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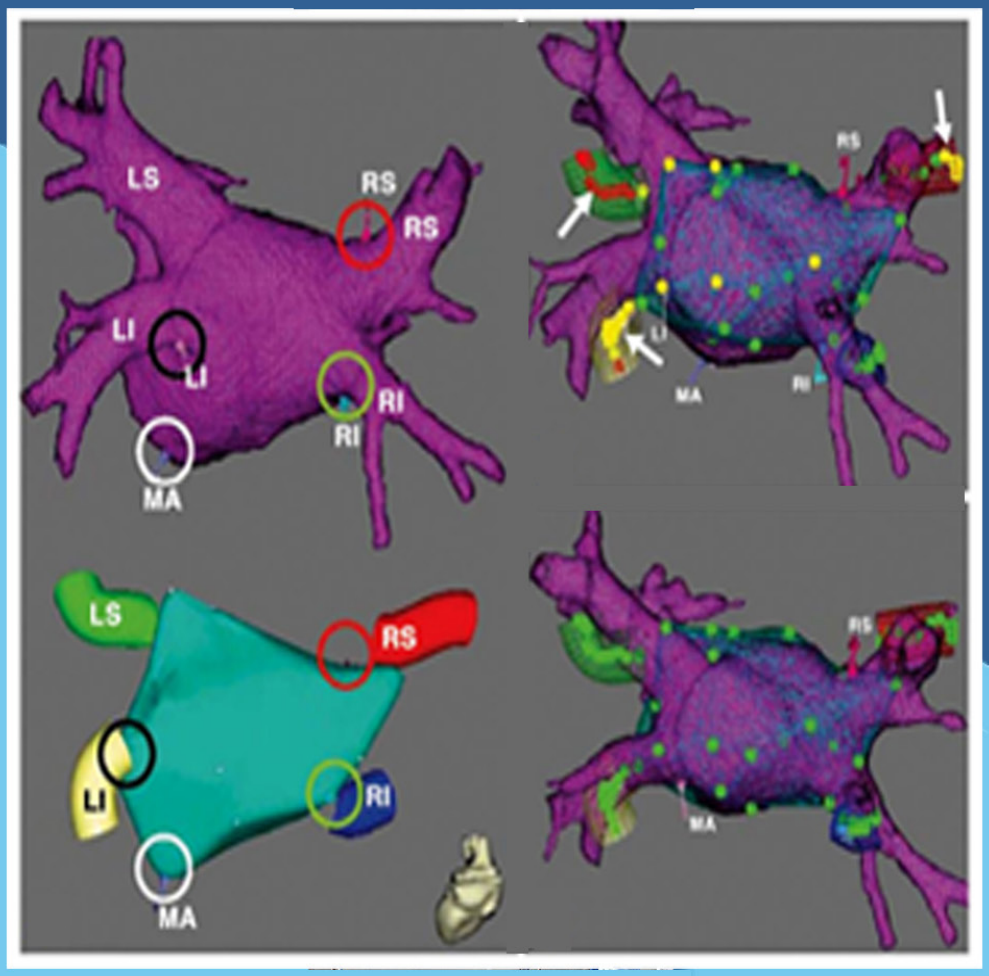

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Left Atrial Image Registration to Guide Catheter Ablation of Atrial Fibrillation: In the Eye of the Technology

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Introduction

PAtrial fibrillation is a common arrhythmia, and its incidence rise sharply with age and with heart failure.Since the beginning of the new millennium, the debate on ectopic foci versus reentry as the mechanism underlying atrial fibrillation (AF) in humans has continuously evolved. The finding of ectopic beats proceeding from the pulmonary veins in the initiation of atrial fibrillation gave a different approach to the therapeutic management of this arrhythmia.[1-4] Recently, the mechanism of AF is considered to be a spiral wave with a continuously changing pattern of the activation wavefront, that is, a random multiple reentry of independent wavelets wandering in the atria around arcs of refractory tissue[5-10] or the accentuation of focal activity originating mainly from the pulmonary veins, the superior or inferior vena cava, the ligament of Marshall, or even the right atrium.[11-17]

The medical treatment of atrial fibrillation with antiarrhythmic drugs, either to control rate or rhythm, is not adequate for all patients and is frequently associated with pharmacological adverse effects.[18-20] Therefore, the number of therapeutic procedures for atrial fibrillation with catheter ablation is rapidly increasing. Since the demonstration of spontaneous initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins, transvenous catheter ablation has become the most exciting and innovative field of interventional electrophysiology.[21-24] However, due to the complex and variable anatomy of atrial structures and pulmonary veins, the success rate of atrial fibrillation ablation is still not ideal, and the association with procedural complications still remains a problem. The left atrium and the pulmonary veins can not be seen with fluoroscopy because they do not present contrast against the surrounding structures. Even with advance techniques to minimize fluoroscopy time and radiation exposure, it is of concern the significant ionizing radiation exposure during prolonged fluoroscopy required to delineate the complex anatomy of the left atrium and the pulmonary veins. Besides, there are multiple variations of pulmonary veins anatomy which include different sizes, a common right or left ostium, and an additional pulmonary vein. Thus, more accurate imaging modalities and their combination are likely to overcome these difficulties and improve ablation success and related safety.

The current standard computer navigation tool used during AF catheter ablations is the electroanatomic mapping, which detects the tip of the catheter in real time.[25-27] The key step in the clini-

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cal use of three dimensional (3D) surfaces is image registration. The surfaces from axial computed tomography (CT) and nuclear magnetic resonance (MR) can only be useful during an ablation procedure if they can be accurately overlaid with the electroanatomic mapping, so that real-time catheter positions can be shown in precise relation to the 3D surfaces.[28-30] Currently available cardiac mapping systems can record cardiac electrical activation information, catheter and lesion location, and are capable of tracking catheters in real time. Combining this electrical and navigational information with the explicit three dimensional anatomy of the left atrial chamber and pulmonary veins, through this process called registration, should increase the efficacy of atrial fibrillation ablation procedures.[31-34] In this issue of the journal, Jasbir Sra reports detailed data on the basic principles, the inherent limitations, and the fundamentals of cardiac image registration.[35] He addresses the different 3D anatomical mapping and imaging systems and their clinical applicability in combination, as well as, the clinical studies utilizing the registration imaging technique. The validity of applying the registration process within the particular constrains of cardiac imaging is also examined. Imaging registration is the process of combining and aligning various images obtained with different imaging modalities. Proper imaging and segmentation involves establishing a correspondence between the spatial information in the image and the equivalent anatomical structure in the heart. Several imaging modalities have been used in an attempt to delineate cardiac structures, namely, contrast fluoroscopy, 3D electroanatomical noncontact mapping, 3D axial computed tomography, and 3D nuclear magnetic resonance. The registration process determines the geometric transformation that aligns anatomical features in one view of an object with the corresponding anatomical features of the same object in another view. It allows real-time visualization of anatomical structures and more accurate tracking and location of the mapping and ablation catheter, this translates into a significant clinical implication in the interventional treatment of atrial fibrillation.[31-34]

Several recent experimental and clinical studies demonstrated the accuracy of targeted ablations guided by cardiac image registration.[36-40] It was shown that registration can be successfully used for the anatomically correct extraction and reconstruction of the left atrium and pulmonary veins anatomy, allowing tailored radiofrequency ablation to individual pulmonary vein and left atrium anatomy during atrial fibrillation ablation procedures. Whether the improvement of catheter navigation by the imaging registration techniques can translate into better outcomes of AF ablation and avoid procedure-related major complications needs to be determined by larger randomized clinical studies.

The necessity to combine various imaging modalities like fluoroscopy, electroanatomic mapping, 3D CT-MR, and intracardiac echocardiography guidance, to optimize the results of atrial fibrillation ablation implies the technical difficulties in performing this therapeutic approach. On the other hand, the necessity to combine different ablation techniques, namely, circumferential, linear, and targeted ablation of complex fractionated electrograms, in order to improve the success rate demonstrates the complexity of the electrophysiological substrate in atrial fibrillation.

A detailed colorful picture can tell more than words can say. There is no doubt that a new hope emerges with a new tool, and left atrial image registration for catheter ablation of atrial fibrillation certainly provides us with a newer landscape in the horizon, but here again, it has to stand the test of time.

References

1. Haissaguerre M, Jaise P, Sha DC, Takahashi A, Hocini M, Quiniou C, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J: Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-666. CrossRef PubMed

2. Jais P, Haissaguerre M, Shah DC, Chouairi S, Gencel L, Hocini M, Clemety J. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation 1997; 95:572-576.

3. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC, Hsu TL, Ding YA, Chang MS. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiologic characteristics, pharmacologic responses, and effects of radiofrequency ablation. Circulation 1999;100:1879–1886.

4. Lu TM, Tai CT, Hsieh MH, Tsai CF, Lin YK, Yu WC, Tsao HM, Lee SH, Ding YA Chang MS, Chen SA. Electrophysiologic characteristics in initiation of paroxysmal atrial fibrillation from a focal area. J Am Coll Cardiol 2001;37:1658-64CrossRef PubMed

5. Davidenko JM, Pertsov AV, Salomonsz R, Baxter W, Jalife J. Stationary and drifting spiral waves of excitation in isolated cardiac muscle. Nature 1992;355:349-51.CrossRef PubMed

6. Ikeda T, Czer L, Trento A, Hwang C, Ong J, Hough D, Fishbein M, Mandel W, Karagueuzian H, Chen CP. Induction of wander-

ing functional reentrant wave front in isolated human atrial tissues. Circulation 1997;96:3013-3020.
7. Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. >Am Heart J 1964;67:200-220.CrossRef PubMed
8. Allessie MA, Lammers WIEP, Bonke FJM, et al. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Cardiac Electrophysiology and Arrhythmias. Zipes DP, Jalife J, eds. Orlando, FL, Grune & Stratton, 1985; 256-276.
9. Centurión OA, Shimizu A, Isomoto S, Konoe A. Mechanisms for the genesis of paroxysmal atrial fibrillation in the Wolff-Parkinson-White syndrome: Intrinsic atrial muscle vulnerability vs. electrophysiological properties of the accessory pathway. Europace 2008;10:294-302.CrossRef PubMed
10/a>. Shimizu A, Centurión OA. Electrophysiological properties of the human atrium in atrial fibrillation. Cardiovasc Res 2002;54:302-314.CrossRef PubMed
11. Centurión OA, Shimizu A, Isomoto S, et al. Influence of advancing age on fractionated right atrial endocardial electrograms. Am J Cardiol 2005;96:239-242.CrossRef PubMed
12. Chen SA, Tai CT, Chen JY, Tasi CF, Hsieh MH, Chen CC, Prakash VS, Ding YA, Chang MS. Right atrial focal atrial fibrillation: electrophysiologic characteristics and radiofrequency catheter ablation. J Cardiovasc Electrophysiol 1999;10:328-35. CrossRef PubMed
13. Kim DT, Lai AC, Hwang C, Fan LT Karaquezian HS, Chen PS, Fishbein MC. The ligament of Marshall: a structural analysis in human hearts with implications for atrial arrhythmias. J Am Coll Cardiol 2000;36:1324-7.CrossRef PubMed
14. Hwang C, Wu TJ, Doshi RN, Peter CT, Chen PS. Vein of marshall cannulation for the analysis of electrical activity in patients with focal atrial fibrillation. Circulation 2000;101:1503-5.
15. Hsu LF, Jais P, Keane D, et al.Atrial fibrillation originating from persistent left superior vena cava. Circulation 2004;109:828–832.CrossRef PubMed
16. Shah D, Haissaguerre M, Jais P, et al. Nonpulmonary vein foci: do they exist? Pacing Clin Electrophysiol 2003;26:1631–5. CrossRef PubMed
17. Oral H, Chugh A, Good E. Tailored approach to catheter ablation of paroxysmal atrial fibrillation. Circulation 2006;113:1824-1831.CrossRef PubMed
18. The AFFIRM investigators. A comparison of rate control and rhythm control in atrial fibrillation. N Engl J Med 2002:347:1825-33.
19. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1834–40. CrossRef PubMed
20. Waktare JEP, Camm AJ. Acute treatment of atrial fibrillation: Why and When to maintain sinus rhythm. Am J Cardiol 1998;81(5A):3C-15C.CrossRef PubMed
21. Pappone, C, Rosanio, S, Oreto, G, et al. Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation. Circulation 2000;102,2619-2628.
22. Pappone C, Rosanio S, Augello G, et al. Mortality, morbidity, and quality of life after circumferential pulmonary vein ostial ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. J Am Coll Cardiol 2003;42,185-197CrossRef PubMed
23. Haïssaguerre M, Sanders P, Hocini M, et al. Changes in atrial fibrillation cycle length and inducibility during catheter ablation and their relation to outcome. Circulation 2004;109:3007-3013. CrossRef PubMed
24. Cappato R, Calkins H, Chen SA, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation 2005;111:1100 –5.CrossRef PubMed
25. Oral H, Chugh A, Good E, Igic P, Elmouchi D, Tschopp DR, Reich SS, Bogun F, Pelosi F Jr, Morady F. Randomized comparison of encircling and nonencircling left atrial ablation for chronic atrial fibrillation. Heart Rhythm 2005;2:1165–1172.CrossRef PubMed
26. Ouyang F, Ernst S, Chun J, Bansch D, Li Y, Schaumann A, Mavrakis H, Liu X, Deger FT, Schmidt B, Xue Y, Cao J, Hennig D, Huang H, Kuck KH, Antz M. Electrophysiological findings during ablation of persistent atrial fibrillation with electroanatomic mapping and double Lasso catheter technique. Circulation 2005;112:3038 –3048.CrossRef PubMed
27. Oral H, Chugh A, Good E, et al. Radiofrequency catheter ablation of chronic atrial fibrillation guided by complex electrograms. Circulation 2007;115:2606-2612.CrossRef PubMed
28. Reddy VY, Malchano ZJ, Holmvang G, Schmidt EJ, d'Avila A, Houghtaling C, Chan RC, Ruskin JN. Integration of cardiac magnetic resonance imaging with three-dimensional electroanatomic mapping to guide left ventricular catheter manipulation: feasibility in a porcine model of healed myocardial infarction. J Am Coll Cardiol 2004; 44:2202-2213.CrossRef PubMed
29. Sra J, Krum D, Hare J, Okerlund D, Thompson H, Vass M, Schweitzer J, Olson E, Foley WD, Akhtar M. Feasibility and validation of registration of three-dimensional left atrial models derived from computed tomography with a non-contact cardiac mapping system. Heart Rhythm 2005;2:55-63.CrossRef PubMed
30. Tops LF, Bax JJ, Zeppenfeld K, Jongbloed MR, Lamb HJ, van der Wall EE, Schalij MJ. Fusion of multi-slice computed tomography imaging with three-dimensional electroanatomic mapping to guide radiofrequency catheter ablation procedures. Heart Rhythm 2005;2:1076-1081.CrossRef PubMed. Tops LF, Bax JJ, Zeppenfeld K, Jongbloed MR, Lamb HJ, van der Wall EE, Schalij MJ. Fusion of multi-slice computed tomography imaging with three-dimensional electroanatomic mapping to guide radiofrequency catheter ablation procedures. Heart Rhythm 2005;2:1076-1081.
31. Sra J, Krum D, Malloy A, Vass M, Belanger B, Soubelet E, Vaillant R, Akhtar M. Registration of three-dimensional left atrial computed tomographic images with projection images obtained using fluoroscopy. Circulation 2005;112:3763-3778.CrossRef PubMed
32. Ector J, De Buck S, Adams J, Dymarkowski S, Bogaert J, Maes F, Heidbüchel H. Cardiac three-dimensional magnetic resonance imaging and fluoroscopy merging-a new approach for electroanatomic mapping to assist catheter ablation. Circulation 2005;112: 3769-3776.CrossRef PubMed
33. Dong J, Calkins H, Solomon SB, Lai S, Dalal D, Lardo AC, Brem E, Preiss A, Berger RD, Halperin H, Dickfeld T. Integrated electroanatomic mapping with three-dimensional computed tomographic images for real-time guided ablations. Circulation 2006;113:186-194.CrossRef PubMed

34. Dong J, Dickfeld T, Dalal D, Cheema A, Vasamreddy CR, Henrikson CA, Marine JE, Halperin HR, Berger RD, Lima JA, Bluemke DA, Calkins H. Initial experience in the use of integrated electroanatomic mapping with three-dimensional MR/CT images to guide catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2006;17:459-466.CrossRef PubMed
35. Sra J. Cardiac image registration. JAFIB 2008;1(3):145-160.
36, Fahmy TS, Mlcochova H, Wazni OM, Patel D, Cihak R, Kanj M, Beheiry S, Burkhardt JD, Dresing T, Hao S, Tchou P, Kautzner J, Schweikert RA, Arruda M, Saliba W. Natale A. Intracardiac echo-guided image integration: optimizing strategies for registration. J Cardiovasc Electrophysiol. 2007: 18: 276-282.CrossRef PubMed
37. Zhong H, Lacomis JM, Schwartzman D. On the accuracy of Cartomerge™ for guiding posterior left atrial ablation in man. Heart Rhythm 2007;4:595-602.CrossRef PubMed
38. Noseworthy PA, Malchano ZJ, Ahmed J, Holmvang G, Ruskin JN, Reddy VY. The impact of respiration on left atrial and pulmonary venous anatomy: implication for image-guided intervention. Heart Rhythm 2005;2:1173-117.CrossRef PubMed CrossRef
39. Solomon SB, Dickfeld T, Calkins H. Real-time cardiac catheter navigation on three-dimensional CT images. J Interv Card Electrophysiol 2003;8:27-36.CrossRef PubMed
40. Sra J, Krum D, Okerlund D, Thompson H. Endocardial imaging of the left atrium in patients with atrial fibrillation. J Cardiovasc Electrophysiol. 2004;27:247.CrossRef PubMed

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Underutilization of Warfarin Therapy in Elderly Patients with Atrial Fibrillation – Fear or False Sense of Security!

