, pulmonary hypertension, and premature systemic hypertension. Patients with cyanosis are also at increased risk for AF due to chronic subendocardial ischemia. Their baseline hemodynamic state is precarious, with limited oxygen reserves and a high viscosity state.[23] If patients with CHD develop AF, they are more likely to have substantial morbidity due to poorly tolerated rapid rates and thromboembolic events. Compared with patients who do not have CHD, patients with CHD develop AF at a younger age, and their AF is more challenging to manage medically, minimally invasively, or surgically.

Pharmacotherapy

AF is poorly tolerated in patients with CHD and requires multimodality and multidrug regimens for adequate rhythm control. Limited knowledge exists regarding safety and efficacy of drug therapy in CHD. Class I antiarrhythmic agents can depress ventricular function, particularly in patients with decreased systolic ejection fraction.[24] Of the class IA agents, quinidine carries a black box warning for use in structural heart disease, and procainamide is relatively contraindicated in the setting of depressed myocardial contractility. The class IC agents, propafenone and flecainide, are relatively contraindicated in structural heart disease, including after a myocardial infarction.[25] They also increase the defibrillation threshold in patients with implantable cardioverter defibrillators (ICDs).[26]-[28] Although class IC agents may be useful for CHD patients with AF who also have an ICD, little data are available to support their use in this setting. The use of non-dihydropyridine calcium channel blockers, verapamil and diltiazem, should be avoided in those with more than mild systemic ventricular dysfunction because they cause depressed myocardial contractility.

Amiodarone has been used for adults since the 1960s and is widely considered to be the most effective antiarrhythmic drug, even for the CHD population. Amiodarone is effective at controlling incessant postoperative atrial arrhythmias, including junctional ectopic tachycardia.[29] It should be administered with caution in adolescents and children because of its daunting long-term side-effect profile, which includes thyroid dysfunction, pulmonary fibrosis, hepatic dysfunction, and corneal deposition.[30] Patients with CHD are more likely to present with arrhythmias that are refractory to single-drug therapy, demonstrate depressed myocardial function, and have an intolerance of agents with negative inotropic effects.[31] Amiodarone also carries additional risks for toxicity in patients with CHD, particularly women, patients with unrepaired cyanotic lesions, and patients who have a prior history of Fontan-type palliation.[32] Close monitoring is necessary in these high-risk groups.[33]

Other class III antiarrhythmic agents have also been used with variable success to manage atrial arrhythmias in patients with CHD. In a small, multicenter, retrospective review of dofetilide treatment in CHD patients with AF, 85% of patients initially responded well, and 55% were free from arrhythmia at 1-year follow-up. Long-term suppression was achieved in 35% of patients.[34] In a study of sotalol treatment in children after palliative surgery for CHD, freedom from arrhythmia was observed to be 96% and 81% after 1 and 2 years, respectively.[35] In a study of CHD patients with refractory tachyarrhythmias treated with sotalol, complete rhythm control was achieved in 41% of patients, and partial rhythm control was achieved in 35% of patients at 13-month follow-up.[36] Amiodarone, dofetilide, and sotalol should all be initiated at lower doses in patients with