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Abstract

Background: Under utilization of warfarin in elderly patients with atrial fibrillation (AF) has been recognized as a significant health care issue. This study examines the rate and reasons for warfarin underutilization in elderly patients with AF at the Kansas City Veterans Affairs Medical Center.

Methods: Retrospective study reviewing electronic medical records of all patients aged 65 and older with the diagnosis of atrial fibrillation. Patients on warfarin were excluded. Reasons for not using warfarin were extracted by reviewing the electronic medical record. Anticoagulation indications for these patients were determined based on the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation.

Results: Warfarin was not used by 407 patients (25%) with known AF. Average age was 79+6.2 years. 60% of patients had persistent or permanent AF. Prevalence of risk factors for thromboembolism included hypertension (74%), heart failure or ejection fraction of <40% (21%), diabetes (27%) and coronary artery disease (48%). CHADS (2) scores were documented in the charts less than 1% of the times. Only 11 patients had CHADS (2) score of 0 and 70 had a score of 1. A class I or IIa indication for warfarin therapy was present in 298 (73%) of patients. Return to sinus rhythm (37%) was the most common reason for not using warfarin. In 30% of cases the reason not to use warfarin was not addressed. Other reasons not to use warfarin included fear of falls (7%), prior head or GI bleed (14%), patient refusal & noncompliance (12%). History of CVA or TIA was documented in 12% of patients.

Conclusions: Underutilization of warfarin in elderly patients with atrial fibrillation remains a common problem despite their high risk for thromboembolic events. A false sense of security about the paroxysmal nature of AF, lack of proper insight about stroke risk (CHADS (2)), and fear of bleeding are the most common reasons for non use of warfarin.

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Introduction

Background

Atrial fibrillation (AF) is the most common sustained arrhythmia in the elderly. Its prevalence increases with age. It is estimated to affect over 4 percent of the population above the age of 60.[1,2] Epidemiologic studies show AF to be responsible for approximately 15% of strokes and associated with decreased quality of life.[3] Underutilization of warfarin in elderly is a common problem ranging up to 30-60 %[4,5,6,7,8,9,10,11,12] and is associated with an increased risk of stroke resulting in disability and significant cost.[13] Physicians' overestimating the chance of bleeding is another factor contributing to the underuse of warfarin.[14] Elderly can require less warfarin to keep their INR in therapeutic range[15,16] and not paying attention to this may increase their chance of bleeding. Study shows that overall age is not a factor for increasing complications with warfarin[17] but a history of falls, a history of bleeding within the previous year and an inability to comply with therapy were rated as important barriers to use of warfarin by 64%, 55% and 53% of physicians.[18] Although neurologists and internists are more involved in the care of patients with stroke, they prescribe warfarin less frequently than cardiologists.[19] The Kansas City Veterans Affairs Hospital (KCVA) is a tertiary care center in the Midwest United States with large population of inpatients and outpatients. It is an academic teaching center affiliated with the University of Kansas School of Medicine. Pharmacists run an anticoagulation clinic and adjust the dose of warfarin for all patients as treated. Although under use of warfarin in atrial fibrillation is well recognized,[4-12] this study was designed to provide further insight for reasons of warfarin underutilization in the elderly. The electronic medical record of the VA hospital facilitated data base searches to identify subjects for this study.

Methods and materials

All patients, 65 years of age or older with atrial fibrillation between 1996 and 2006 were included in this study. Patients who were taking warfarin were excluded. The electronic records of the remaining AF patients were reviewed individually. Demographic data, reasons for stopping or not starting warfarin, and concomitant co-morbidities were extracted. Anticoagulation indications for these patients were assessed based on the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation, this included class I indications based on CHADS2 scores, as well as class IIa indications including CAD, female gender, or age 65 to 74 years. The study and the waiver of consent were approved by the Institutional Review Board and the Human Subject Committee.

Statistical Analysis

Categorical variables are expressed as frequencies and percentages. The chance that a patient with atrial fibrillation was not receiving warfarin was analyzed by contingency table. Chi square was used to compare discrete data. A P value less than 0.05 was considered significant.

Results

One thousand six hundred and thirty five (n=1635) patients 65 or older had a diagnosis of atrial fibrillation. A total of 407 patients (25% of total) were not using warfarin and were included in the study. Their ages ranged from 65 to 93 year old with an average age of 79 + 6.2 years. Documentation of the type of AF was found in only 20% of charts, of them 40% of them had paroxysmal atrial fibrillation and the remainder had persistent or permanent AF. A diagnosis of CVA or TIA was present in 47 patients (12%), hypertension in 303 patients (74%), heart failure or impaired systolic LV function (LVEF <40%) in 85 patients (21%), diabetes in 111 patients (27%), and coronary artery disease in 195 patients (48%), Only 37 patients (9%) did not have a history of CVA, TIA, hypertension, DM, or CAD (Table- 1). Frequency of CVA/TIA was 7.1% in 65-69 age group and 11.7% in 85 years of age and higher.

Discussion

In the elderly, atrial fibrillation is the single most important cause of stroke. The risk of stroke is increased at least 6-fold in subjects with atrial fibrillation[22] and attributable risk of atrial fibrilla-

tion for stroke approaches 30%. There are several medications that currently are used for reducing chance of thromboembolism in patients with atrial fibrillation. The most common of them are aspirin and warfarin which can decrease chance of stroke.[23] Previous studies showed warfarin was superior to aspirin in decreasing thromboembolic events.[24,25] Substitution of aspirin for warfarin may be considered in situations when there is contraindication to warfarin or in very low risk patients.[20] In our study, only 4 patients had allergy to warfarin, 39 patients refused taking warfarin, and non-compliance with warfarin was documented in 10 patients. All of these patients should have at least been considered for aspirin therapy.

There are some data that suggest an increased risk of intracranial hemorrhage[24,26,27] or mortality due to intracranial hemorrhage[28] in elderly patients on warfarin. In addition there is data that shows warfarin can decrease ischemic stroke[24,29] and death.[28,29,30] This is probably because ischemic strokes related to atrial fibrillation tend to be more severe in comparison to other types of strokes.[31] In this study only 6 patients had some kind of CNS bleeding. At the same time, presence of CVA or TIA puts a patient in a high risk category for another stroke. Current guidelines emphasize the use of warfarin in this subset of patients.[20] Nevertheless, in our study, 47 patients with a prior diagnosis of CVA or TIA were not on warfarin.

Conversion of atrial fibrillation to sinus rhythm can happen in different situations including recurrent or paroxysmal atrial fibrillation which may be associated with established disease states. In this study, 77 patients (51%) were not taking warfarin because of being in sinus rhythm. A significant number of these patients (62/77) had a CHADS 2 score of more than 2. Presence of sinus rhythm during one of the follow up visits should not preclude physicians from offering continued anticoagulation therapy in patients of this age group who are

Table 1 Age distribution of patients with atrial fibrillation not on warfarin and concomitant co-morbidities.

Age Group	CAD Number of Patients/Percent within the same age group	CHF or LVEF <40% Number of Patients/Percent within the same age group	DM Number of Patients/ Percent within the same age group	HTN Number of Patients/Percent within the same age group	CVA/TIA Number of Patients/ Percent within the same age group
65-69	10 (35.7%)	4 (14.3%)	9 (32.1%)	24 (85.7%)	2 (7.1%)
70-74	27 (34.2%)	13 (16.5%)	29 (36.7%)	58 (73.4%)	7 (8.9%)
75-79	51 (54.3%)	21 (22.3%)	CABGx4/ MVR	71 (75.5%)	10 (10.6%)
80-84	69 (53.5%)	32 (24.8%)	25 (19.4%)	97 (75.2%)	19 (14.7%)
85 and above	38 (49.4%)	15 (19.5%)	16 (20.8%)	53 (68.8%)	9 (11.7%)
Total	195 (47.9%)	85 (20.9%)	111 (27.2%)	303 (74.4%)	47 (11.5%)

usually at high risk for systemic thromboembolism. The newest practice guidelines consider antithrombotic use as a Class-IIa indication in patients with any form of atrial fibrillation (paroxysmal or permanent).[20] Furthermore, data from AFFIRM and RACE trials indicate that the pharmacological or electrical cardioversion to sinus rhythm in patients with at-risk CHADS-2 scores, does not reduce the risk of stroke and is not an indication to discontinue anticoagulation.

Data from this study reveal that use of warfarin dramatically drops after 85 years of age. Previous studies have shown that the risk of thromboembolic disease continues to increase as age goes up, as is seen in this study as well. Warfarin has been shown to be safe in the elderly patients even in patients 90 years of age or older when INRs are kept at target range of 2.0-3.0.[32] Risk of falls was documented as the reason for not taking warfarin in 7.6% of patients who were not taking warfarin for atrial fibrillation. One study that reviewed 49 published anticoagulation trials of patients with atrial fibrillation found that intracranial hemorrhages were uncommon. In fact the calculated risk of subdural hematoma from falling, according to that study, is so small that a person with an average risk of stroke from AF (5 percent/year) would have to fall approximately 300 times in a year for the risk of anticoagulation to outweigh its benefits.[33,34]

The nationwide trend of the use of anticoagulation in AF patients is not quite clear at this point in time. Use of warfarin in patients with atrial fibrillation increased from 7% in 1980 to 32% in 1993.[35] A study on Medicare beneficiary patients revealed that warfarin use for elderly patients with atrial fibrillation increased from 24.5% in 1992 to 56.3% in 2002.[36] In our study, 75% of patients were using warfarin. But at least 10% of patients with atrial fibrillation who met class-I indication for warfarin use were not on that medication.

Table 2 Age distribution of patients with atrial fibrillation not on warfarin and concomitant co-morbidities.

Cause of stopping or not restarting warfarin	Number of Patients	Percent (total=407)
Sinus Rhythm @ follow up	150	36.9
Patients Refused	39	9.6
75-79	31	7.6
History of GI Bleeding	26	6.3
History of CNS Bleeding	6	1.4
History of Bleeding (Others)	15	3.7
Patient Noncompliance	10	2.5
Physicians Communication Problem	10	2.5
Contraindications	4	1
Unknown (Not documented)	108	26.5
Others	10	2.5

Despite several advantages of electronic medical record in the VA system and access of health care providers to the patient's health data in a short fraction of time, still 2.5% of subjects were not receiving warfarin due to communication errors. We could not find another study that looked at the same problem in subjects with atrial fibrillation. And it also shows that VA's electronic system has potential for improvements if it can alert health care providers for these errors.

Study Limitations

This study was performed retrospectively by using medical records on patients with a documented diagnosis of atrial fibrillation. We did not examine the accuracy of the diagnosis. Incomplete documentation poses some limitations on data interpretation as well. We did not include INR values in this study which may reflect patient compliance with the medication and follow up. Also we did not include aspirin in our record review since documentation of its use was expected to be significantly less accurate since most VA patients buy aspirin over the counter. Only 5 patients were female which represents a typical VA population. Gender does not change Class-I indication for warfarin use but has a small role in Class-IIa indications.[20]

Conclusions

Underutilization of warfarin in elderly patients with atrial fibrillation remains a common problem despite their high risk for thromboembolic events. A false sense of security about the paroxysmal nature of atrial fibrillation, lack of proper insight about stroke risk (CHADS2), and fear of bleeding are the most common reasons for non use of warfarin.

Table 3 Age distribution of CHADS(2) scores (number of subjects and percentage in each age group)

CHAD(2) Scores	0	1	2	3	4	5	6	Average score	Total number of patients
65-69	3 (10.7%)	13 (46.4%)	8 (28.6%)	4 (14.3%)	0	0	0	1.46	28
70-74	11 (13.9%)	37 (46.8%)	22 (27.8%)	5 (6.3%)	2 (2.5%)	2 (2.5%)	0	1.44	79
75-79	0	14 (14.9%)	33 (35.1%)	32 (34%)	12 (12.8%)	3 (3.2%)	0	2.54	94
80-84	0	15 (11.6%)	62 (48.1%)	34 (26.4%)	11 (8.5%)	6 (4.7%)	1 (0.8%)	2.49	129
85-89	0	12 (19%)	31 (49.2%)	12 (19%)	5 (7.9%)	3 (4.8%)	0	2.3	63
>89	0	2 (14.3%)	6 (42.9%)	3 (21.4%)	2 (14.3%)	1 (7.1%)	0	2.57	14
Total	14 (3.4%)	93 (22.9%)	162 (39.8%)	90 (22.1%)	32 (7.9%)	15 (3.7%)	1 (0.2%)	2.2	407

References

1. Halperin JL; Hart RG. Atrial fibrillation and stroke: new ideas, persisting dilemmas. Stroke 1988 Aug;19(8):937-41

2. Kannel WB; Abbott RD; Savage DD; McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med 1982 Apr 29;306(17):1018-22

3. Ezekowitz MD, Netrebko PI. Anticoagulation in management of atrial fibrillation. Curr Opin Cardiol. 2003 Jan;18(1):26-31. CrossRef PubMed

4. Frykman V, Beerman B, Ryden L, Rosenqvist M. Management of atrial fibrillation: discrepancy between guideline recommendations and actual practice exposes patients to risk for complications. Eur Heart J. 2001 Oct;22(20):1954-9.CrossRef PubMed

5.McCormick D, Gurwitz JH, Goldberg RJ, Becker R, Tate JP, Elwell A, Radford MJ. Prevalence and quality of warfarin use for patients with atrial fibrillation in the long-term care setting.Arch Intern Med. 2001 Nov 12;161(20):2458-63.CrossRef PubMed

6. Ruigomez A, Johansson S, Wallander MA, Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. J Clin Epidemiol. 2002 Apr;55(4):358-63. CrossRef PubMed

7.Ono A, Fujita T. Stroke prevention in patients with atrial fibrillation. J Clin Neurosci. 2003 Jan;10(1):71-3.CrossRef PubMed

8. Nagpal S, Anderson D, Putnam W, Flowerdew G, Gardner M, Cox J. Stroke prevention in hospitalized patients with atrial fibrillation: a population-based study. Can J Clin Pharmacol. 2003 Winter;10(4):197-201

9. Lau E, Bungard TJ, Tsuyuki RT. Stroke prophylaxis in institutionalized elderly patients with atrial fibrillation. J Am Geriatr Soc. 2004 Mar;52(3):428-33.CrossRef PubMed

10.White S, Feely J, O'Neill D. Community-based study of atrial fibrillation and stroke prevention. Ir Med J. 2004 Jan;97(1):10-2

11. Blich M, Gross B. Thromboembolic prophylaxis in nonrheumatic atrial fibrillation: utilization patterns, efficacy, and complications in a long-term follow-up of community patients. Int J Cardiol. 2004 Jul;96(1):89-95.CrossRef PubMed

12. Marcu CB, Ghantous AE, Caracciolo EA, Donohue TJ. Patterns of anticoagulation in patients hospitalized with atrial fibrillation: warfarin is underused in paroxysmal atrial fibrillation. Con Med. 2003 Nov-Dec;67(10):595-8

13.Caro JJ. An economic model of stroke in atrial fibrillation: the cost of suboptimal oral anticoagulation. Am J Manag Care. 2004 Dec;10(14 Suppl):S451-58

14.Gross CP, Vogel EW, Dhond AJ, Marple CB, Edwards RA, Hauch O, Demers EA, Ezekowitz M. Factors influencing physicians' reported use of anticoagulation therapy in nonvalvular atrial fibrillation: a cross-sectional survey. Clin Ther. 2003 Jun;25(6):1750-64.CrossRef PubMed

15.Garcia D, Regan S, Crowther M, Hughes RA, Hylek EM. Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. Chest. 2005 Jun;127(6):2049-56.CrossRef PubMed

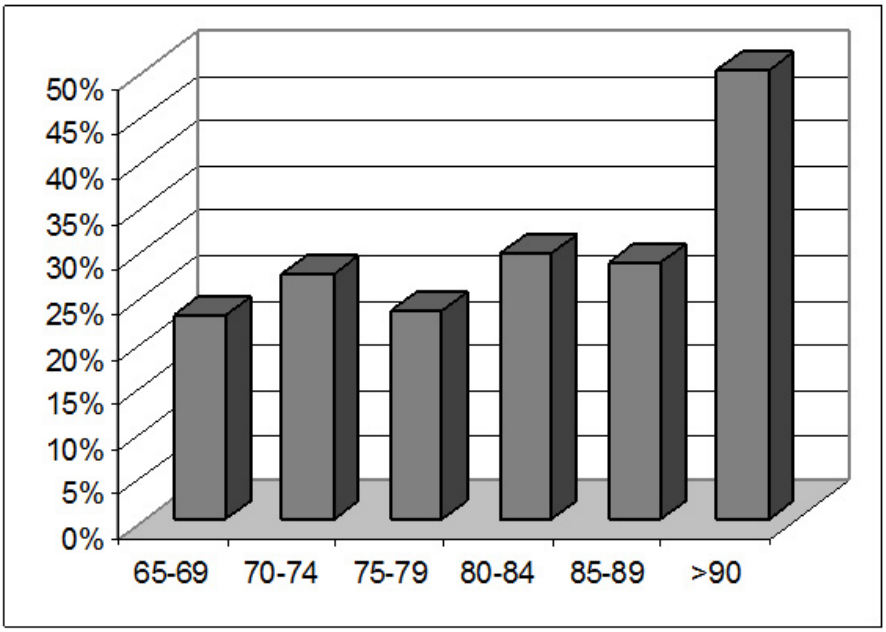
16.Singla DL, Morrill GB. Warfarin maintenance dosages in the very elderly. Am J Health Syst Pharm. 2005 May 15;62(10):1062-6

17.Putnam W, Nicol K, Anderson D, Brownell B, Chiasson M, Burge FI, Flowerdew G, Cox J. Anticoagulation in atrial fibrillation. Is there a gap in care for ambulatory patients? Can Fam Physician. 2004 Sep;50:1244-50

18.Bungard TJ, Ghali WA, McAlister FA, Buchan AM, Cave AJ, Hamilton PG, Mitchell LB, Shuaib A, Teo KK, Tsuyuki RT. The relative importance of barriers to the prescription of warfarin for nonvalvular atrial fibrillation. Can J Cardiol. 2003 Mar 15;19(3):280-4

19.Rahimi AR, Wrights B, Akhondi H, Richard CM. Clinical correlation between effective anticoagulants and risk of stroke: are we using evidence-based strategies? South Med J. 2004 Oct;97(10):924-31.CrossRef PubMed

Figure 1: The percentages of patients with atrial fibrillation not on warfarin per total number of patients with the same diagnosis at the same age.



20. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey J-Y, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc J-J, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation:a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol 2006;48:e149 –246.PubMed

21.Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001 Jun 13;285(22):2864-70.CrossRef PubMed

22.Ferro JM. Atrial fibrillation and cardioembolic stroke. Minerva Cardioangiol. 2004 Apr;52(2):111-24

23.Ezekowitz MD, Falk RH. The increasing need for anticoagulant therapy to prevent stroke in patients with atrial fibrillation. Mayo Clin Proc. 2004 Jul;79(7):904-13

24.Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, Jensvold NG, Selby JV, Singer DE. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA. 2003 Nov 26;290(20):2685-92.CrossRef PubMed

25.Evans A, Perez I, Yu G, Kalra L. Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? Stroke. 2001 Dec 1;32(12):2828-32. CrossRef PubMed

26.Karni A, Holtzman R, Bass T, Zorman G, Carter L, Rodriguez L, Bennett-Shipman VJ, Lottenberg L. Traumatic head injury in the anticoagulated elderly patient: a lethal combination. Am Surg. 2001 Nov;67(11):1098-100

27.Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. Arch Intern Med. 2004 Apr 26;164(8):880-4.CrossRef PubMed

28.Gage BF, Birman-Deych E, Kerzner R, Radford MJ, Nilasena DS, Rich MW. Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall. Am J Med. 2005 Jun;118(6):612-7.CrossRef PubMed

29.Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, Singer DE. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med. 2003 Sep 11;349(11):1019-26.CrossRef PubMed

30.Tsivgoulis G, Spengos K, Zakopoulos N, Manios E, Peppes V, Vemmos K. Efficacy of anticoagulation for secondary stroke prevention in older people with non-valvular atrial fibrillation: a prospective case series study. Age Ageing. 2005 Jan;34(1):35-40. CrossRef PubMed

31. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. Neuroepidemiology. 2003 Mar-Apr;22(2):118-23.CrossRef PubMed

32.Joffe HV, Goldhaber SZ. Effectiveness and safety of long-term anticoagulation of patients >/=90 years of age with atrial fibrillation.Am J Cardiol. 2002 Dec 15;90(12):1397-8.CrossRef PubMed

33.Man-Son-Hing, M, Nichol, G, Lau, A, Laupacis, A. Choosing antithrombotic therapy for elderly patients with atrila fibrillation who are at risk for falls. Arch Intern Med 1999; 159:677.CrossRef PubMed

34.Man-Son-Hing, M, Laupacis, A. Anticoagulant-related bleeding in older persons with atrial fibrillation: physicians's fears often unfounded. Arch Intern Med 2003; 163:1580.CrossRef PubMed

35.Stafford RS, Singer DE. National patterns of warfarin use in atrial fibrillation. Arch Intern Med. 1996 Dec 9-23;156(22):2537-41. CrossRef PubMed

36.Lakshminarayan K, Solid CA, Collins AJ, Anderson DC, Herzog CA. Atrial fibrillation and stroke in the general medicare population: a 10-year perspective (1992 to 2002). Stroke. 2006 Aug;37(8):1969-74.CrossRef PubMed

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Echocardiographic Predictors of Symptomatic Atrial Fibrillation In Patients with Rheumatic Mitral Stenosis and Normal Sinus Rhythm

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Abstract

Introduction:Rheumatic mitral stenosis (RMS) increases the risk of both atrial fibrillation (AF) and thromboembolism.
Methods: Patients with mitral stenosis and normal sinus rhythm were enrolled in the study prospectively.The present study was designed to study whether echocardiographic evaluation in patients with mitral stenosis and normal sinus rhythm could predict the occurrence of symptomatic AF . Results: Sixty-two patients (51 females) with mitral stenosis and normal sinus rhythm were included in the study. Seven patients (11.3%) developed symptomatic AF and the remaining 55 were free of AF during a followed-up of 22±5 months. The following echocardiographic parameters were significantly increased and predicted the development of AF; left atrial (LA) mediolateral diameter (5.5 ± 0.5 cm vs 4.7 ± 0.7 cm), right atrial mediolateral diameter (4,7 ± 1.0 cm vs 3.6 ± 1.3 cm), LA area in the apical two chamber view (31 ± 3.2 cm2 vs 25 ± 5.8 cm2), right atrial volume (52 ± 22 cm3 vs 34 ± 19 cm3), and interatrial conduction time (IACT) (142 ± 22 msec vs 115 ± 16 msec).
Conclusions: OThis study revealed that echocardiography can be used to predict symptomatic AF in patients with RMS and sinus rhythm.

Introduction

Background

In rheumatic mitral stenosis (RMS), mitral valve area is reduced, creating an obstruction to the blood flow between the left atrium (LA) and the left ventricle (LV), causing an elevation in LA pressure. Elevation in LA pressure has several important effects including enlargement of the LA, atrial arrhythmias, and an increase in pulmonary venous pressure. RMS increases the risk of both atrial fibrillation (AF) and thromboembolism, causing an important health care problem in developing countries. The prevalence of AF in patients with MS is between 17 to 80% and related to both the severity of valve obstruction and patient age .[1] The incidence of systemic embolism is greater in rheumatic mitral valve disease than in any other common form of valvular heart disease.

Patients with AF and mitral stenosis have high incidence of thrombus formation in the LA.[2,3] AF is the most commonly encountered cardiac arrhythmia in this subset of patients with an increased risk of thromboembolism.[4] Although mitral stenosis is considered as a strong risk factor for AF, the parameters in mitral stenosis that predict the risk of

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future AF have not been determined. Echocardiography is the primary and relatively simple tool to follow up the patients with RMS. AF is generally associated with structural changes in the atria and echocardiography provides a detailed anatomical evaluation. In addition, flow characteristics and chamber pressure can also be detected by echocardiography.

The aim of the present study was to investigate cardiac parameters that may predict prospectively in preceeding symptomatic AF in patients with mitral stenosis and normal sinus rhythm. Clinical and echocardiographic parameters were studied in prediction of AF.

Methods and materials

Patients

Patients with mitral stenosis and normal sinus rhythm have been selected prospectively among a total of 1512 patients seen in our out-patient clinic between July 2003 and July 2004. Any patient with a new or previous diagnosis of mitral stenosis was evaluated for the study. Patients with a history of AF or valve disease other then RMS (with an exception of mild tricuspid or pulmonary valve regurgitation), who had undergone valve replacement, or those with poor echocardiographic images were excluded. None of the patients included in this study were on anti-arrhythmic drugs. The initial evaluation of the patients included history, physical examination, electrocardiography (ECG) and trans-thoracic echocardiography. At the end of the follow-up, patients were grouped into those who developed AF (group 1) and those who were free from AF (group 2).

Echocardiography

The echocardiographic evaluation was performed by transtohoracic approach (General Electrics-Vivid 3 USA) and included standard parameters and atrial volumes, mitral valve area, transmitral pressure gradient and interatrial conduction time (IACT).
Atrial volumes were calculated by the ellipse formula: Atrial volume: 4 Π /3 x D1/2 x D2/2 x D3/2, where D1 (mm) is anteroposterior, D2 mediolateral and D3 superoinferior dimension.[5] The anteroposterior dimension of the left atrium (LA) was measured in the parasternal view, and the mediolateral and superoinferior dimensions of LA were measured in the apical four-chamber view. For the right atrium (RA), the mediolateral diameter was used for both D2 and D3 in the formula. Mitral valve area was calculated by planimetry and the pressure half-time methods.

Interatrial conduction time was defined as the time interval between the onset of the P-wave and the LAA (left atrial appendage) ejection flow.[6] After the apical two-chamber view was obtained, the transducer was angulated anteriorly until LAA came into the view. A pulse Doppler sample volume in 1/3 proximal portion of LAA was used to obtain flow recordings. The ECG was recorded simultaneously via a single lead. The IACT was measured as the time interval between the beginning of the P wave on the ECG and the onset of LAA flow. The mean IACT value over 5 cardiac cycles was used in the data analysis (Figure).

Follow-up

All patients in the study were followed up with clinical evaluation every three months. The patients were asked to visit their primary physician if they experienced any palpitations. Patients who reported palpitations at their follow-up visits were subjected to 24-hour Holter monitoring. Episodes of AF were defined to be relevant if they exceeded duration of 30 seconds per day and coincided with the symptoms. The patients who underwent cardiac surgery have not been excluded from the study but not been followed-up for further. Percutaneous valvuloplasty was not a criterion for exclusion from the study or from follow-up.

Statistical Analysis

The Mann-Whitney U test was used for comparison of data between those with AF and without AF. Multiple logistic regression analysis was used to assess whether clinical and echocardiographic parameters and IACT were related to AF occurrence. Spearman's test was used to detect whether any of the assessed parameters correlated with AF occurrence. P value less than .05 was regarded as signifi-

cant.

Results

A total of 64 patients (11 males and 53 females) with mitral stenosis and normal sinus rhythm were initially enrolled in the study. Two patients were excluded from the study due to poor visualization of LAA by trans-thoracic echocardiography. The remaining 62 patients were followed prospectively for a mean period of 22±5 months. Seven (11.3%, 7/62) patients developed symptomatic AF during follow-up and were assigned to Group 1. Six of the group 1 patients were demonstrated to have an AF episode by ECG recordings obtained when they were admitted to an emergency room due to palpitations. 10 patients presented palpitation and received Holter monitoring. A mbulatory Holter ECG monitoring revealed an AF episode in one patient. Group 2 consisted of the remaining 55 (88.8%) patients who did not develop AF during follow-up. The demographics, drug usage, and other characteristics of the patients are listed and compared between groups (Table 1). Age, functional capacity and follow-up periods were similar between groups. During the follow-up period, eight patients underwent percutaneous mitral balloon valvuloplasty. One patient had anterior myocardial infarction. Six patients underwent mitral valve surgery and were not followed-up further. In these patients, the mean time of follow-up from the time of inclusion to the surgery was 13±6 months in those patients. No other major cardiac events have been reported.

Echocardiographic Parameters

The basal echocardiographic parameters of the study population are summarized in Table 2. Mitral valve area, trans-mitral pressure gradients, the degree of mitral regurgitation, LA volume, LA and RA superoinferior diameters and volumes obtained in apical 4-chamber and 2-chamber views did not differ between the groups. However, the following four echocardiographic parameters were found to be associated with AF occurrence: left atrial mediolateral diameter (LAML2), right atrial mediolateral diameter (RAML2), right atrial volume (RAV) in apical 4-chamber view, and left atrial area in apical 2-chamber view (LA area3). Those parameters were found to be independent predictors of symptomatic AF.IACT was statistically significantly prolonged in group 1 (Mean IACT value was 142 ± 22 msec in group 1, 115 ± 16 msec in group 2, p = 0.04). No significant correlation was detected between IACT and other AF-predictive echocardiographic parameters.

Discussion

To the best of our knowledge this is the first prospective study that determined the echocardiographic parameters that predict symptomatic AF in patient with rheumatic mitral valve disease and sinus rhythym. Previous studies have provided information about AF recurrence or have compared chronic AF patients to control subjects with a normal sinus rhythm.[7] Some clinical, electrocardiographic and echocardiographic parameters have been proposed as predictors of AF recurrence such as advanced age, left atrial enlargement and structural heart disease, although the results are conflicting.[8,9] The role of left atrial diameter in predicting AF remains controversial. Kinay et al found no significant difference in left atrial diameter in patients with and without recurrent AF.[6] In contrast, Diker et al has suggested that age, left atrial diameter and mean trans-valvular gradient may predict AF occurrence in their retrospective study .[10] In our

Table 1 The comparison of the demographics and patient characteristics between groups. (CVA: Cerebrovascular accident).

	All patients (n= 62)	Group 1 (n=7)	Group 2 (n=55)	p value
Age (years)	42 ± 9	42 ± 13	41 ± 9	0.913
Functional Class	1.85 ± 0.70	2.00 ± 0.58	1.84 ± 0.72	0.556
Follow-up period (months)	22 ± 5	24 ± 3	21 ± 5	0.244

study, left and right atrial mediolateral diameters at apical 4-chamber view were significantly large in group 1. But only the volume of right atrium was found to be significantly high in group 1. This can be explained by that the mediolateral diameter of the right atrium has been used for both D2 and D3 in the volume formula. Additionally, an eccentric enlargement of the atria can also contribute these results.

Age appears to be predictive of AF recurrence only in patients older than 70-year old.[11] However, age cannot be considered as a predictive parameter for AF recurrence in patients with mitral stenosis.

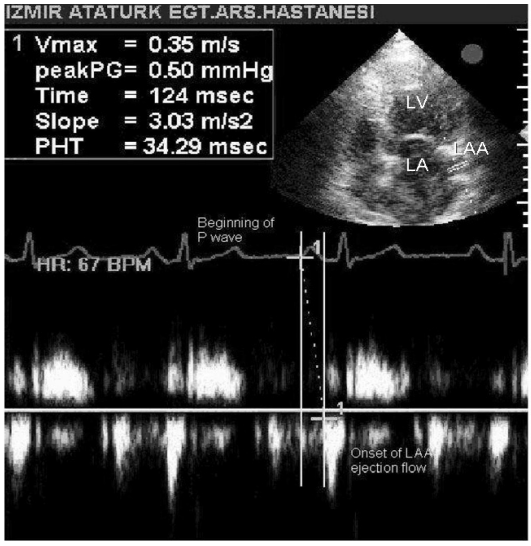
The presence of an interatrial conduction delay has been shown to be associated with occurrence and recurrence of AF and some authors claim that clinically reducing interatrial conduction time via bi-atrial pacing could reduce AF recurrences in patients with interatrial conduction delay.[12] Interatrial conduction delay may endorse AF by facilitating micro-reentry circuits.[13] There is an ongoing debate concerning the mechanism of these issues. A standard non-invasive method of measuring interatrial conduction time is missing. Fuenmayor et al demonstrated that IACT measured invasively by electrode catheters, correlated with IACT measured by trans-thoracic echocardiography as the time interval from the beginning of the P wave to the beginning of the mitral A wave.[14] Dilation of LA structures in patients with mitral stenosis makes it easy to view the LAA by trans-thoracic echocardiography, abolishing the need of more invasive trans-esophageal echocardiography.[15] Although an electrophysiological test has not been performed in our patients, a significant correlation between IACT and electrophysiological IACT was previously reported by our group.[16] In this study, IACT determined by trans-thoracic echocardiography correlated with symptomatic AF occurrence in patients with mitral stenosis, independent of any other clinical and echocardiographic parameters. Kinay et al. found that IACT was prolonged in patients with recurrent AF.[6] But our study reveals that IACT has been prolonged before the episodes of symptomatic AF have been established.

There are conflicting results regarding whether enlarged atrial diameter predicts AF or occurs as a result of atrial remodeling due to AF. The present results support that atrial enlargement may be a structural substrate enabling symptomatic AF to occur. However large scale studies are needed to confirm this hypothesis.

Limitations

The design of our study does not include those patients without symptom due to AF, since we detected episodes of AF based on the symptoms. None of the patients who developed AF was detected coincidently. This may cause underestimation of the patients with AF, and the patients with asymptomatic AF will be listed in group 2,

Figure 1: Interatrial conduction time is calculated as the time interval between the beginning of the surface p wave and the onset of LAA ejection flow. (LV: Left Ventricle, LA: Left Atrium, LAA: Left Atrial Appendage).



instead of group 1. This will reduce the power of the statistics. For these reasons, conclusions of our study can not be applied to asymptomatic AF patients with MS. Asymptomatic AF is a clinical challenge and causes underestimation of the incidence of AF in clinical studies. The incidence of asymptomatic patients has been reported to be 17%[17] In the literature, absence of symptoms are escpecially evident in old patients. In contrary, the average age of the patients in our study is around 40 and represents a relatively young population. Fortunatelly, the patients with mitral stenosis are tent to be symptomatic when they develop AF, since rapid heart rate causes relatively more hemodynamic deterioration. On this assumption and according to the above data, we expect less asymptomatic patients with AF in this particular group on comparison to general AF population. Termination of the follow-up of the patients who underwent the surgery may interfere the results. Following surgery the incidence of AF due to pericardial irritation reaches 50% in some series with normal LA. Finally, due to the limited number of the subjects studied and short time of follow-up, effects of gender, age, and surgery could not be assessed.

In conclusion, the present study showed that echocardiographic IACT measurement and the other four echocardiographic atrial parameters may predict the development of symptomatic AF in patients with mitral stenosis and sinus rhythm. These parameters may point out the group of patients prone to symptomatic AF and those who need close clinical follow-up.These parameters may be new targets for studies to address novel approaches to identify patients who require additional attention and modified treatment, such as early anti-coagulation and anti-arrhythmic medications. Large scale studies are necessary before making a certain comment on these issues.

Clinical implications

The patients with rheumatic mitral valve disease and sinus rhythm still has a substantial risk of systemic embolism and is, therefore, they are possible candidates for long-term warfarin therapy. There are no reliable clinical markers in such cases. Based on our study, prolonged IACT and enlarged atri-

Table 2 Comparison of echocardiographic parameters between groups.