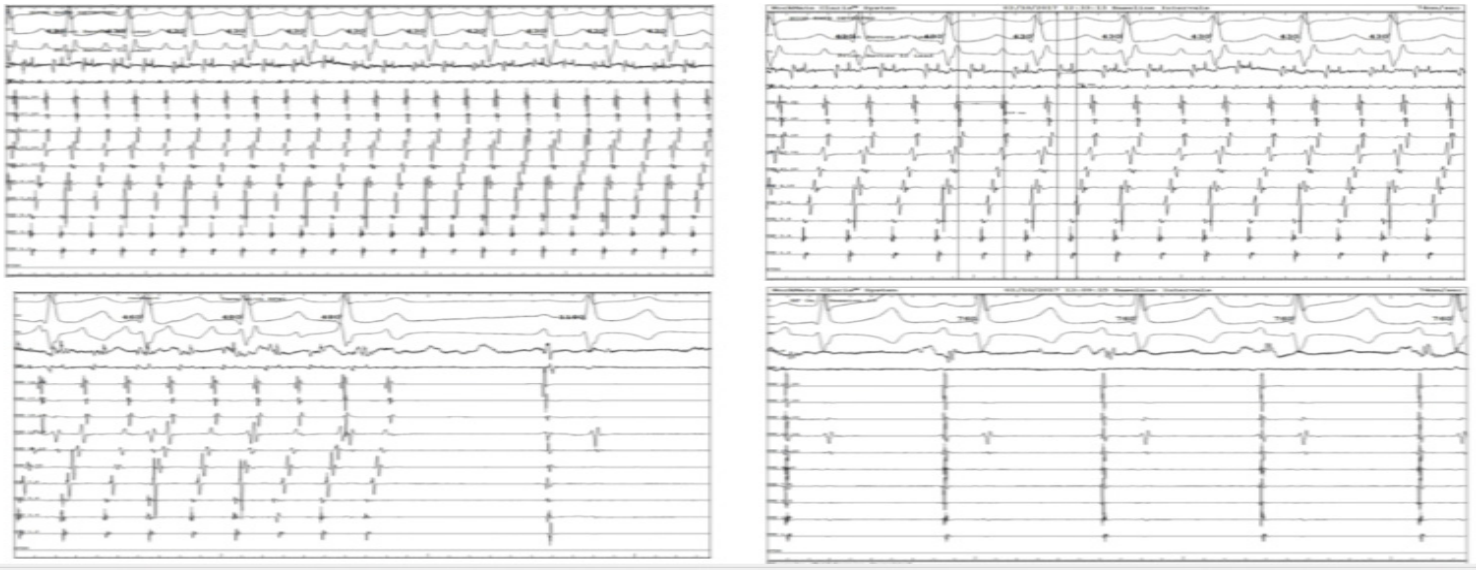

Figure 3: Automaticity demonstrated pre-and post ablation in a patient with single ventricle heart disease who is status post-Fontan.

CHD because medication toxicity appears to be higher. Additionally, intravenous ibutilide has also demonstrated a 71% success rate in cardioverting AF and atrial flutter in children with CHD, which is comparable to the success rate in non-CHD populations.[37]

Anticoagulation is recommended for AF to decrease the risk of thromboembolic phenomena. The 2014 management guidelines for AF recommend anticoagulation for a CHA_2DS_2-VASc score of 1 or more; however, this scoring system has not been validated for CHD patients.[17] Patients with CHD and atrial tachyarrhythmias have been reported to have a 42% prevalence of left or right atrial thrombi during preprocedural transesophageal echocardiography before cardioversion.[38] Fortunately, thromboembolic stroke after cardioversion appears to be rare, particularly in patients with a single atrium or single ventricle. Additionally, patients with single ventricle who have undergone surgical repair before the routine use of the Damus-Kaye-Stansel reconstruction have a pulmonary artery stump that is oversewn with a resultant pulsatile swirling of blood, creating a high-risk nidus for thrombus formation. This type of repair necessitates life-long anticoagulation even in the setting of normal rhythm.[39] Patients with Fontan repairs are uniquely challenging because they are likely to develop progressive cardiac cirrhosis, leading to changes in the intrinsic and extrinsic clotting cascade. Such changes may increase the risk of both bleeding and thrombosis due to decreased production of vitamin K–dependent clotting factors (factors II, VII, IX, and X), as well as the anticoagulants protein C and protein S.[40] Additionally, the novel oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban do not have indications or data to support their use in patients with CHD. Thus peri procedural and long term anticoagulation in this group of patients is largely accomplished through the use of well monitored warfarin and/or LMW heparin.

Transcatheter Therapies

The pathophysiology of AF in CHD appears to be comparable to that of normal adults in that pulmonary vein foci drive coarse AF. Isolation of the pulmonary veins through radiofrequency ablation appears to be of comparable therapeutic benefit. [Figure 3]. Only one study to date has evaluated the success of pulmonary vein isolation in patients with complex CHD, which included 36 patients with CHD and drug-refractory AF who underwent pulmonary vein isolation.[41] Freedom from symptomatic AF at 300 days post-ablation was 42% in patients in the absence of antiarrhythmic therapy and 84% in patients taking antiarrhythmic therapy. At 4-year follow-up, these success rates decreased to 27% and 61%, respectively. Additionally, atypical atrial flutter may mimic AF on the surface electrocardiogram [Figure 4]; however, the true mechanism of arrhythmia may only become apparent during an electrophysiologic study at the time of ablation. An electrophysiology study revealed rapid scar based left atrial intraatrial reentrant tachycardia with a slowly conducting critical zone accounting for 97/205 milliseconds of the atrial flutter cycle length. Ablation of the critical zone resulted in atrial flutter termination.

Obtaining vascular access for ablation procedures in CHD patients may be challenging due to the presence of scar tissue, particularly in patients who have had a number of cardiac catheterization procedures, percutaneously inserted central lines, or periods of extracorporeal membrane oxygenation. Femoral and internal jugular venous access sites are also frequently occluded. In order to use catheter-based ablation techniques, the first hurdle to overcome is access into the pulmonary venous atrium. Although the incidence of atrial tachycardia after Fontan surgery is high, access to the pulmonary venous atrium, a frequent site of arrhythmia origin, is often limited. Thus conventional transseptal access to the left atrium is usually achievable in those CHD patients with a separated 2 ventricle circulation. In Fontan patients, transseptal access is largely limited to those with an "old style" atriopulmonary Fontan and can be quite challenging due to the degree of atrial enlargement and hypertrophy and the lack of commercially available appropriately sized transeptal catheters. In atrial switch (Mustard or Senning) patients, transcatheter access to the pulmonary veins can only be accomplished with a magnetic navigation catheter ablation system.

The transhepatic approach is well documented in a number of fields, with indications for treatment of portal hypertension, hemodialysis, and also catheter-based ablation therapies.[42],[43] Under fluoroscopic and ultrasound guidance, a percutaneous needle is advanced into a hepatic vein and exchanged for a vascular sheath over a wire. Catheters are then advanced into the systemic venous atrium

for mapping and ablation.[44] This approach is useful in those CHD patients with acquired occlusion of the IVC and those patients with heterotaxy syndrome and congenital interruption of the IVC with azygous vein continuation. The presence of conventional basket type IVC filters has not been a significant impediment to catheterization.

Transthoracic percutaneous access with fluoroscopic guidance provides a direct route to the pulmonary venous atrium for successful mapping and radiofrequency ablation in patients after a Fontan palliation. Nehgme et al[45] performed 6 transthoracic ablation procedures in patients with a lateral-tunnel Fontan. Under biplane fluoroscopy, a percutaneous needle was advanced toward the pulmonary venous atrium. Mapping and ablation catheters were placed in the atrium, and additional catheters were placed in the baffle and esophagus for pacing and reference. Complications included 1 pneumothorax and 2 hemothoraces that were drained. Another new procedure that was recently described involves a CT-guided transconduit puncture in patients with an extracardiac Fontan, in which the dilator tip is grasped with a snare catheter.[46] Subxiphoid and epicardial approaches may be used in patients without CHD, however, they are generally not employed for patients with CHD.[47] Both these approaches rely on the ability to access the pericardial sac in patients who have had multiple sternotomies. Nevertheless, these patients frequently have a pericardium that is immobile and often scarred with thick adhesions.[48]

Surgical Therapies

Surgical ablation is considered the gold standard for invasive rhythm control in patients with CHD. The initial surgical treatment of CHD with concomitant surgical ablation began with an atriopulmonary to total cavopulmonary Fontan conversion performed in conjunction with surgical ablation for AF.[49] Fontan conversion that did not include surgical ablation has been associated with a high incidence of atrial arrhythmias postoperatively.[50] The surgical approach has since progressed from isthmus ablation, to a modified right-sided maze procedure, and eventually to the MAZE-Cox III (right and left-sided maze) procedure for AF.[51],[52] Referral for surgical ablation includes patients for whom catheter ablation has failed, patients with concomitant CHD and arrhythmias, and patients with low body mass

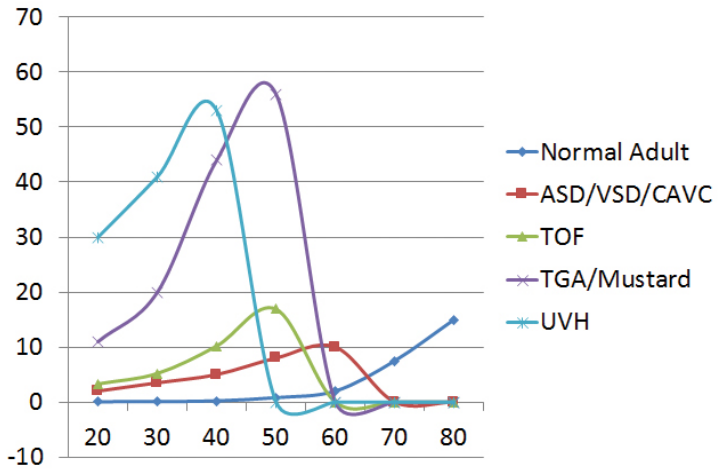

Figure 4: Prevalence of atrial fibrillation by age and defect

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for whom size precludes the use of catheter-based approaches.[53],[54] In one study, ablative surgery during surgical revision of complex congenital heart defects had a 93% success rate with approximately 7% rate of recurrence.[55] A right-sided atrial maze performed during surgical repair of Ebstein's anomaly has also been associated with good short-term outcomes.[56]

A surgical approach that incorporates a modification to the Fontan for the prophylaxis of intraatrial reentrant tachycardia should be considered as a part of preoperative planning. In a small feasibility study, an interventional atrial incision placed during the Fontan operation resulted in an increase in intraatrial conduction time without any spontaneous or inducible intraatrial reentrant tachycardias during electrophysiologic testing.[57] Although the procedure was shown to fundamentally change the atrial substrate, its long-term efficacy in reducing the incidence of intraatrial reentrant tachycardias is unknown.

A hybrid approach may be useful in select situations, for example, in patients with tetralogy of Fallot and inducible ventricular tachycardia on electrophysiologic testing before they undergo thoracotomy for other congenital cardiac surgery.[58],[59] With 3-dimensional mapping and pace-mapping techniques, the focus of ventricular arrhythmias can by marked by an ablation catheter. This allows for the localization and surgical excision of the arrhythmogenic tissue, thereby substantially reducing the possibility of future ventricular arrhythmias and resultant ICD discharges.[60] Patients with a single ventricle that are scheduled to undergo Fontan revision may be appropriate candidates for similar hybrid approaches that include surgical resection of arrhythmogenic atrial tissue. With advanced planning, patients undergoing open-thoracotomy procedures can have epicardial leads placed intraoperatively, potentially avoiding another open thoracotomy if they develop a pacing indication in the future.

Care of patients who have undergone Fontan palliation continues to be challenging both from an arrhythmia and an access perspective. Fontan surgery has progressed from a classic Fontan (right atrial to pulmonary artery), to a lateral-tunnel Fontan (inferior vena cava and superior vena cava to the pulmonary artery within the right atrium), and finally to an extracardiac Fontan circuit. Each of these procedures has a unique set of access and arrhythmia challenges.[61]-[63] Therefore, any opportunity to perform a surgical ablation during an open-thoracotomy procedure should be considered as a part of the preoperative planning discussion. Finally, elective surgical excision of thrombogenic structures such as the left atrial appendage and residual ligated blind ended pulmonary artery stump should be performed at the time of concomitant open heart cardiac surgical repairs.