	All patients (n=62)	Group 1 (n=7)	Group 2 (n=55)	P value
MVA Pln (cm2)	1.50 ± 0.41	1.60 ± 0.32	1.49 ± 0.32	P=0.445
MVA PHT (cm2)	1.52 ± 0.42	1.58 ± 0.35	1.52 ± 0.43	P=0.632
PGr (mmHg)	16.84 ± 8.89	16.59 ± 5.43	16.88 ± 8.19	P=0.601
MGr (mmHg)	8.62 ± 5.32	7.44 ± 3.28	8.78 ± 5.53	P=0.647
MR (degree)	1.24 ± 0.83	1.50 ± 0.76	1.21 ± 0.84	P=0.406
TTGr (mmHg)	33.55 ± 16.52	33.86 ± 18.19	33.51 ± 16.48	P=0.845
LA AP1(cm)	5.33 ± 0.49	5.36 ± 0.50	5.10 ± 0.41	P=0.039
LA area (cm2)	27.54 ± 6.10	31.48 ± 5.91	27.04 ± 5.99	P=0.071
LASL (cm)	7.11 ± 0.96	7.26 ± 1.08	7.09 ± 0.95	P=0.556
LAML2 (cm)	4.81 ± 0.68	5.51 ± 0.50	4.72 ± 0.65	P=0.002
LA area2 (cm2)	28.23 ± 5.83	31.51 ± 5.23	27.81 ± 5.82	P=0.116
RAML2 (cm)	3.74 ± 1.32	4.74 ± 1.04	3.61 ± 1.31	P=0.013
RASL (cm)	4.94 ± 1.24	4.95 ± 1.77	4.93 ± 1.18	P=0.711
RA area 2 (cm2)	15.08 ± 4.48	17.75 ± 6.65	14.74 ± 4.09	P=0.218
LAAP3 (cm)	5.63 ± 1.46	6.01 ± 1.27	5.58 ± 1.48	P=0.273
LASl3 (cm)	5.87 ± 1.29	6.00 ± 1.84	5.85 ± 1.23	P=0.485
LA area3 (cm2)	25.91±5.79	30.70±3.17	25.30±5.78	P=0.006
LAV (cm3)	107.84 ± 45.73	131.36 ± 42.63	104.85 ± 45.61	P=0.101
RAV (cm3)	36.12 ± 20.12	51.94 ± 22.33	34.10 ± 19.12	P=0.018

al diameter can be used to select a subgroup of patients who may actually benefit from anticoagulant therapy in patients with RMS and sinus rhythm.

References

1. Catherine M, Otto and Robert O. Valvular Heart Disease . Braunwald's Heart Disease. 8th ed. New York Saunders Elsevier 2008;1652.
2. Vaziri SM, Larson MG, Benjamin EJ, et al: Echocardiographic predictors of non rheumathic atrial fibrillation.Circulation 1994; 89: 724-30.
3. Uslu N, Nurkalem Z, Orhan AL, et al: Transthoracic echocardiographic predictors of the left atrial appendage contraction velocity in stroke patients with sinus rhythm.Tohoku J. Exp. Med 2006; 208: 291-8. CrossRef PubMed
4. Kannel WB, Abbott RD, Savage DD, et al: Epidemiological features of chronic atrial fibrillation: The Framingham Study.N Eng J Med 1982; 306: 1018-22.
5. Sanfilippo AJ, Abascal VM, Sheehan M, et al: Atrial enlargement as a consequence of atrial fibrillation: A prospective echocardiographic study.Circulation 1990; 82: 792–7.
6. Kinay O, Nazli C, Ergene O, et al: Time interval from the initiation of thr electrocardiographic P wave to the start of left atrial appendage ejection flow: A novel method for predicting atrial fibrillation recurrence.J Am Soc Echocardiogr 2002; 15:> 1479-84.
7. Flaker GC, Flotcher KA and Rothbart RM. Clinical and echocardiographic features of intermittent atrial fibrillation that predict reccurent atrial fibrillation. Am J Cardiol 1995; 76: 355-8. CrossRef PubMed
8. Henry WL, Morganroth J, Pearlman AS, et al: Relation between echocardiographically determined left atrial size and atrial fibrillation.Circulation 1976; 53: 273-9.
9. Ewy GA, Ulfers L, Hager WD, et al: Response of atrial fibrillation to therapy, role of ethiology and left atrial diameter. J Electrocardiol 1980; 13: 119-24. CrossRef PubMed
10. Diker E, Aydogdu S, Ozdemir M, et al: Prevelance and predictors of atrial fibrillationin rhomatic valvular heart disease. Am J Cardiol 1996; 77: 96-8. CrossRef PubMed
11. Michelucci A, Padeletti L, Chelucci A, et al: Influence of age, load axis, frequency of arrhythmic episodes, and atrial dimensions on P wave triggered SAECG in patients with lone paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 1996; 19: 758-67. CrossRef PubMed
12. Yu WC, Chen SA, Tai CT, et al: Effects of different atrial pacing moes on atrial electrophysiology: Implicating the mechanism of biatrial pacing in prevention of atrial fibrillation. Circulation 1997; 96: 2992- 6
13. Elvan A, Wylie K and Zipes DP. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs. Electrophysiological remodeling. Circulation 1996; 94: 2953-60.
14. Fuenmayor AJ, Ramirez L and Fuenmayor AM. Validation of inter-atrial conduction time measurment by means of echo-Doppler. Arch Cardiol Mex. 2002; 72: 125-8.
15. Pozzoli M, Selva A, Skouse D, et al: Visualization of left atrial appendage and assessment of its function by transthoracic second harmonic imaging and contrast-enhanced pulsed Doppler. Eur J Echocardiogr 2002; 3: 13-23. CrossRef PubMed
16. Karaca M, Kinay O, Nazli C, et al: The time interval from the initiation of the P-wave to the start of the left atrial appendage ejection flow: Does it reflect interatrial conduction time. Echocardiography 2007;24: 810-5. CrossRef PubMed
17. Page RL, Tilsch TW, Connolly SJ, et al. Asymptomatic or "silent" atrial fibrillation: frequency in untreated patients and patients receiving azimilide. Circulation 2003;107:1141–5. CrossRef PubMed

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GIANT Flutter Waves in ECG Lead V1: a Marker of Pulmonary Hypertension

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Abstract

Atrial flutter (AFl) may exist with or without underlying structural heart disease. Typical AFl presents as a "sawtooth" pattern on the ECG – with inverted flutter (F) waves in the inferior leads and upright F waves in V1. This morphology offers no direct clues as to the underlying cardiac disorder, if any. Occasionally we have encountered giant F waves, most prominently in lead V1, reaching 5 mv or more in height – sometimes exceeding the QRS voltage. The significance of this pattern has not been investigated and reported on. To determine if giant F waves in V1 provide any insight into the presence/type/absence of specific underlying cardiac pathology, the history of 6 consecutive patients with giant F waves was reviewed. Upon review, the only factor common to each patient was the presence of or history of pulmonary hypertension. Right ventricular dilation and/or dysfunction and right atrial enlargement with or without tricuspid insufficiency were present in each by echocardiography. Giant F waves appear to occur in the setting of right heart dysfunction in patients with a history of or the continued presence of pulmonary hypertension. Their detection should indicate the need for right heart evaluation.

Atrial flutter (AFl) is a common arrhythmia[1] that may occur in the presence or absence of underlying structural heart disease and may occur in conjunction with or in the absence of periods of atrial fibrillation.[2-4] Most often, atrial flutter takes the form of a right atrial reentrant arrhythmia revolving around the RA isthmus in a clockwise or counterclockwise direction, in which it is referred to a "typical" AFl and produces a "sawtooth" pattern to the flutter waves – especially in the inferior ECG leads; other forms morphologically and/or in location have been considered as "atypical" flutter .[5-6]

Among the many structural heart disease alterations to which AFl has been linked is pulmonary hypertension,[7] whether from congenital[8] or acquired disorders.However, no specifics of the morphological characteristics of the flutter in the setting of pulmonary hypertension have been described. Accordingly, we found it of note that in six consecutive patients who presented with "giant" flutter waves – 5 mv or greater in height in lead V1, often taller than the QRS complex in the same lead, each had a common underlying finding: that of a history of or active presence of pulmonary artery (PA) hypertension and structural right heart alterations.

Methods

The records of six consecutive patients who pre-

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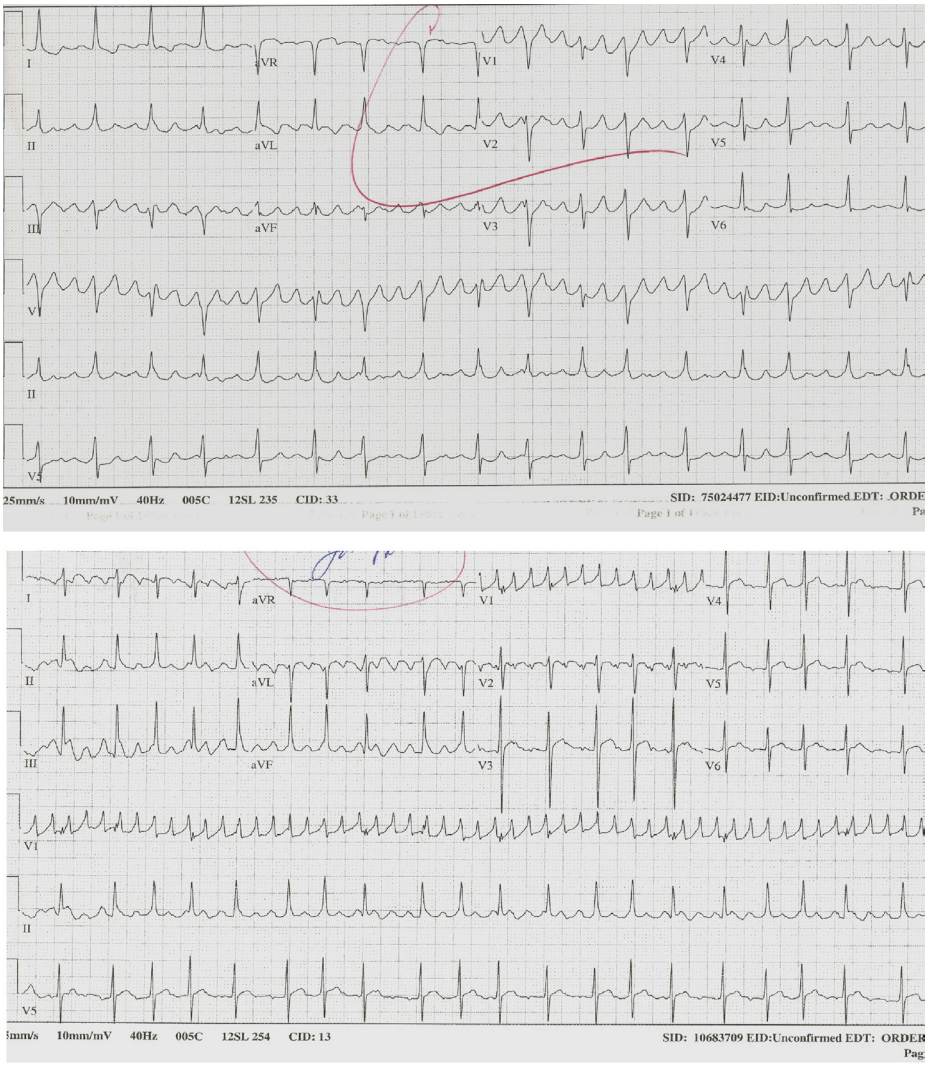
sented in atrial flutter with "giant" flutter waves as defined above were reviewed retrospectively. Patient ages were 36 to 73 years; 5 were women. Each underwent echocardiography in addition to other tests deemed clinically necessary in their particular circumstances.

Figure 1-3:12 lead electrocardiograms from three of the six patients that demonstrate "giant" flutter waves. In the remaining 3 patients, the flutter waves strongly resembled those in panel 2.



Patient #1 was a 36 year old female with primary pulmonary hypertension who was treated with an atrial balloon septostomy. Her pre-procedure PA pressures were 84/48 mm Hg.Patient #2 was a 38 year old female with idiopathic pulmonary fibrosis who ultimately underwent lung transplantation. Her pre-operative PA pressures were 99/52 mm Hg.Patient # 3 was a 59 year old female with a history of rheumatic aortic and mitral valve disease who was s/p mechanical mitral and aortic valve replacement. She also had chronic obstructive pulmonary disease. Estimated systolic PA pressure by echocardiography was 48 mm Hg.Patient #4 was a 73 year old female with a history of rheumatic mitral valve disease, having undergone valvuloplasty in 1954 and eventually prosthetic valve replacement 50 years later. Her estimated PA systolic pressure by echocardiography was 45 mm Hg.Patient #5 was a 37 year old female with primary pulmonary hypertension who ultimately underwent bilateral lung transplantation. Her pre-operative PA pressures were 92/49 mm Hg.Patient #6 was a 62 year old male with a familial hypertrophic cardiomyopathy and mitral insufficiency who was treated medically. Her estimated PA systolic pressure by echocardiography was 50 mm Hg.

Results

In each of the 6 patients described, the ECG presentation of their atrial flutter revealed "giant" flutter waves. None of the patients had atrial fibrillation in the time frame of their atrial flutter. There was no underlying left heart disease in the three patients with primary pulmonary hypertension or idiopathic pulmonary fibrosis. Representative ECGs from three of the patients are shown [figures 1-3]. In addition to the presence of "giant" flutter waves on their electrocardiogram, and an underlying pathology that included the presence of or history of pulmonary hypertension, each of the patients on echocardiography had findings of right ventricular dilation and/or mechanical dysfunction and visually assessed right atrial enlargement. RA planimetry was not routinely performed in all patients. Four also had more than trace tricuspid insufficiency. Flutter was treated medically in each patient and none has undergone electrophysiologic study. In only 1 patient (patient #1) was the flutter "typical" RA isthmus-dependent by 12 lead ECG (not shown).

Discussion

Atrial flutter is a commonly encountered atrial tachyarrhythmia. It may occur as an isolated disorder ("lone") or alternate with "lone" atrial fibrillation or it may occur in the setting of demonstrable underlying cardiac disease. To date, however, the magnitude of the flutter waves on the electrocardiogram has not been a focus of diagnostic interest. In the six patients we encountered whose data are described above, the magnitude of the flutter waves in ECG lead V1 was "giant," that is, 5 mv or more. In each there was an underlying common finding of primary or secondary pulmonary hypertension with right ventricular and right atrial enlargement. We have not encountered "giant" flutter waves in any other setting. Thus, we suggest that the detection of "giant" flutter waves should indicate a high degree of suspicion for pulmonary hypertension and right heart pathology and lead to an appropriate evaluation if not already performed.

References

1. Lee KW, Scheinman MM. Atrial flutter: a review of its history, mechanisms, clinical features, and current therapy. Current Problems in Cardiology 2005; 30:121-67. CrossRef PubMed

2. Waldo AL, Feld GK. Interrelationships of atrial fibrillation and atrial flutter mechanisms and clinical implications. J. Am. Coll. Cardiol. 2008; 51:779-86. CrossRef PubMed

3. Waldo AL. The interrelationship between atrial fibrillation and atrial flutter. Prog. In Cardiovasc Dis 2005; 48:41-56. CrossRef PubMed

4. Calo L, Lamberti F, Loricchio ML, De Ruvo E, Bianconi L, Pandozi C, Santini M. Atrial flutter and atrial fibrillation: which relationship? New insights into the electrophysiological mechanisms and catheter ablation treatment. Ital. Heart J 2005; 6:368-73."

5. Garan H. Atypical atrial flutter. Heart Rhythm 2008; 5:618-21. CrossRef PubMed

6. Cosio FG, Martin-Penato A, Pastor A, Nunez A, Goicolea A. Atypical flutter: a review. PACE 2003; 26:2157-69. CrossRef PubMed

7. Tongers J, Schwerdtfeger B, Klein G, Kempf T, Schaefer A, Knapp JM, Niehaus M, Korte T, Hoeper MM. Incidence and clinical relevance of supraventricular tachyarrhythmias in pulmonary hypertension. Am. Heart J. 2007; 153:127-32. CrossRef PubMed

8. Li W, Somerville J. Atrial flutter in grown-up congenital heart (GUCH) patients. Clinical characteristics of affected population. International J of Cardiology 2000; 75:129-37. CrossRef PubMed

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Cardiac Image Registration

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Abstract

Long procedure time and somewhat suboptimal results hinder the widespread use of catheter ablation of complex arrhythmias such as atrial fibrillation (AF). Due to lack of contrast differentiation between the area of interest and surrounding structures in a moving organ like heart, there is a lack of proper intraprocedural guidance using current imaging techniques for ablation. Cardiac image registration is currently under investigation and is in clinical use for AF ablation. Cardiac image registration, which involves integration of two images in the context of the left atrium (LA), is intermodal, with the acquired image and the real-time reference image residing in different image spaces, and involves optimization, where one image space is transformed into the other. Unlike rigid body registration, cardiac image registration is unique and challenging due to cardiac motion during the cardiac cycle and due to respiration. This review addresses the basic principles of the emerging technique of registration and the inherent limitations as they relate to cardiac imaging and registration.
Key words:atrial fibrillation, imaging, registration

Introduction

Fluoroscopy does not provide adequate anatomic visualization, due to poor soft tissue contrast, and fluoroscopically-guided intracardiac catheter-based procedures, such as AF ablation, are becoming increasingly complex. Improved intra procedural imaging of relevant anatomy would, therefore, aid in guiding the accurate and efficient placement of ablation lesions in complex anatomy such as the LA during AF ablation.

Three-dimensional (3D) imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) offer high quality anatomic visualization, given their excellent tissue contrast characteristics and high spatial and temporal resolution. Registration involves an optimal strategy of aligning different images.[1,2] It provides a means for physicians to incorporate within a single view the varied information captured by different imaging modalities. Intrasubject intermodal registration using 3D imaging modalities is an area of current focus with regards to radiofrequency catheter ablation procedures.[3-11] Cardiac motion of the heart and interpatient variability of anatomical features make the registration of cardiac images a unique challenge. Objective validation of the registration technique is, therefore, necessary before its utility as a tool for image-guided therapy can be properly assessed.

This review addresses the basic principles of registration and their impact on registration results and examines the validity of applying the registration process within the particular constraints of cardiac

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imaging. Although any modality can be used for registration, given the current interest in image-guided therapy for AF, LA-CT imaging and registration is the main focus of this review.