Conclusions

The adult CHD population is increasing rapidly, and patients with CHD are more likely to be referred for cardiac electrophysiology procedures. AF occurs at a younger age in patients with CHD who are less tolerant of the arrhythmia and whose comorbid conditions make medical arrhythmia therapy more difficult to manage. Multiple drugs and many interventions will likely be required. Amiodarone is an effective antiarrhythmic agent but has long-term toxicity risks for this young population but is a very good short term bridging therapy; dofetilide and sotalol may be viable long term alternatives. Before any catheter-based therapy is undertaken, identification of vascular access to the systemic and pulmonary venous atria is essential. This generally mandates the use of advanced imaging such as CT

or MRI with 3D reconstruction. Any time an open-thoracotomy operation is planned, a discussion of concomitant surgical ablation of the arrhythmogenic substrate and excision or exclusion of residual thrombogenic structures should occur. A preoperative diagnostic EP study without ablation is often useful in guiding subsequent surgical ablation. In conclusion, patients with complicated CHD and atrial arrhythmias should have the benefit of referral to or collaboration with an adult congenital center of excellence prior to invasive rhythm management therapies.

Conflict Of Interests

None.

Disclosures

None.

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Scar homogenization in AF ablation: Evolution and practice

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Abstract

Laboratory studies, histology studies, image studies and the clinical studies all prove the positive correlation between atrial fibrillation and atrial fibrosis from different perspectives. Atrial fibrosis, by separating myocardial cell coupling, diminishing conduction velocity and promoting anisotropic conduction, produce the substrate to sustain atrial fibrillation (AF). These fibrotic areas can be translated into signal abnormalities (low voltage and complex electrgram), and be depicted by electroanatomic high density map. Ablation targeting these areas after circumferential pulmonary vein isolation as the additional substrate modification strategy has proved its beneficial results. However, the unified methodology regarding the scar definition, the mapping rhythm (AF or sinus rhythm) and the modification endpoint is yet to be negotiated. Large-scale clinical trials, long-term follow-up results are needed to prove its contribution to the overall success rate of AF ablation.

Introduction

Atrial fibrillation (AF) is a common but insidious cardiac arrhythmia. Over half a century passed between the first description of AF on ECG and the development of the most recent catheter ablation treatment, however, the electrophysiological mechanisms underlying AF initiation and maintenance have not been well defined. In the literature, one thing is clear regarding the mechanisms of AF, that is, it requires substrates to perpetuate. These substrates, either electrical or histological, play an important role in AF maintenance. Theoretically, electrical substrate remodeling is often transient and reversible [1] and carries more weight for sustaining paroxysmal AF, while histological remodeling tends to be irreversible and progressive [2] and is the dominant mattress for both paroxysmal and persistent AF perpetuation.

Atrial Fibrosis and Atrial Fibrillation

Any disturbance of the atrial architecture potentially increases the susceptibility to AF [3]-[6] because focal or diffused injury of the atrial myocardium can cause inhomogeneity of atrial repolarization or conduction, thus inducing AF. Such changes (e.g., inflammation, fibrosis, and hypertrophy) occur most commonly in the setting of underlying heart disease associated with hypertension, coronary artery disease, valvular heart disease, cardiomyopathies, and heart failure, which tend to increase left atrium (LA) pressure, cause atrial dilation, and alter wall stress. Similarly, atrial ischemia from coronary artery disease and infiltrative diseases, such as amyloidosis, hemochromatosis, and sarcoidosis, can also promote AF. Additional promoters, including extra-cardiac factors such as hypertension, sleep apnea, obesity, alcohol/medications, and hyperthyroidism—which have pathophysiologic effects on the atrial cellular structure and function—can predispose the atrium to develop AF. Even in patients with lone paroxysmal AF without recognized structural heart disease, atrial biopsies have revealed inflammatory infiltrates consistent with myocarditis and fibrosis [7]. This condition indicates that unexplained atrial myocardial disease underlies lone AF, reflecting a unique type of atrial cardiomyopathy [8]. In fact, all of the above causes, which can be called AF risk factors, will finally give rise to electrical and histological remodeling and therefore promote the genesis of AF.