CT-MR Imaging and Segmentation Patients

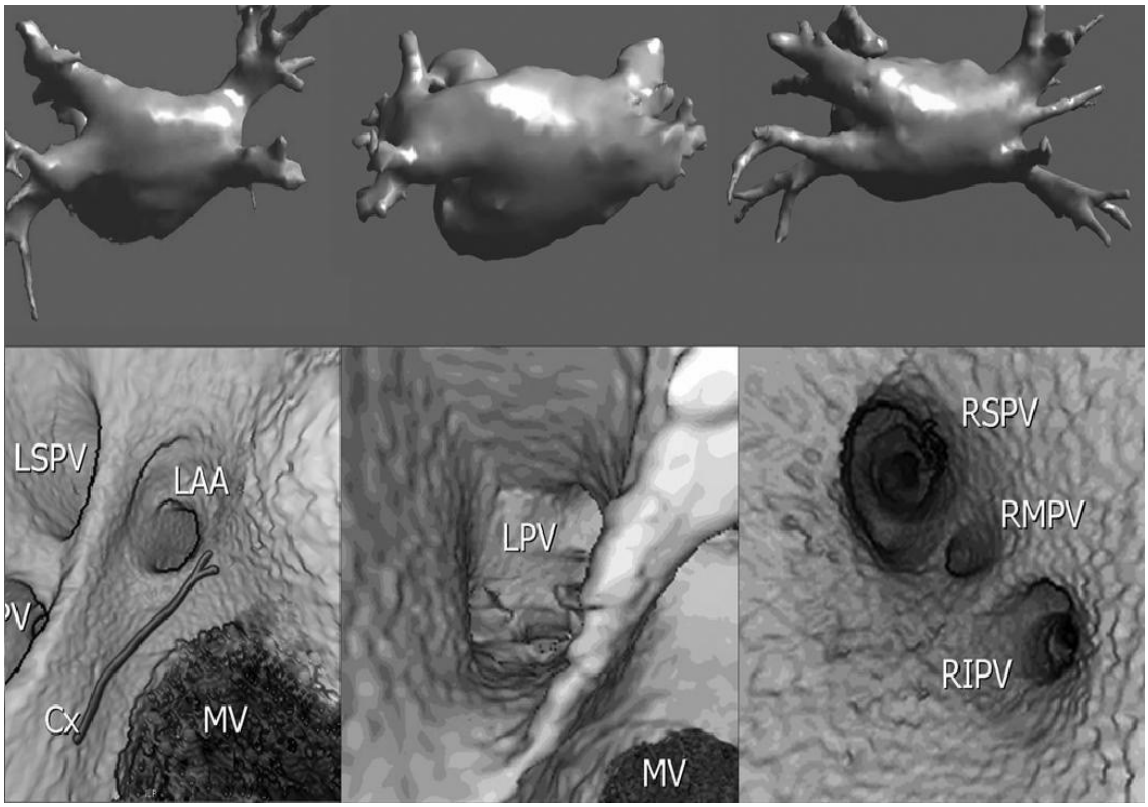
Technical Considerations

Most medical images are in a digital format and are made up of a rectangular array of small square or rectangular elements called pixels. Each pixel provides the coordinate system of the image and an element in the image can be assessed by its two-dimensional (2D) position within this array. A typical CT slice, for example, is formed of 512x512 pixels and each corresponds to a portion of the cut through the patient measuring about 0.5x0.5 mm2 .[12] The matrix and the pixel size are related to the display field of view (FOV). If for example, the FOV is 25 cm, each pixel will be FOV/matrix size, 25/512 = 0.48 mm2. This dimension determines the limiting in-plane spatial resolution of the image. The 2D axial slices are then stacked together to form a 3D volume. Each pixel corresponds to a small volume element, called the voxel. The height of the voxel is determined by the slice thickness. If the axial slice thickness, in the above example, was 1.5 mm, the voxel size would be is 0.48 x 0.48 x 1.5 mm3. For MR brain imaging, typical voxels may be 0.9 x 0.9 x 3 to 5 mm3 with 256 x 256 pixels in a slice. It is also possible to acquire MR images with cubic voxels which can be used for registration.

CT Imaging

In a CT imaging system configuration, an x-ray projects a fan-shaped beam that is collimated to lie within an X-Y plane of a Cartesian coordinate system, generally referred to as the imaging plane. The

Table 1: Three-dimensional (3D) and endocardial left atrial image reconstruction. Representative examples of 3D models of three different pulmonary vein morphologies, along with endocardial views, are depicted. As opposed to the standard four pulmonary veins in the left panel, the middle panel shows a common pulmonary vein and the right panel shows an additional right middle vein. The respective endocardial views, along with the mitral valve (MV), are shown in the bottom panel. The location of the circumflex artery (Cx) in the left panel is also shown. LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RMPV = right middle pulmonary vein; RSPV = right superior pulmonary vein. Reproduced with permission from Sra et al. J Cardiovasc Electrophysiol Images 2004; 15:247



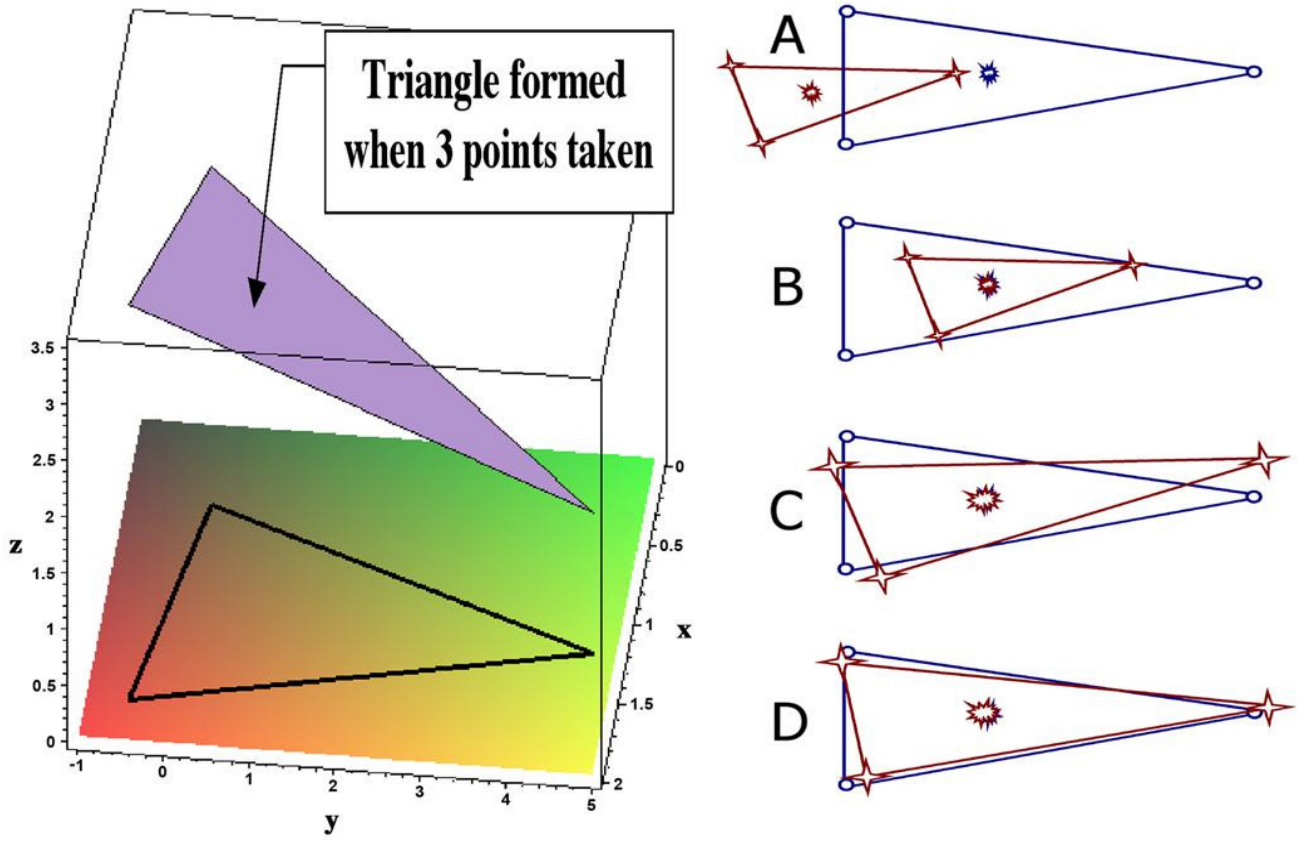
x-ray beam, after being attenuated by the organ through which it passes, impinges upon an array of radiation detectors. The intensity of the x-ray beam received at the detector array is dependent upon the attenuation of the x-ray beam by the object.

Pixel values are a measure of the x-ray attenuation in Hounsfield units (HU) where the HU= 1000-(4μ/μw-1), and μ is the average linear attenuation coefficient of the volume element represented by the pixel and μw is a linear coefficient of water for the effective energy at the beam exiting the patient. Thus water has an HU number of 0 and a region with a CT number of 100 HU has a linear attenuation coefficient that is 1% greater than the linear attenuation coefficient of water.

In the ECG-gated helical CT acquisition, the x-ray tube (and detector array) rotates continuously about the patient collecting the data, while the patient table (and the patient) is moved at a constant speed through the imaging plane, thus collecting a continuous sequence of consecutive axial images from a volume of patient's anatomy. Faster scanning, as currently done with 64 slice CT scanners, allows a large volume of data in short periods of time. This allows 3D reconstruction of the image set resulting in true depiction and a more highly diagnostic anatomic image across the patient population.

The factors selected in scanning a patient include slice width, FOV, gantry rotation speed and volume of coverage as well as basic contrast injection protocols. Scan time is calculated from the scan volume (total distance traveled by the table) divided by the table speed. Also important is the pitch which is defined as ratio of distance the table moves per 360º rotation. A pitch of 1.0 thus means the patient table moves a distance of one slice. Similarly, a pitch of 0.2 means the gantry rotates 5 times as the table moves a distance equal to the collimator width.

Figure 2: Simplified rigid body registration process. Left panel shows that once 3 fiducial points are taken a triangle is formed. In the right panel, A represents projection of CT (red) and reference image (blue). Panel B depicts initial step which involves translation of centroids. Panel C involves scaling to calibrate both images. Panel D shows rotation of the image to minimize the sum of the squared distances between fiducial points



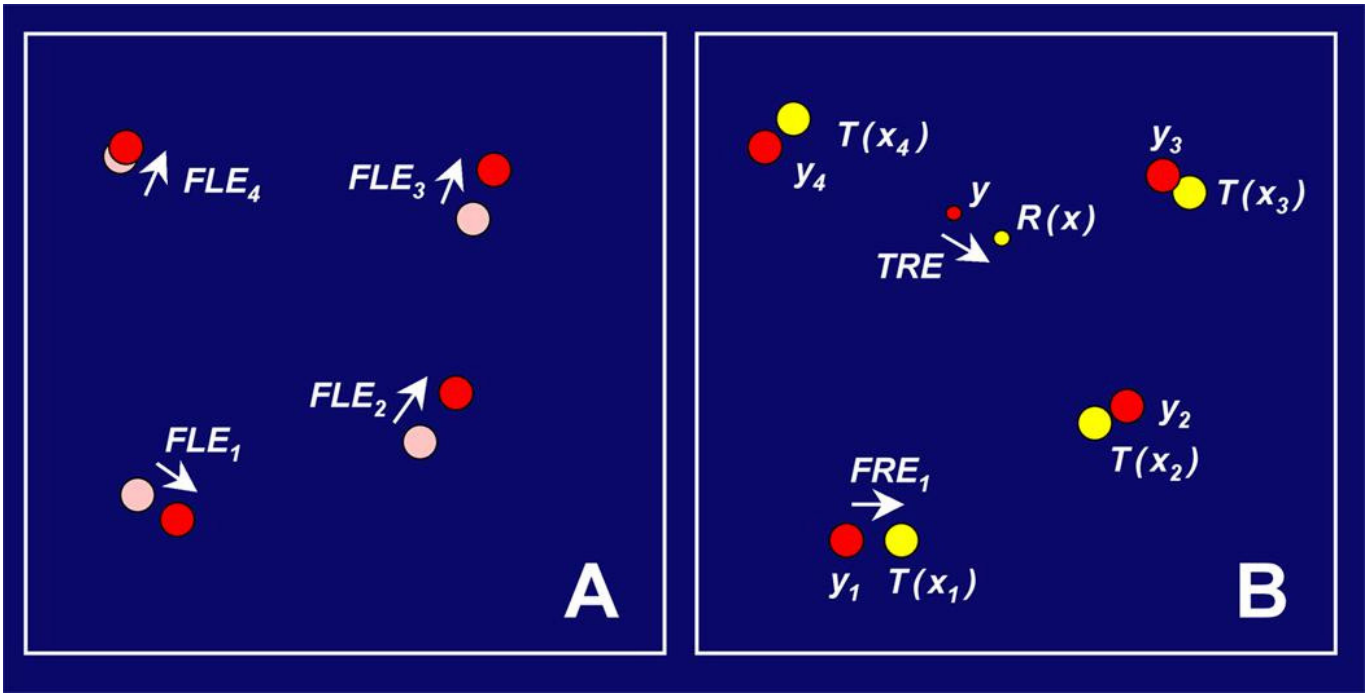
To avoid respiration artifacts, scanning is performed during the breath held in inspiration or expiration. The acquired data is synchronized with the collection of the ECG (QRS) signal. The data acquired during consecutive cardiac time intervals can then be combined to produce an image of the heart at the same phase of the cardiac cycle throughout the volume. Retrospective gating allows alignment of images during any phase of the cardiac cycle due to the continuous helical acquisition.

A medical image standard known as DICOM (Digital Information and Communications in Medicine) is widely used. This allows data to be exchanged between scanners and viewing consoles. The American Radiological convention is to display axial images with the right side of the patient at the left and posterior side at the bottom when looking at the computer workstation screen.

MRI Imaging

MRI is based upon the principles of nuclear magnetic resonance, a spectroscopic technique to obtain microscopic chemical and physical information about molecules.[12] MRI started out as a tomographic imaging technique, producing an image of the nuclear magnetic resonance signal in a thin slice through the human body. MRI has now advanced beyond a tomographic imaging technique to a volume imaging technique. Microscopic imaging is based on the absorption and emission of energy in the RF range of the electromagnetic spectrum. The human body is primarily fat and water. Fat and water possess hydrogen atoms. Hydrogen nuclei have an NMR signal which is imaged by MRI. Cardiac motion compensation is performed by synchronization of the image acquisition to the ECG signal. Both prospective and retrospective ECG gating can be performed. In addition to cardiac cycle motion, another source of image distortion is respiratory motion. Due to the development of faster MR imaging techniques, such as echo-planar imaging and turbo field echo imaging, it is possible to acquire images during short breath-hold of around 15 seconds. Recent technical advances have make it possible

Figure 3: Schematic of point-based registration depicting errors. Panel A depicts the fiducial localization (FLE) error. Red circles represent positions at which the points are determined by the localization process in one of the two spaces involved in the registration process. The light circles represent the actual position. Panel B depicts point-based registration illustrating two measures of registration error. The red circles represent position y in one space. The lighter circles represent position x in the other space after they have been mapped by the registering transformation T. The larger, numbered circles are the points used to effect the registration. Fiducial registration error (FRE) is the alignment error between these. Target registration error (TRE) is the relevant registration error at a point (smaller circles) not used in the registration. Reproduced with permission from Sonka M, Fitzpatrick JM (eds). Handbook of Medical Imaging. V.II. Bellingham, WA:SPIE Press; 2000



to acquire a stack of 12 slices, with around 25 cardiac phases each, in a single breath-hold of 20 seconds. As with the use of CT, PV anatomy can be clearly delineated using MRI.

LA Imaging and Segmentation

The process of dividing images into different regions to visualize areas of interest is called segmentatio.[13-14] Because of issues such as spatial resolution, poor contrast, ill-defined boundaries, noise, or acquisition artifacts, segmentation is a difficult task. Image segmentation methods can be grouped into thresholding, boundary detection, and region identification.

Thresholding is the simplest but most effective segmentation method. During thresholding, pixels with intensities below a threshold value are assigned one class and the remaining pixels a different class. Regions are then formed by connecting adjacent pixels of the same class. Boundary edges are needed in various image analysis applications. Thus boundary extraction methods use informa-

Figure 3: Left atrium (LA) registration. A: Landmark pairs (highlighted with colored circles) at the 6 o'clock mitral annulus (MA) position and the junctions of the LA and right superior pulmonary vein (RS), right inferior pulmonary vein (RI), left inferior pulmonary vein (LI) were annotated on the 3D CT LA surface reconstruction (upper image, shown as wire-frame) and the LA electroanatomic map (lower image, shown as solid shell) with colored tubes representing pulmonary veins (PVs). B: After landmark registration, the 3D LA surface reconstruction was superimposed on the electroanatomic map (shown as mesh). Note, the misalignment of the LS, LI, and RS between the two image datasets, indicated by the yellow or red color of the PV points (arrows) sampled in those PVs. C: After surface registration was executed, the PV alignment between the two image datasets was significantly improved, indicated by the green color of the PV points. The green, yellow, and red colors of the electroanatomic map points indicate their distance of <5 mm, 5–10 mm, and >10 mm, respectively, from the registered CT reconstruction surface. Reproduced with permission from Dong et al. J Cardiovasc Electrophysiol 2006;17:459-466

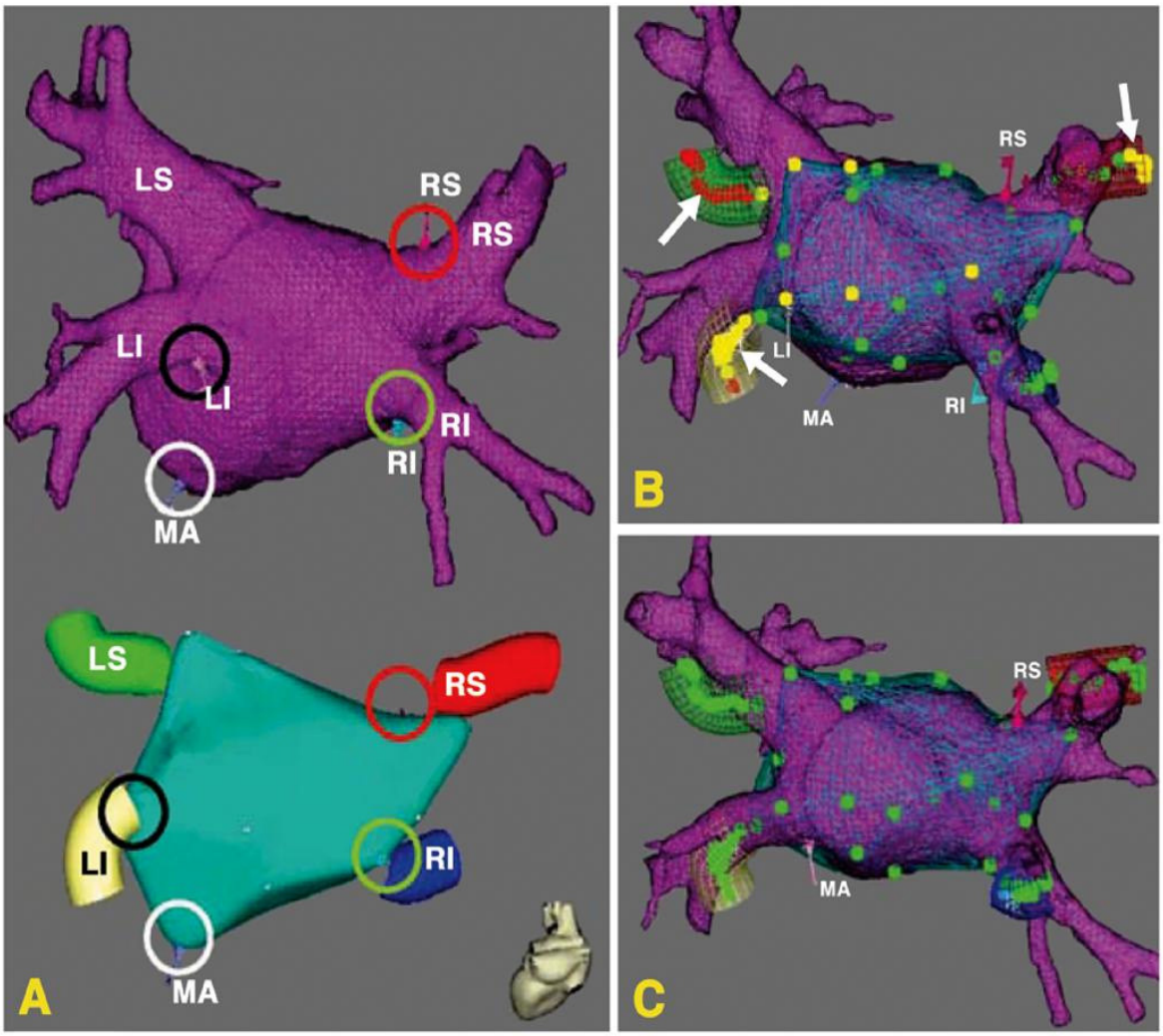
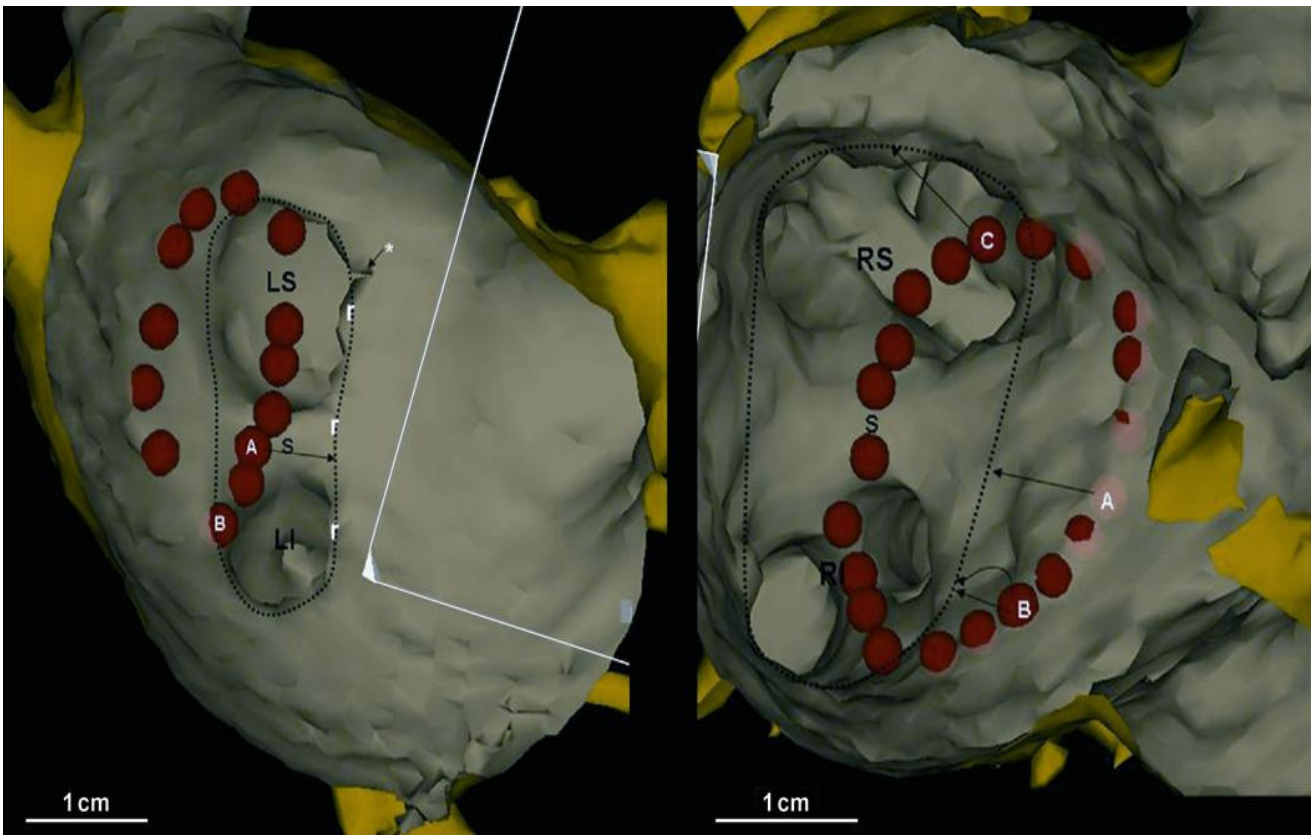


Figure 5: CCartoMerge image demonstrating a cut-away view of the right (right) and left (left panel) pulmonary vein region. Endocardial aspects are gray, and epicardial aspects are yellow. The actual lesion path is shown by the dotted line. Each red sphere demarcates an electroanatomic point taken along this path, which was acquired using ICE guidance while blinded to the CartoMerge image. Reprinted from Heart Rhythm, Vol. 17, Zhong et al. On the accuracy of CartoMerge for guiding posterior left atrial ablation in man, pages 595-60, 2007 with permission from Elsevier



tion about intensity differences between adjacent regions to separate the regions from each other. If the intensities within a region vary gradually but differences of intensities between adjacent regions remain large, boundary detection methods will delineate the region. Region identification techniques then form regions by combining pixels of similar properties.

Detailed CT and MR studies[15-17] have shown that anywhere from 65% to 80% of patients have 4 PVs, with left common and right middle seen in others. Part of the main trunk of the right superior PV passes immediately behind the right superior-SVC junction. It has also been shown that the right superior PV trunk branches out significantly sooner than do the left PVs. In 10% to 20% of cases, a middle PV arises independently on the right side./p>

The right inferior PV arises inferiorly and laterally to the right superior PV. It divides almost immediately, within 5 to 10 mm, into superior and inferior branches. The distance between the right superior and right inferior PVs across the canal ridge varies from 2 to 8 mm.

The left superior PV lies superior and posterior to the LA appendage. It enters the LA in a more vertical direction. It usually has multiple branches which ordinarily arise 10 to 20 mm from its base. The left inferior PV enters the LA more horizontally from a posterior and lateral position. It branches almost immediately. A common antrum of the left superior and inferior PVs is seen in 3% to 30% of patients. In a series of over 500 CT scans, in addition to the left common and right middle PVs (Fig 1),[18] we have seen other unusual anatomies including a common right PV, 3 PVs on the right and left, and a common ostium of the left inferior PVs

Registration

Fundamentals of Image Registration

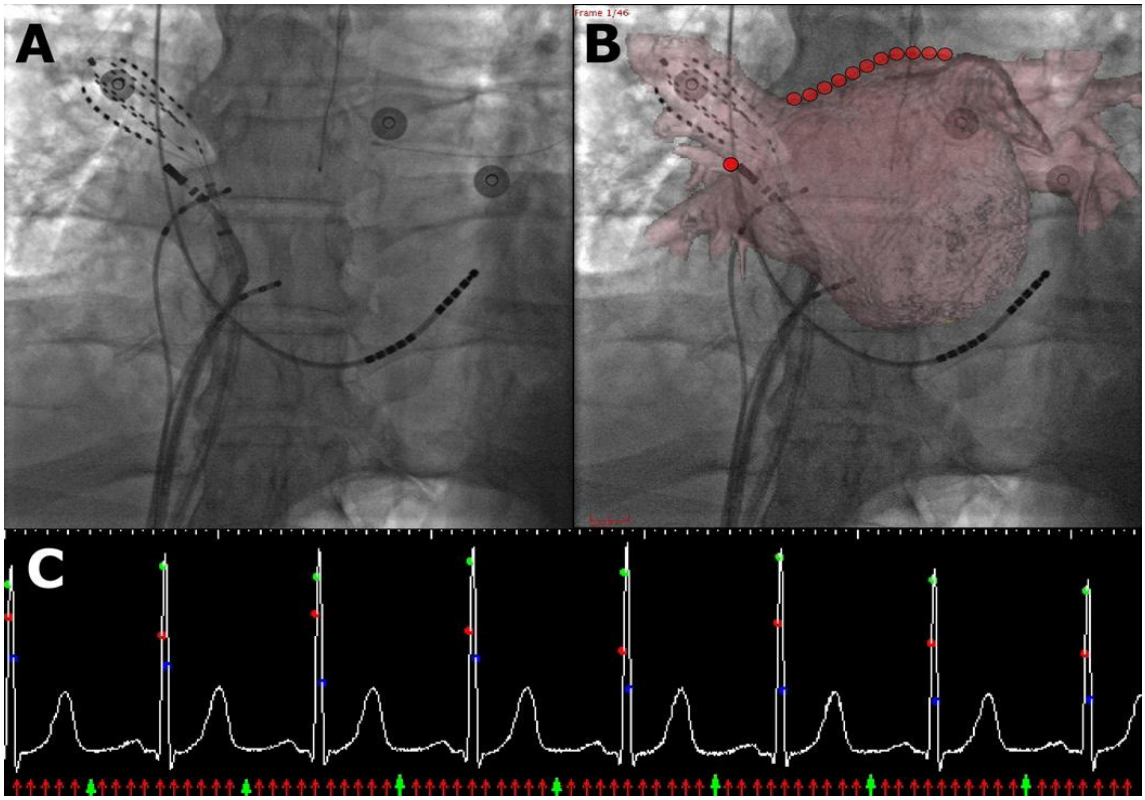
The image registration process entails combining

images from two different image coordinate spaces, such that multiple anatomic features or points of interest are aligned.[1,19,20]These points, called the fiducial points, are marked on the two image spaces. During the actual registration process, the image to be registered undergoes a mathematical transformation in all of its degrees of freedom, such that its image coordinate space is mapped onto that of the other image. For 3D structures, there are 6 degrees of positional freedom (translation along three orthogonal directions, and rotation along three axes). In addition, for the purpose of calibration, scaling factors between two image spaces must be accounted for in three dimensions. This registration process can be accomplished with a minimum of 3 non-collinear fiducial points matched in each of the image spaces. More points would increase the accuracy of the registration process. A translation factor can be achieved by using techniques and processes to align the center of the anatomical structures. Proper rotation can be calculated in terms of three angles (θx, θy, and θz). Assuming that the systems used for registration are calibrated such that the patient centered referential is the same in terms of orientation, there will be minimal rotation between the two systems. However, some rotational error may still occur due to movement of the heart and during respiration.

Several assumptions are generally made during this process. First, the structure undergoing registration is assumed to be a rigid body, which has undergone no changes or deformations from the time of imaging to the time of registration. This assumption may introduce limitations into the registration process when applied to a moving structure such as the heart. Furthermore, the final registration error is limited by how accurately fiducial points were identified in the respective image spaces.

Cardiac registration, in the context of the LA during AF ablation, is intermodal, with the acquired images and real-time reference image residing in different imaged spaces. Registration algorithms involve the optimization of a cost function by the choice of a transformation (T) which transforms one image space into the other. T can either be linear or nonlinear [19-21]. Linear transformations

Figure 6: ECG and respiration-gated registration. Fluoroscopic image is taken during the same cardiac cycle phase (75% as shown by green arrows), and respiration-gated (during inspiration) as CT imaging. Accurate registration is seen. System also allows marking of the ablation site (seen as red circles)



are shape-preserving and are composed solely of rotations, translations, and isotropic scaling. Nonlinear transformations may deform both shape and size between images. A linear or nonlinear transformation decides the number of parameters involved in its definition. A linear transformation between 3D spaces is defined by 6 parameters (or degrees of freedom), where two positions of a rigid body can always be related to one another in terms of three translations and three rotations. As the voxel sizes in each image may not be similar for calibration purposes, three extra degrees of freedom, equating to scaling in each direction, are needed (Fig. 2). A nonlinear transformation, as it may deform both shape and size, will require more degrees of freedom.

The cost function is a measure of similarity (or dissimilarity) between the reference image and the transformed image and optimization is usually required to make the registration process accurate. Gradient descent method[19] is used to calculate the cost function for the set of registration parameters described above. The direction of the greatest decrease of cost function can be mathematically computed at that set of parameters. A search is done in the direction of the greatest decrease until a new minimum is found. The parameter set is then updated to be the point at which the new minimum occurs. This process continues until minimal change occurs in the cost function with successful steps.

Registration methods fall into two broad categories, based on either geometric similarities between images or voxel intensity similarities. Voxel similarity-based methods have traditionally been used to assess serial changes in the brain using MR images and are not relevant to this review and will not be discussed further.

Geometry-Based Methods

Geometry-based methods can be point-based or surface methods applied to both 3D-3D and 3D-2D registration models. Point-based registration methods depend upon the appropriate definition of two sets of corresponding fiducial points in each set of images to be registered. The cost function, the residual sum of squares (RSS) between the transformed points of the acquired image and

Table 1 Registration Techniques and Errors

Author	Ref	Registration Technique	Pts./other	Error mm	Comments
Sra	HR, 2005	CT/ESI	Animal Model	2.0±3.6	target registration error
Tops	HR, 2005	CT/CARTO	16	1.8±1	feasability- mapping points and CT surface
Dong	JCE, 2006	CT/CARTO	16 (8 CT)	3.0±0.4	technique as above
Malchano	JCE, 2006	CT/CARTO	13	12±11 (insp) 4.7±0.9 (exp)	technique as above
Kistler	JCE, 2006	CT/CARTO	47	2.4±0.4	technique as above-CartoMerge (83% vs. 60%)
Dong	Circ, 2006	CT/CARTO	Animal Model	1.8±1.0	target registration error
Fahmy	JCE, 2007	CT/CARTO	124	5.6±3.2 (post) 9.1±2.5 (ant)	ICE-guided assessment
Zhong	HR, 2007	CT/CARTO	16	16±12 (right) 11±7 (left)	ICE-guided assessment
Sra	Circ, 2006	CT/fluoro	Phantom, 20 Pts	1.4±0.5	feasability
Sra	JCE, 2007	CT/fluoro	50	---	outcome study (84% vs. 67%)

their corresponding points in the real-time image, is determined and then applied to the entire acquired image data set. Thus, if 1N denotes the set of fiducial points in the acquired image, {y}1N denotes the corresponding points on the real-time image, i.e., the choice of T minimizes the error iN=1 IIt(x)-y1 II2. Fiducial point sets are either automatically determined based on external skin markers or manually determined based on anatomical landmarks. The former method is usually used in the registration of neuro images, as the static nature of the brain allows its internal organization to be characterized by its external features. The latter method has been used in cardiac image registration.[20,21] For rigid structures such as the brain, three non collinear fiducial points may be sufficient to establish the transformation between the 3D image volumes. However, the larger the number of points used, the more any error occurring during collection of the points is averaged out. The algorithm for calculating the transformation between the 3D images involves first computing the average of the "centroids" of each set of points. The difference between the centroids in the 3D images tells us the translation that must be applied to one set of points. These points are then rotated about the new centroids until the sum of the squared distances between each corresponding point pair is minimized. The square root of the mean of this squared distance is referred to as fiducial registration error (FRE). The mathematical solution is known as the solution to the orthogonal Procrustes problem,[22] named after a robber in Greek mythology who fitted his guests to a bed of the wrong size. The manual aspect of the fiducial point localization, however, has an inherent error, the fiducial localization error (FLE), associated with each point.

Surface-based methods are used in registering a 3D image. Surface structure information is extracted from the CT or MR. Hence surface-based methods are mostly used in conjunction with these modalities. The process involves characterizing the surface represented in each of the images to be registered then deriving the best transformation T between them. The cost function here is a display function which provides a measure of distance between the surfaces. One of the surfaces is represented by a set of discrete points while the other has a surface representation. Surface can be represented as faceted surfaces, implicit surfaces or parameterized surfaces. Initially, a correspondence between the point set and the surface must be chosen. T is then optimized to minimize registration errors. One problem with the method is that, although T is not rigid in the context of cardiac registration, to achieve computational efficiency with this method, it is often assumed to be rigid. Another potential problem with this technique is that it is highly dependent upon identification of corresponding surfaces, yet different imaging modalities can provide very different image contrast between corresponding structures.