Atrial cellular impairment and its consequent repairing and remodeling, whatever the etiology, will ultimately result in AF histological substrate. This was confirmed by atrial histological investigations. The atrial histological substrate of AF and its relation to biventricular histological findings were investigated by performing right atrial and biventricular endomyocardial biopsies in patients with paroxysmal lone AF refractory to conventional antiarrhythmic therapy [7]. The atrial biopsies in all cases showed detectable abnormalities, but the histologic findings varied, being compatible with a diagnosis of myocarditis in 66% of patients, with a non-inflammatory cardiomyopathy process in 17% of patients, and with patchy fibrosis in the remaining 17% of patients, likely resulting from myocardial healing caused by a toxic or inflammatory process. In the same population, the histological findings of biventricular biopsies were abnormal only in 25% of patients and confirmed the finding of atrial myocarditis. The results of this study suggest that atrial disease can be independent of and not always secondary to the ventricular disease. Whatever the origin, the inflammation of atrial myocardium is increasingly recognized as a main cause of atrial tachycardia [9], permanent AF [10], [11] and paroxysmal lone AF. Inflammatory

Key Words

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markers, such as C-reactive protein and interleukin-6, are elevated in atrial fibrillation patients and may predict the risk of developing future atrial fibrillation [12]. In fact, the final outcome of inflammation is fibrosis. The expression of major extracellular matrix proteins, such as collagen I, collagen III, and fibronectin, confirmed the relationship between AF and fibrosis [13]. When atrial tissue samples from patients with lone AF, AF with mitral valvular disease and sinus rhythm were obtained from the left atrial free wall near the interatrial septum during cardiac surgery, an increase of approximately 100% in collagen I, 50% in collagen III (which was confined to AF with mitral valvular disease), and a slight non-significant increase in fibronectin in left atrial tissue samples of patients with AF were observed [13]. In surgical maze procedures for valvular atrial fibrillation, left atrial tissues in the posterior-wall and right-atrial appendage were obtained from 47 patients [14]. Patients with preoperative AF had larger atrial cell sizes (19.0±5.0 μm vs 13.9±3.5 μm in the left atrium and 17.0±4.8 μm vs 12.3±2.8 μm in the right atrium, $p < 0.01$, respectively) and a larger amount of intercellular fibrosis (15.8±8.8% vs 6.9±2.4% in the left atrium and 15.2±6.2% vs 6.2±2.9% in the right atrium, $p < 0.01$, respectively) in both atria compared with those with preoperative sinus rhythm. Additionally, for patients with preoperative AF, those in the unsuccessful maze group had significantly larger atrial cell sizes and a larger amount of intercellular fibrosis in the left atrium compared with those in the successful group. Furthermore, a larger amount of left-atrial intercellular fibrosis compared with the right atrium was observed only in the unsuccessful maze group. Corradi and colleagues [15] evaluated regional left-atrial interstitial remodeling in patients with chronic AF undergoing mitral valve surgery and suggested that the left-atrial free wall around the pulmonary vein ostia was a region characterized by marked interstitial remodeling compared with the left-atrial appendage. A postmortem study [16] provided strong evidence for interstitial atrial fibrosis in patients with AF. These laboratory and clinical studies established a positive correlation between atrial fibrosis and AF from different perspectives.

With atrial fibrosis, the interstitial space between cardiomyocytes is increased due to the accumulation of fibrotic collagen [17], [18], and the electrical side-to-side junctions between muscle bundles are disrupted [19], [20]. The poor tissue coupling, discontinuous propagation and non-uniform anisotropic conduction are the electrophysiological premise for AF.

Detecting the LA scar in AF patients

Electrophysiologically, by separating myocardial cell coupling and diminishing conduction velocity, atrial fibrosis produces lower-amplitude electrograms [21], electrogram fractionation, and conduction heterogeneity and manifests as abnormal signals that can be identified using electroanatomic mapping during sinus rhythm. Thus, the fibrotic areas can be translated into abnormal electrical signals and can be imposed on a three-dimensional map [22], [23]. Two similar studies [22], [23], using a high-density mapping technique, compared the electrophysiological substrate in a different AF population. They found that with the progress of AF, there was a gradual reduction of overall LA mean voltage, prolongation of LA activation time, higher incidence of low voltage zone (LVZ) detection and increased prevalence of complex electrogram. More importantly, in Dr. Lin's study [23], the definitions of LVZ (bipolar voltage range: 0.1-0.4 mV) and TZ (transitional zone) (bipolar voltage range: 0.4-1.3 mV) were established. Thirteen patients without any cardiovascular risk factors,

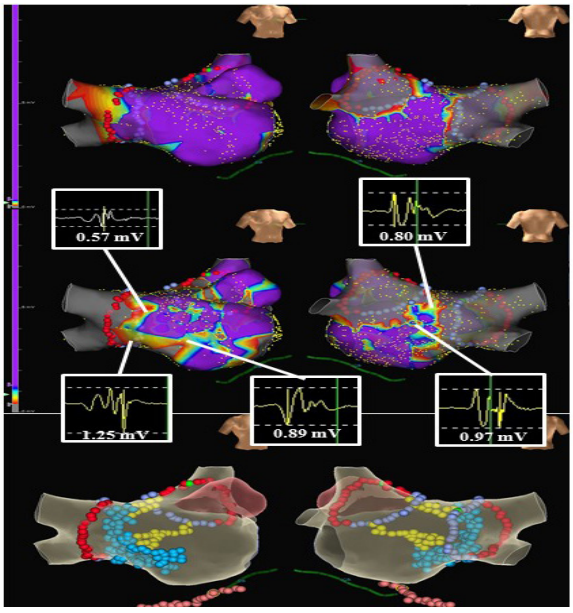

Figure 1: **A case example of sinus rhythm substrates obtained from high-density mapping in the LA after circumferential pulmonary vein isolation; cavo-tricuspid isthmus ablation and cardioversion. Upper panel: low voltage zone (LVZ) defined by 0.1-0.4 mV; Middle panel: Transitional zone (TZ: 0.4-1.4 mV) with complex electrograms; Lower panel: the corresponding lesion placement. Notice that homogenization of the LVZs, elimination of the complex electrograms in TZ region and dechanneling were performed.**