Registering 3D and 2D Images

FIf the geometry of the image acquisition is tightly controlled, 2D images may be registered purely via a rotation and two orthogonal translations. Clinically relevant examples of this are rare. 3D to 3D image registering using CT or MR is becoming more widespread. The assumption is usually made that the internal anatomy of the patient has not distorted or changed in spatial relationship between organs so that the imaged part of the body behaves as a rigid body. In this case, three translations and three rotations will bring the image into registration as described before. The rigid transformations, a subset of linear transformations, are composed solely of rotations and translations. If T is rigid between images of the same dimensions, the use of the singular value decompositions (SVD) method has been determined to provide T with a good degree of accuracy and stability, and is favorable for its noniterative time efficiency.[23] SVD is a technique for expressing a given matrix as a product of three component matrices which reveal structural information about the original matrix. Orthogonal matrices are square matrices with row and column vectors directionally perpendicular to each other, having measurable magnitudes. Thus, if T is rigid, it can be expressed as follows: T (x) = (x) + t where is an orthogonal rotation matrix and t is a translational vector.

The process of registration becomes more complicated if one of the images represents a projection of physical space, as is the case with most optical images and conventional x-ray radiographs. These images are called "projection" images. One point in an x-ray image will correspond to some combination of the x-ray attenuation value along the line in

the patient leading from the x-ray source to the imaging plane. This means that one point in the radiograph will correspond to a line of points through a CT or MR image. In optical images, only the visible surface will contribute to the image.

When T is constrained to be a perspective projection transformation from a 3D space to a 2D space, the problem is referred to as Projection Procrustes Problem.[22] If, for example, x1 is a matrix of image points in a 3D image space, x2 a matrix of corresponding points in the 2D image space and a projection transformation, a solution of the Projection Procrustes Problem minimizes II x1 - x2 II. This problem is iteratively solvable when x1 and x2 are known; a non iterative solution based upon the SVD technique described before can also be found in a similar manner to that outlined before.

For computational efficiency, transformations are restricted to scaling, translations and rigid rotations in the x-ray space, and are based on the optimized alignment of corresponding features or other image properties. The details may vary, but they are described mathematically as Â (af (x) +t) » y where f is a choice function that selects an appropriate 2D slide of the CT volume. Based on the orientation of the x-ray C-arm, a is a scaling parameter that standardizes the sizes of the images, t is a 2D translational parameter that aligns the centers of the images and Â is a rotational matrix that completes the alignment process. In the CT x-ray registration, a, t , and Â are the usual parameters involved; however, the choice function f can also be thought of as an additional parameter. Registrations that are non rigid and incorporate more parameters generally produce more accurate results. However, as results for interventional purposes need to be obtained in real time, a compromise has to be reached in registration design between accuracy and quick computational design. Surface-based methods are used in registering a 3D image. Surface structure information is extracted from the CT or MR. Hence surface-based methods are mostly used in conjunction with these modalities. The process involves characterizing the surfaces represented in each of the images to be registered then deriving the best transformation T between them. The cost function here is a display function which provides a measure of distance between the surfaces. One of the surfaces is represented by a set of discrete points while the other has a surface representation. Surfaces can be represented as faceted surfaces, implicit surfaces or parameterized surfaces. Initially, a correspondence between the point set and the surface must be chosen. T is then optimized by some form of the gradient descent technique described before. The optimization algorithm selects T to minimize the sum of weighted distances in the disparity function between the reference image surface and the set of transformed points and it is known as the iterative closest-point algorithm.

One problem with the method is that, although T is not rigid in the context of cardiac registration, to achieve computational efficiency with this method, it is often assumed to be rigid. Another potential problem with this technique is that it is highly dependent upon identification of corresponding surfaces, yet different imaging modalities can provide very different image contrast between corresponding structures. Currently, computer-assisted segmentation almost always requires some manual editing and adjustment.

Clinical Applications for (LA) Registration

Many studies have been performed recently to implement semi-automated 3D-3D and 3D-2D registration strategies. This section describes some recent advances made in the registration of acquired, structurally-revealing 3D images with real-time images. Table 1 depicts different registration techniques for the LA and various errors reported with some of these studies..

3D Anatomical Mapping Systems

Anatomical mapping systems provide the 3D position of a navigational catheter within the cardiac chamber of interest and, in some instances, can also be used to construct 3D maps of the cardiac chamber. Magellan and CARTO (Biosense Webster, Inc., Diamond Bar, CA, USA).[24,2] use the electromagnetic position of the catheter tip, based on an electromagnetic locator pad which is placed below the patient, and a reference catheter at a fixed external (usually posterior) location. LocaLisa (Medtronic, Inc., Minneapolis, MN, USA) and NavX (St. Jude's Medical. Inc., Minneapolis, MN, USA) use voltage gradients generated by external electrical fields to spatially

orient and localize the catheter tip.[26,27] EnSite balloon (St. Jude's Medical, Inc., Minneapolis, MN, USA)[28] uses an electrically-coded catheter and a multielectrode mapping balloon to create maps and define the location of the navigational catheter.

Point and Surface-Based Registration

In one of the earlier studies, point-based registration was performed using CT images and the EnSite system.[4] Fiducial points (≥ 3 non collinear points) were manually inserted in the form of pacing leads into the LA of a canine model and CT images were recorded. Following segmentation of the LA, a wire-frame model of the LA was imported to the noncontact, multielectrode array-based EnSite mapping system. Goodness-of-fit was evaluated qualitatively by observing a cloud of points post registration. When registration was tested by navigating the catheter to the buried electrodes and delivering radiofrequency pulses at these points, the mean fiducial registration error was 6.9±2.2 mm and the target registration error was 2.0±3.6 mm.

A study by Solomon et al[25] attempted the registration of porcine cardiac CT images with the real-time catheter location provided by the Magellan mapping system. A point-based registration method was used with fiducial points determined by external markers placed on the swine's chest prior to CT imaging. Accuracy of the registration was determined by position error, distance between the actual location of the marker and the location where the navigational system registered the point (fiducial registration error). The accuracy was determined to be within 4.69±1.70 mm. A reference catheter taped to the swine's chest indicated that lateral motion due to respiration accounted for increased inaccuracy.

Reddy et al[3] performed a similar study on the registration of MR images using the CARTO system. The main difference was that a surface-based method was chosen for registration in which the MR images were created and the points were marked out on the left ventricle and aorta via the CARTO. An iterative closest-point algorithm was used to register the image. The results indicated that registration of the left ventricle alone resulted in inaccurate alignment. Inclusion of the aorta in the registration process rectified this error.

A clinical application of this technique is now available which uses the CARTO system and either CT or MR (CartoMerge™).[5,8-11] A combination of landmark and surface registration is used to register CT or MR with the CARTO system. Initially, several landmarks, usually 3, are manually chosen and annotated. Following this, the 3D LA reconstructed image from the CT or MR is superimposed upon the electroanatomic map created by the CARTO mapping system (Fig. 4).

In a feasibility study,[5,16] patients undergoing AF ablation underwent fusion of LA images obtained from a multislice CT scan with an electroanatomic mapping system using the CartoMerge™. A detailed electroanatomic map of the LA was created first. The 3D CT image and the electroanatomic map were displayed simultaneously on the CARTO screen. Using fluoroscopy and intracardiac echocardiography guidance, a landmark was then placed on the electroanatomic map and on the CT image on the same spot. Next, the surface registration algorithm was implemented. This algorithm composed the best fit of the two structures based on minimizing the distance between the two landmarks and the distance between all mapping points and the CT image. Following this, it was shown that it was feasible to perform registration guided therapy.

A main concern in this and prior studies was that they assumed the transformation between the CT or MR and the interventional system was rigid in nature and thus did not take into account cardiac motion errors.

Several recent studies have tested the accuracy of CT-MR registration. Dong et al,[8] attached 2.3 mm CT fiducial markers to the epicardial surface of each cardiac chamber in 9 mongrel dogs. CT images were registered to the electroanatomic maps of each cardiac chamber. To assess accuracy, targeted ablations were performed at each of the fiducial markers guided only by the reconstructed images. At autopsy, the position error was 1.92±0.9 mm for the right atrium, and 1.8±1.0 mm for the LA. Retrospective analysis revealed that a combination of landmark registration and the target chamber surface registration resulted in < 3mm accuracy in all chambers.

However, other clinical studies have shown significant errors during registration using these techniques. One study showed poor registration during inspiration but good alignment during expiration.[11] In a study by Fahmy et al[29,124] patients underwent AF ablation guided by registration of images of the left atria created using CartoMerge™. Different fiducial landmarks were selected and spatial accuracy was further validated using intracardiac echocardiography. Surface registration was then performed and its impact on integration using the fiducial markers was assessed. The best landmark registration was achieved when the posterior points on the PVs were selected (5.6±3.2). Landmarks taken on the anterior wall, the LAl appendage or the coronary sinus resulted in greater registration error (9.1±2.5). As opposed to the previous study, in this study, surface registration resulted in shifting of the initially registered landmarks leading to a more significant level of error (from 5.6±3.2 to 9.2±2.1 mm; 95% CI 4.2-3.05).

Another recent study measured the accuracy of CartoMerge™ in guiding posterior LA ablation .[30] In this study in 16 patients undergoing AF ablation, CT images of the LA were merged with CARTO. Encircling of the left and right PV vestibules was then performed, guided solely by intracardiac echocardiography, with point locations saved on a CartoMerge™ image to which the operator was blinded. The accuracy of the CartoMerge™ image was then assessed by measuring the distance from the location of each ablation point on the image to its actual anatomic location. A significant error of 1.6±1.2 cm in the right vestibule and 1.1±0.7 cm from the planned path of ablation was observed (Fig.5). Accuracy was improved when an end atrial contraction CT image was used.

These reports suggest that these registration techniques have inherent limitations. Use of appropriate locations for fiducial points, cardiac cycle location and respiration could potentially help these approaches to registration.

Fluoroscopy-Based Registration

For low infrastructure and procedural costs, x-ray fluoroscopy remains the standard catheter navigation tool used in interventional laboratories. 3D-2D registration is much more complicated than the 3D-3D registration described before.

Registration of MR using biplane fluoroscopy and CT with single-plane fluoroscopy has been successfully performed.[7,31,32] However, as only CT-fluoro integration has been tested in the context of AF ablation, this section discusses recent advances in fluoroscopy-based registration but focuses mainly on studies involving registration of 3D-LA models with 2D x-ray fluoroscopy.

X-ray-3D Catheter Model

In the study by Meyer et al,[31] a registration algorithm was developed to register ultrasound-based 3D catheter coordinates, x1 as the fluoro view of the catheter with the corresponding coordinates given by the matrix x2. The study approximated the projection P, as described before, and then iteratively solved for the rigid transformation T such that II T (x1)- x2 II was minimized. The study developed an initialization routine for T which resulted in a convergence of iterates in all the test cases. Four methods of error were defined and the method was tested using mathematical simulations and a multi-catheter phantom. The study concluded that use of a larger set of fiducial points along the catheter, with a wide spatial distribution, yielded registration results that were less sensitive to noise in the entries of x1 and x2.

MRI-X-ray Registration

The study by Rhode et al[32] utilized a combined x-ray and MR interventional suite which produces both x-ray and MR images as separate outputs. The transformation that registered MR to x-ray images was presented as a product of point-based rigid transformations between each distinct space in the suite followed by a perspective projection transformation. The transformations were determined sequentially using a calibration object with ≥ 6 markers forming the set of fiducial points.

The registration was tested on a phantom and on post procedure patient images. A 2D target registration error was computed from the displacement of the MR transformed from the actual marker position on the x-ray fluoro view, representing the accuracy of registration. 3D target registration error was computed from 3D displacements be-

tween MR image markers and the reconstructed 3D positions of the markers on the x-ray image. The 3D reconstruction was done from the biplane x-ray images using the epipolar constraint. The 2D error for in vitro tests was 4.2 mm and the 3D error was 4.6 mm.

In the study by Ector et al,[7] cardiac MR images were acquired in patients undergoing catheter ablation. Detailed 3D models of the LA were obtained. After contouring of endocardial cavities with cross-checking of different imaging planes, 3D models of the right atrium were merged with the contrast-filled right atrium seen on biplane fluoroscopy using custom-built software. The feasibility and accuracy of this merging process was determined in heart cast experiments and using electroanatomic mapping in patients. The reported error on heart casts was 0.2 ± 0.3 mm, and 1.9 to 2.5 mm in patients.

CT-X-ray Registration

Fluoroscopic images are conic projections, with greater magnification of peripheral regions as compared to central ones. In contrast, CT images represent the synthesis of many x-ray projections obtained circumferentially around the object, thus essentially canceling the effect of this distortion. Assuming that the patient is positioned in the same position as when the CT scan was obtained, the height of various cardiac structures with respect to the table can be ascertained from the CT scan. Fortunately, the theoretical scaling of structures at each height above the table position is also well described with respect to the geometry of the fluoroscopy system (i.e. source and image-intensifier position). This information can then be used to scale and transform the CT image to match the fluoroscopic image space.

As fiducial selection (described in 3D to 3D image registration) in each of the image spaces introduces several challenges, we have instead used a coronary sinus catheter positioned through the superior vena cava as a fiducial marker and have used a transformation to align the coronary sinus catheter seen on fluoroscopy with the superior vena cava and the coronary sinus in the exported 3D model. In addition, for the purpose of scaling, the coronary sinus catheter is placed at a location identified by the intersection of a horizontal plane and the line joining the focal point of the fluoroscopic image. The horizontal plane is defined by the elevation above the anatomical reference system, the patient table. Once the location of the catheter and the actual and apparent dimensions of the elevation in the 3D model are known, the actual size of the same anatomical structure in the 3D and the fluoroscopic image can be determined. We recently described an implementation of a semi automated 3D-2D CT-fluoroscopy registration strategy.[6] The accuracy of this system was found to be within 1.4 mm in phantom studies. This strategy was also assessed in patients undergoing AF ablation. Accurate registration was confirmed by: 1) PV angiography and 2) position and recordings on a 64-pole basket catheter located in the PVs. In a recent study[33,50] patients with AF undergoing ablation were randomized to standard ablation techniques or ablation guided by the CT-fluoro registered images. Fluoroscopy time and total procedure time was significantly reduced in the CT-fluoro group ($p<0.01$) and there was a trend toward better outcome. It is also possible to mark ablation points on these images and synchronize the images to the cardiac cycle. This technique has been used in 154 patients and should be available for general use in the next 18 months.

As in the 3D-3D registration described before, the largest source of error with the 3D-2D registration strategy may be due to cardiac and respiratory motion. The complex translational, rotational, and conformational changes that occur with cardiac and respiratory motion will introduce error into the registration process when, as in 3D-3D registration, a static image is "aligned" with the real-time fluoroscopic image. Attempts at gating the registration process so that image integration occurred during the same phase of the cardiac cycle were successful in experiments conducted in our laboratory, thus fluoro images can be taken at the same phase as the segmented CT images, i.e., during diastole . Movement of the LA during respiration could potentially be eliminated by synchronizing registration to the respiratory cycle. In addition to cardiac gating, we have been able to take into account respiration gating and deposit ablation points on the surface of registered images as depicted in Figure 6.

Ultrasound-Based Registration

Ultrasound-based registration has not been studied in detail, possibly due to difficulty in achieving automatic processing of these images in conjunction with images from other modalities.

Registration of 3D ultrasound has been attempted in the field of stress echocardiography[34] where pre and post stress 3D ultrasound images were temporarily aligned and then spatially registered by optimization of mutual information between image voxel intensity sets, thus providing voxel intensity-based registration.

In the study by Packer et al,[35] data on 5 patients was integrated from electroanatomic or noncontact mapping, CT anatomy, and intracardiac ultrasound. CT images of the LA were created. Ultrasound images of the PVs were generated using intracardiac, phased-array ultrasound with imaging at 5.5-10.0 MHz. A fused, CT ultrasound activation sequence was then constructed from an image set. On this framework, electroanatomic or noncontact mapping was demonstrated.

MR-Based Registration and Navigation

In a recent study, an electromagnetic catheter positioning system was superimposed on 3D MR images using fiducial markers.36]. This allowed display of the catheter position on the anatomy obtained using the MR images in real time. In phantom models, the accuracy was 1.11±0.06 mm. Subsequently, in the swine model, in vivo accuracy was 2.74±0.52mm. Radiofrequency lesions were repeated in the right atrium within an accuracy of 3.92 ±0.5 mm. This study suggests that ablation can be performed on the real-time images obtained using MR images. MR compatible catheters and the absence of 3D images may be some of the limitations which will need to be overcome.

Sources of Registration Error

The registration techniques described above afford a significant advantage over the less detailed geometry created by the currently available mapping systems, however, there are significant inherent limitations, as registration algorithms that assume rigid transformations between image spaces have been applied in many of these techniques. As described before, the initial fiducial points are picked up by the operator using fluoroscopy; the exact location of these points in the 3D space may be deceptive. As multiple points are needed for surface registration, the process takes more time, the manual component becomes more laborious. Given the dynamic motion of the heart and the large number of variables that influence its movement and shape, careful validation of any technique used for cardiac image registration is important.

This section explores the unique sources of error that make cardiac image registration challenging. An understanding of the potential errors inherent in the registration technique is essential to create error-free registration.

Errors common to intermodal registration

In the registration algorithms, the voxel and pixel dimensions have to be accurately reported by the imaging system. CT imaging systems, for example, often produce images where the thickness of reconstructed 2D slides are different from the voxel height and width, due to the somewhat limited resolution capabilities of the system along the z axis.