who underwent left-sided accessory pathway ablation, were supposed to have "normal" LA. In this normal population, 95% of the points had bipolar voltage above 0.38 mV. Therefore, the upper limit cutoff value of the LVZ was defined as 0.4 mV. The complex electrograms during sinus rhythm were defined as any multiphasic electrogram with ≥3 positive or negative distinct peaks and electrogram duration ≥50 ms, suggesting a local conduction delay. When analyzing the distribution of these complex electrograms in the LA body in patients with non-paroxysmal AF, 95% of patients were distributed in the areas with the bipolar voltage <1.32 mV. As such, TZ with bipolar voltages between 0.4 mV and 1.3 mV was defined to facilitate the search for these abnormal electrograms. Theoretically speaking, diseased atria are not only "black and white" with a clear line; therefore, setting LVZ as the profound scar and TZ as the moderate fibrotic area is more reasonable.

The first study addressing the LA scar and its correlation with the catheter ablation outcome was Dr. Verma's work [24]. The prevalence of the LA scar in AF patients was approximately 6% detected by electroanatomic mapping (bipolar voltage <0.5 mV). AF patients with the LA scar had a significantly higher recurrence rate than those without the LA scar. Image studies, using the technique of late gadolinium-enhanced (LGE)-MRI, demonstrated a significant correlation between LGE-MRI identified enhancement and the burden of fibrosis present on the biopsied tissue [25]. The atrial tissue substrate in the three different AF clinical phenotypes (paroxysmal AF, persistent AF and long-standing persistent AF) was also studied using LGE-MRI. A weak correlation was found between the extent of atrial fibrosis and the presence of persistent AF [26], [27]. There was significant overlap in the degree of fibrosis between patients with different AF phenotypes such that the phenotype did not accurately predict the degree of atrial fibrosis. Moreover, patients with so-called

"lone AF", i.e., AF with no other cardiovascular disease condition, had the same burden of atrial fibrosis as those with non-lone AF [28]. Clinically, Mahnkopf et al. [28] reported that the detection of increased enhancement within the left atrium by delayed-enhanced magnetic resonance imaging was strongly associated with AF recurrence after PVI. Later, the multicenter DECAAF study demonstrated that baseline atrial fibrosis prior to ablation was a major predictor of arrhythmia recurrence. The investigators classified the degree of fibrosis using the MRI image [29]. The MRI data were analyzed at the core laboratory for image quality and for quantification of atrial fibrosis. Based on the degree of detected fibrosis from delayed enhancement MRI, the following 4 stages were defined: stage 1, less than 10% of the atrial wall; stage 2, 10% or greater but less than 20%; stage 3, 20% or greater but less than 30%; and stage 4, 30% or greater. There were 49 patients (18.9%) in stage 1, 107 patients (41.2%) in stage 2, 80 patients (30.8%) in stage 3, and 24 (9.2%) in stage 4. The trial concluded that the overall success rate of AF ablation was independent of ablation strategy, but depends on the extent of atrial fibrosis. Huang et al. [30] elegantly showed that left atrial scarring areas, which were detected using LGE-MRI, correlate well with low voltage areas on electroanatomic maps of the LA. Interestingly, by reviewing the evidence from clinical mapping techniques in combination with imaging and computational modeling, Haissaguerre et al. concluded that AF drivers are located within heterogeneous structural/fibrotic atrial regions [31]. This finding was also described in two other studies, which, by placing the circular mapping catheter at the LVZ during AF, could record the rotational activation [37], [39].

Scar homogenization as the ablation strategy for the treatment of AF

Since the atrial fibrotic areas correlate strongly with AF, catheter ablation targeting these areas as the substrate modification beyond CPVI is a new strategy.

Regional and linear ablation base on the bipolar voltage mapping

In the study of Rolf et al., 178 patients with paroxysmal or persistent AF were included. The confined LVZs were targeted for regional ablation, which aimed to homogenize the diseased LA tissue by radiofrequency ablation [32]. The end point for areal radiofrequency lesions was reached with a significant reduction in local electrograms, defractionation, and loss of capture while stimulating the ablation catheter with high output (10 V; 2 ms). Strategic linear lesions were performed whenever ablative substrate homogenization could not be completed because of potential collateral damage (e.g., septal near the AV-node or posterior close to the esophagus) or when extensive regional ablation might have created critical isthmus sites for potential macro reentrant tachycardias (e.g., near the roof or anterior LA to prevent roof-dependent or perimitral flutter). These strategic linear lesions either connected non-conducting tissues with other anatomic electrical battier structures traversing target LVZs or encircled large LVZs to electrically isolate the diseased tissue from the rest of the healthy atrium. The end point for strategic lesion creation was reached with the confirmation of a complete block (e.g., perimitral conduction) as indicated by (1) reduction of local electrogram amplitude, (2) loss of local capture, (3) confirmation of double potentials on the line and analysis of activation sequence, while stimulating near the linear lesion line. After circumferential PVI with or without substrate modification, burst pacing (10 V; 2 ms) from the proximal coronary sinus was conducted (10-s periods, decreasing cycle lengths from 300 ms until refractoriness in 20-ms steps). Inducible regular atrial tachycardias (AT) were targeted for radiofrequency ablation with AT termination and non-inducibility as the clinical end point. In case of AF inducibility, no further substrate modification was conducted. Success rate at 12 months was 70% in patients with LVZs, and 62% in patients without LVZs. Success rate did not differ significantly in paroxysmal versus patients with persistent AF (69% versus 61%; P=0.28). Similarly, Hans et al. applied box isolation of fibrotic areas [33], [34] in both paroxysmal and non-paroxysmal AF patients and achieved favorable results.

Voltage-guided ablation of the posterior wall beyond CPVI may also improve arrhythmia-free survival [35]. After vein isolation was achieved, posterior wall voltage mapping was performed using a 3-D electroanatomical mapping system during sinus rhythm. The presence of scar was defined as a region that reproducibly demonstrated an area of > 0.5 × 0.5 cm on the posterior wall with a voltage less than 0.5 mV. Posterior wall ablation, if low voltage was found, was preferably performed using a posterior roof line and a floor line completing a posterior wall "box." Importantly, the borders of the box were intended to encompass the area of low voltage. The low voltage to be targeted without completion of the "box" was allowed if clinically indicated, such as esophageal temperature concerns. Voltage-guided ablation increased 1-year AF/AT free survival in patients compared to standard ablation (80% vs. 57%; P = 0.005).

Another study compared the long-term outcome in patients with paroxysmal AF and severe LA scarring identified by 3-D mapping, in which pulmonary vein antrum isolation (PVAI) only, PVAI and the scar homogenization, or PVAI + ablation of the non-PV triggers was applied [36]. In this particular population, the long-term outcome of scar homogenization plus PVAI was only slightly improved.

Substrate ablation based on the abnormal electrograms during sinus rhythm mapping

According to the voltage mapping, a strategy of selective electrophysiologically guided atrial substrate modification in sinus rhythm (SR) after circumferential pulmonary vein isolation and cavotricuspid isthmus ablation was used [37]. The authors enrolled 86

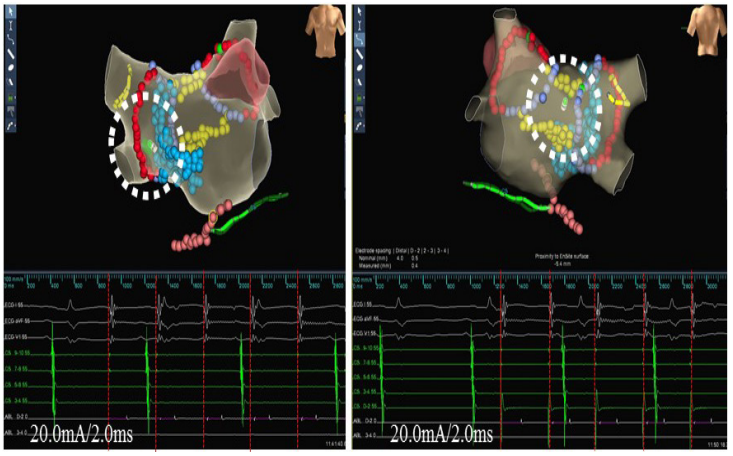

Figure 2: **Checking the homogenized or isolated regions using pacing maneuvers. High output pacing from the deflectable ablation catheter placed in the homogenized or isolated regions failed to capture the local myocardium in the same case. Tracings are the surface ECG (I, avL, V1), endocardial recordings of coronary sinus from proximal to distal and the ablation catheter.**

patients with persistent and long-standing persistent AF. Once SR was restored by cardioversion, high-density bipolar voltage mapping of LA was performed using A-Focus catheter to identify the LVZ (0.1–0.4 mV) and TZ (0.4–1.3 mV). All the electrograms in LVZ were ablated to achieve an absolute bipolar electrogram of <0.1 mV. If SR-AEs were identified in TZ, ablation targeting SR-AE was performed to achieve electric silence or elimination of SR-AE. Additional short linear lesions were placed to transverse potential conducting channels for re-entrant activity between isolation lines or anatomic conduction barriers and LVZs [Figure 1] and [Figure 2]. Among the patients converted to SR, 70% (55/79) had LVZs and TZs with SR-AEs and received additional ablation, whereas in 30% (24/79) of patients without electrophysiological substrate, no further ablation was performed. A total of 78 matched patients who had traditional stepwise ablation strategy were used as the control group. During a follow-up period of >30 months, the Kaplan-Meier estimated probability to maintain SR was 69.8% versus 51.3%. After a single procedure, 3.5% developed post procedural AT in the study group compared with 30% in the control group (P=0.0003). This strategy proposed a more comprehensive substrate modification approach not only targeting the profound fibrotic areas (LVZ) but also addressing the moderate fibrotic areas (TZ). It is analogous to what has been used in conventional pathologic ventricular tachycardia ablation and is supposed to be the combination of both curative (AF) and preventative (AT) strategies. The other reproducible study is from Dr. Yamaguchi's work [38]. However, modification in transitional areas was not applied.

Ablation based on electrogram characteristics during AF mapping

During atrial fibrillation, Amir S. Jadidi et al. applied ablation to sites with distinct activation characteristics within/at border zones of LVZ in addition to PVI. This strategy seems to be more effective than the conventional PVI-only strategy for persistent AF [39]. The procedural end point was AF termination and the target areas were defined with electrogram voltage <0.5 mV and electric activity >70% of AF cycle length. In this work, patients presenting in SR were induced by atrial burst pacing from distal or mid-coronary sinus (CS) at a cycle of 250 to 180 ms. If repeat atrial burst stimulation up to 180 ms did not induce AF sustaining for >6 minutes, the patients were considered as non-inducible AF and underwent LA voltage mapping in SR or CS-paced rhythm (at 800 ms pacing cycle length). LA low voltage in sinus or CS paced rhythm was defined as areas with bipolar voltage <1.0 mV. Spontaneous or induced AF underwent initial mapping in the LA and CS, whereas mapping in the right atrium was performed only after unsuccessful LA ablation to reduce procedure length and radiation exposure to patients. Radiofrequency energy was delivered at each low-voltage site displaying the above-mentioned electrogram patterns for 20 s to 40 s. As a result, single procedural arrhythmia freedom at 13 months median follow-up was achieved in 59 of 85 (69%) patients, which was significantly higher than the matched control group (31/66 [47%], P<0.001).

Using the same definition during atrial fibrillation, LVZ-guided substrate modification was performed after PVI in patients with LVZ [40]. A total of 201 patients were enrolled, and more than 80% were non-paroxysmal patients. Larger areas with LVZ were ablated across or along its borders. Isolated LVZ regions were ablated and connected to the closest ablation line or to the mitral annulus. Narrow isthmuses <15 mm were ablated even if local voltage was >0.5 mV, with the exception of the lateral isthmus, which was only ablated if it contained significant LVZ. The authors found after the index procedure, 144 (72%) patients were free from AF at 12 months. With multiple procedures, 148 (74%) patients during a median follow-up of 3.1 years were free from the recurrence [40].

Controversies

With the evolution of scar homogenization as the additional substrate modification strategy for the treatment of AF, several points remain unclear:

Definition of LVZ

1) Regional variation. Suraj et al. suggested that a bipolar voltage cutoff value of 0.27 mV provided the best discrimination between healthy and unhealthy LA myocardium on DE-CMRI [41]. This value was very close to the lower cutoff value of 0.2 mV that they determined from EAM to identify the scar in the LA-PV junction and LA posterior wall. However, for other LA locations on EAM, a voltage cutoff value of 0.45 mV is more useful in discriminating relatively healthy from scarred LA myocardium. They therefore proposed cutoff values ranging from 0.2 mV to 0.45 mV instead of a single cutoff value, which allows better discrimination of the LA scar when considering regional heterogeneity in LA bipolar voltage distribution. However, in all of the published papers, only one value was used to guide LVZ ablation.

2) Heterogeneity of the electrode spacing of the mapping catheter. Most of the above-mentioned studies used the bipolar voltage of 0.5 mV to define the scar, yet the electrode spacing of the circular mapping catheter and the ablation catheter was obviously different.

3) Variation of the mapping rhythm. Most of the scar definition was based on the signals taken during sinus rhythm; however, the definition of a scar in some other studies was based on the mapping results during AF or CS pacing. Although there was a linear voltage correlation between sinus rhythm and AF, suggesting that a similar extent of left atrial fibrotic substrate could be identified on electroanatomical voltage mapping by adjusting the voltage cutoff [42], the matching value during different rhythm has not been settled.

Methodology of scar homogenization

1) Scar homogenization, scar isolation, scar-based linear lesions and dechanneling are the most common substrate modification strategies applied in recent studies. However, a unified end-point is lacking.

2) The fibrotic substrate is heterogeneous and cannot only be defined as healthy (normal) or unhealthy (scar).

3) Whether the right atrium scar mapping and ablation can further improve the overall success rate is unclear.

Conclusions

Image studies and electroanatomic mapping studies of the AF population have provided a better understanding of the human atrial substrate that maintains AF. This has led to the concept of fibrosis-guided substrate modification. This strategy, though very promising, currently lacks sufficient supportive evidence from the larger population and long-term follow-up results. More clinical evidence should be accumulated, randomized clinical trials should be conducted, and, more importantly, the methodology should be unified. In the near future, the 3-D mapping system, working towards high density and high-resolution map, will help to make scar homogenization more accurate.

Conflict Of Interests

None.

Disclosures

None.

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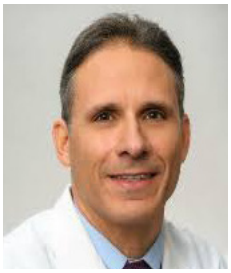

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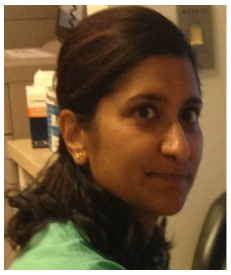

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