In 3D to 3D registration, this limited resolution capability has been shown to cause anisotropic error measurement in three dimensions, with the error echoing the reported voxel dimensions.[37] A sub pixel/voxel measurement could eliminate these errors. Standardizing the size of images involves approximate measurements which can potentially introduce errors into the registration process. Since the actual position and size of the heart may not be known, approximate measurements of the expected distances and heights is sometimes used.[38] The ratios of the actual versus the apparent diameters of ablation catheters in the registered image can be considered to help determine scale.

As described before, the x-ray image is a conic projection with greater magnification present in the peripheral regions of the image than in the central region. The 3D CT image, on the other hand, does not have this nonisotropic magnification. Thus, if error is present in the computation of scale, its effect would be amplified throughout the registration process.

Fiducial Point/Feature Selection Location of fiducial

points needs to be accurate. However, as these points are usually taken using 2D fluoroscopy, there are inherent limitations in using fiducial points selected based on fluoroscopy alone. As demonstrated in the prior study,[29] fiducial points taken in posterior PV locations seem to give the best registration results. It is also important to take at least 3 non collinear points to get the best results. As discussed before, resolution differences also exist between CT and other 3D or 2D images.

i Manual interaction is needed for feature segmentation or point localization, which can be associated with the well-documented fiducial localization error.[19] Some choices of cost and optimization functions are more sensitive to accuracy of fiducial points. Registration based on alignment of features that may not represent identical regions is thus a potential source of error.

Studies have shown that accuracy is sensitive to the potential accuracy of spatial distribution of fiducial points. Wide asymmetric distribution of fiducial points produces more accurate registration. Similarly, regarding the selection of fiducial features, registration based solely on alignment of features that may not represent identical regions is also a potential source of error.

Errors Specific to Cardiac Image Registration

In addition to the errors described before, the possible sources of error specific to cardiac image registration are: 1) inconsistency in patient positioning, 2) cardiac gating during CT acquisition, 3) cardiac chamber movement in various stages of the cardiac cycle, and 4) cardiac chamber movement due to respiration.

Patient Alignment

Efforts should be made to align the patient identically on each imaging table to help ensure same orientation during both imaging modalities. Some variability in patient alignment and posture[37] can result in a corresponding variability in the orientation of the imaged cardiac chamber. Factors that influence this variability include differences in imaging table surfaces, such as curvature and cushioning. Additionally, it is impossible to guarantee that the patient is in exactly the same position since there is usually a significant time-lapse between acquisitions.

The orientation of the cardiac chamber changes with the orientation of the body. For this reason, this type of interscan movement can be described as a rigid body rotation of the heart with the spine. A change in the interscan angle of 5 degrees, for example, may give a rotational error of 0.44 cm in a 5 cm organ with a field-of-view of about 20 cm. Thus it is important that any changes in interscan imaging are taken into account and minimized.

Cardiac and Respiration Gating

In addition to interscan movement resulting in different orientations of the imaged chamber, movement of the object between the same acquisitions can cause errors, as it is not possible to physically arrest the heart. In the cardiac chamber, this issue is amplified several-fold due to continuity and extent of movement of the heart. The cardiac deformities caused by non rigid cardiac motion have been broken down into as many as nine different modes.

Correction for some of these problems during the CT gating technique[38] involves the patient holding breath for several heartbeats while 2D axial slices are sequentially obtained at fixed points of the cardiac cycle. These slices are stacked together and interpolated to create a smooth, static 3D CT image. Although the likelihood that the heart returns to a fixed shape at fixed points of the cardiac cycle is questionable, due to the variability in cardiac deformation,[39] it is important that both the CT and the second image are ECG-gated to eliminate, as much as possible, errors due to cardiac motion. In the studies done in our lab, it was shown that the best images of the LA were obtained during segmentation of the LA at 75% of the cardiac cycle in sinus rhythm or at 45% during AF due to shorter R-R intervals.

Given the proximity of the heart to the diaphragm and given that the displacement of the diaphragm occurs in the direction of the heart, the effects of respiration are expected to be more pronounced. McLeish et al[40] have determined that translations

in the craniocaudal direction are the main types of movement seen in the cardiac chamber due to respiration. Less significant movements include translation and rotation in other directions. Noseworthy et al[41] used MR angiography of the reconstructed LA and PVs at both end-expiration and end-inspiration. Their quantitative assessment of 3D images during respiratory phases revealed splaying of the PVs and reduction in the size of PV caliber in the right-sided PVs during held-inspiration. CT scanning can be done both during inspiration and now, due to rapid scanning techniques, during expiration. There is evidence based upon prior studies that respiration gating during expiration may be optimal.

The above findings do suggest that the effects of respiration need to be considered as their effect on target registration error may be amplified through the steps of the registration process.

Validation Strategies for Registration

Knowledge of the various sources of error is thus key to establishment of a gold standard since these errors will have to be accounted for in the simulation. An allowance for cardiac movement and respiration must be incorporated into the overall strategy, distinguishing cardiac image registration from other registration processes involving more static organs and structures. This could be accomplished either by distinguishing each component of a movement and introducing them into the simulation in combination or treating the movement as a single random process at a fixed point of the cardiac cycle. Animal studies can then be undertaken to complete the validation process.

Conclusions

Inadequate depiction of cardiac anatomy hinders the widespread application of fluoroscopy for AF ablation. Image registration involves correspondence between two images or an image and a physical space and provides a means for physicians to incorporate into a single view the varied information captured by different modalities which can then be used for the purpose of interventional planning and treatment. The deformations caused by cardiac chamber and respiration motion present unique problems for cardiac image registration. Although significant work has been done in the field of cardiac imaging, there is much room for the development of validation strategies for cardiac image registration. It is important that the issue of patient-specific movement of the cardiac chamber be quantified in evaluating registration algorithms. Proper application of the registration process, with careful adjustment for the constraints mentioned and use of the power of the computer to automate the process can greatly improve and simplify this technique.

References

1. Hajnal JV, Hill DLG, Hawkes DJ. Medical image registration. The Biomedical Medical Engineering Series. 2001:1-70.
2. van den Elsen PA, Pol EJD, Viergever MA. Medical image matching: a review with classification. IEEE Eng Med Biol. 1993; 2: 26-39. CrossRef
3. Reddy VY, Malchano ZJ, Holmvang G, Schmidt EJ, d'Avila A, Houghtaling C, Chan RC, Ruskin JN. Integration of cardiac magnetic resonance imaging with three-dimensional electroanatomic mapping to guide left ventricular catheter manipulation: feasibility in a porcine model of healed myocardial infarction. J Am Coll Cardiol. 2004; 44: 2202-2213. CrossRef PubMed
4. Sra J, Krum D, Hare J, Okerlund D, Thompson H, Vass M, Schweitzer J, Olson E, Foley WD, Akhtar M. Feasibility and validation of registration of three-dimensional left atrial models derived from computed tompgraphy with a noncontact cardiac mapping system. Heart Rhythm. 2005; 2: 55-63. CrossRef PubMed
5. Tops LF, Bax JJ, Zeppenfeld K, Jongbloed MR, Lamb HJ, van der Wall EE, Schalij MJ. Fusion of multislice computed tomography imaging with three-dimensional electroanatomic mapping to guide radiofrequency catheter ablation procedures. Heart Rhythm. 2005; 2: 1076-1081. CrossRef PubMed
6. Sra J, Krum D, Malloy A, Vass M, Belanger B, Soubelet E, Vaillant R, Akhtar M. Registration of three-dimensional left atrial computed tomographic images with projection images obtained using fluoroscopy. Circulation. 2005; 112: 3763-3778. CrossRef PubMed
7. Ector J, De Buck S, Adams J, Dymarkowski S, Bogaert J, Maes F, Heidbüchel H. Cardiac three-dimensional magnetic resonance imaging and fluoroscopy merging-a new approach for electroanatomic mapping to assist catheter ablation. Circulation. 2005; 112: 3769-3776. CrossRef PubMed
8. Dong J, Calkins H, Solomon SB, Lai S, Dalal D, Lardo AC, Brem E, Preiss A, Berger RD, Halperin H, Dickfeld T. Integrated electroanatomic mapping with three-dimensional computed tomographic images for real-time guided abla-

tions. Circulation. 2006; 113: 186-194. CrossRef PubMed
9. Dong J, Dickfeld T, Dalal D, Cheema A, Vasamreddy CR, Henrikson CA, Marine JE, Halperin HR, Berger RD, Lima JA, Bluemke DA, Calkins H. Initial experience in the use of integrated electroanatomic mapping with three-dimensional MR/CT images to guide catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2006; 17: 459-466. CrossRef PubMed
10. Kistler PM, Earley MJ, Harris S, Abrams D, Ellis S, Sporton SC, Schilling RJ. Validation of three-dimensional cardiac image integration: use of integrated CT image into electroanatomic mapping system to perform catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2006; 17: 341-348. CrossRef PubMed
11. Malchano ZJ, Neuzil P, Cury RC, Holmvang G, Weichet J, Schmidt EJ, Ruskin JN, Reddy VY. Integration of cardiac CT/MR imaging with three-dimensional electroanatomical mapping to guide catheter manipulation in the left atrium: implications for catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2006; 17: 1221-1229. CrossRef PubMed
12. Higgins CB, de Roos A. MRI and CT of the Cardiovascular System-Second Edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.
13. Liou SP, Jain RC. An approach to three dimensional image segmentation. Computer Vision Graphics and Image Processing. 1991; 53: 237-252.
14. Justice RK, Stokeley EM, Strobel JS, Ideker RE, Smith WM. Medical image segmentation using 3D seeded region growing. In Proceedings of SPIE: Image Processing 1997; 3034: 900-910.
15. Packer DL, Asirvatham S, Seward JB, Robb RR, Breen JF, Robb RA. Imaging of the cardiac and thoracic veins In: Chen SA, Haïssaguerre M, Zipes DP, editors, Thoracic Vein Arrhythmias. Malden, MA: Blackwell-Futura; 2004; 77-98. Reproduced with permission
16. Kato R, Lickfett L, Meininger G, Dickfeld T, Wu R, Juang G, Angkeow P, LaCorte J, Bluemke D, Berger R, Halperin HR, Calkins H. Pulmonary vein anatomy in patients undergoing catheter ablation of atrial fibrillation: lessons learned by use of magnetic resonance imaging. Circulation. 2003; 22 :2004-2010. CrossRef PubMed
17. Schwartzman D, Lacomis J, Wigginton WG. Characterization of left atrium and distal pulmonary vein morphology using multidimensional computed tomography. J Am Coll Cardiol. 2003; 41: 1349-1357. CrossRef PubMed
18. Sra J, Krum D, Okerlund D, Thompson H. Endocardial imaging of the left atrium in patients with atrial fibrillation. J Cardiovasc Electrophysiol. 2004; 27: 247. CrossRef PubMed
19. Sonka M, Fitzpatrick JM, editors. Handbook of Medical Imaging. V.II. Bellingham, WA: SPIE Press; 2000.
20. Mäkela T, Clarysse P, Sipilä O, Pauna N, Pham QC, Katila T, Magnin IE. A review of cardiac image registration methods. IEEE Trans Med Imaging 2002; 21:1011-1021. CrossRef PubMed
21. Luenberger D. Linear and Nonlinear Programming. Reading, MA: Addison-Wesley System, Inc. 1996.
22. Gower JC, Kijksterjuis GB. Procrustes Problems. New York, NY: Oxford University Press; 2004. CrossRef
23. Arun KS, Huang TS, Blostein SD. Least-square fitting of two 3D point sets. IEEE Trans Pat Anal Mach Int. 1987; 9: 698:700.
24. Ben-Haim SA, Osadchy D, Schuster I, Gepstein L, Hayam G, Josephson ME. Nonfluoroscopic, in vivo navigation and mapping technology. Nat Med. 1996; 2: 1393-1395. CrossRef PubMed
25. Solomon SB, Dickfeld T, Calkins H. Real-time cardiac catheter navigation on three-dimensional CT images. J Interv Card Electrophysiol. 2003; 8: 27-36. CrossRef PubMed
26. Wittkampf FH, Wever EF, Derksen R, Wilde AA, Ramanna H, Hauer RN, Robles de Medina EO. LocaLisa: new technique for real-time 3 dimensional localization of regular intracardiac electrodes. Circulation. 1999; 99: 1312-1317.
27. Sra J, Hauck J, Krum D, Schweitzer J. Three-dimensional right atrial geometry construction and catheter tracking using cutaneous patches. J Cardiovasc Electrophysiol. 2003; 14 :897. CrossRef PubMed
28. Peters NS, Jackman WM, Schilling RJ, Beatty G, Davies DW. Human left ventricular endocardial activation mapping using a novel noncontact catheter. Circulation. 1997; 95: 1658-1660.
29. Fahmy TS, Mlcochova H, Wazni OM, Patel D, Cihak R, Kanj M, Beheiry S, Burkhardt JD, Dresing T, Hao S, Tchou P, Kautzner J, Schweikert RA, Arruda M, Saliba W. Natale A. Intracardiac echo-guided image integration: optimizing strategies for registration. J Cardiovasc Electrophysiol. 2007: 18: 276-282. CrossRef PubMed
30. Zhong H, Lacomis JM, Schwartzman D. On the accuracy of CARTOMERGE™ for guiding posterior left atrial ablation in man. Heart Rhythm. 2007; 4: 595-602. CrossRef PubMed
31. Meyer SA, Wolf PD. Registration of three-dimensional cardiac catheter models to single- plane fluoroscopic images. IEEE Trans Biomed Eng. 1999; 46: 1471-1479. CrossRef PubMed
32. Rhode KS, Hill DL, Edwards PJ, Hipwell J, Rueckert D, Sanchez-Ortiz G, Hegde S, Rahunathan V, Razavi R. Registration and tracking to integrate X-ray and MR images in an XMR facility. IEEE Trans Med Imaging. 2003; 22: 1369-1378. CrossRef PubMed
33. Sra J, Narayan G, Krum D, Malloy A, Cooley R, Bhatia A, Dhala A, Blanck Z, Nangia V, Akhtar M. Computed tomography fluoroscopy image integration guided catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2007; 18: 409-414. CrossRef PubMed
34. Shekhar R, Zagrodsky V, Garcia MJ, Thomas JD. Registration of real-time 3-D ultrasound images of the heart for novel 3-D stress echocardiography. IEEE Trans Med Imaging. 2004; 23: 1141-1149. CrossRef PubMed
35. Packer DL, Monahon KH, Peterson LA, Kamp J, Robb R, Valverde A. Integration of multimodality 5D mapping for atrial arrhythmias. Pacing Clin Electrophysiol. 2003; 26: 107.
36. Dickfeld T, Calkins H, Zviman M, Kato R, Meininger G, Lickfett L, Berger R, Halperin H, Solomon SB. Anatomic stereotactic catheter ablation on three dimensional magnetic resonance images in real time. Circulation. 2003; 108: 2407-2413. CrossRef PubMed
37. Schnabel JA, Tanner C, Castellano-Smith AD, Degenhard A, Leach MO, Hose DR, Hill DL, Hawkes DJ. Validation of non-rigid image registration using finite-element methods: application to breast MR images. IEEE Trans Med Imaging. 2003; 22: 238-247. CrossRef PubMed
38. Ohnesorge B, Flohr T, Becker C, Kopp AF, Schoepf UJ, Baum U, Knez A, Klingenbeck-Regn K, Reiser MF. Cardiac imaging by means of electrocardiographically gated multisection spiral CT: initial experience. Radiology. 2000; 217: 564-571.

39. Shechter G, Shechter B, Resar JR, Beyar R. Prospective motion correction of X-ray images for coronary interventions. IEEE Trans Med Imaging. 2005; 24: 441-50. CrossRef PubMed
40. McLeish K, Hill DLG, Atkinson D, Blackall JM, Razavi R. A study of the motion and deformation of the heart due to respiration. IEEE Trans Med Im. 2002; 21: 1142-1150. CrossRef PubMed
41. Noseworthy PA, Malchano ZJ, Ahmed J, Holmvang G, Ruskin JN, Reddy VY. The impact of respiration on left atrial and pulmonary venous anatomy: implication for image-guided intervention. Heart Rhythm. 2005; 2: 1173-1178. CrossRef PubMed

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Sinus Node Dysfunction in Atrial Fibrillation: Cause or Effect?

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Abstract

Atrial fibrillation (AF) and sick sinus syndrome (SSS) are two conditions that frequently coexist. Despite a wealth of available knowledge, the link between these two entities is poorly understood. Whether AF is a harbinger of SSS or whether SSS predisposes to AF has been the subject of much debate. AF results in sinus node remodeling on a cellular and molecular basis that may promote SSS. However, not all patients with atrial fibrillation have SSS. Though "AF begets AF", AF may also beget SSS; and SSS may also beget AF. Multiple studies have demonstrated that sinus node dysfunction may precede the onset of AF. This review will focus on alterations to sinus node structure and function, overdrive suppression, ion channel remodeling, and transient myocardial ischemia as possible mechanisms associated with AF induced SSS. In addition, we will review evidence suggesting that SSS, characterized by a combination of atrial extrasystoles, dispersion of excitability recovery and sinus node ischemia, may lead to AF. Additional factors common to both conditions such as aging and interstitial atrial fibrosis, may explain their coexistence. All this raises many therapeutic challenges associated with the interplay of AF and SSS.

Introduction

A connection between Sick Sinus Syndrome (SSS) and atrial fibrillation (AF) has been recognized in the literature as early as 1960 and is well described by Irené Ferrer[1] in her early classic book on SSS. In this article we will review the evidence supporting AF inducing SND. In addition we will explore the evidence supporting the notion that SND causes and promotes the development of AF.

SSS definition/etiology:

The term SSS was coined by Ferrer in 1968 who grouped together all the anatomic etiologies of sinus node disease (SND).[1] Table1. We will explore how some patients with underlying SND can have coexisting AF either the effect of SND on atria via various mechanisms or via the underlying disease of the atria. SND is frequently associated with AF, forming the basis of the "tachycardia-bradycardia syndrome."[2]

AF definition/etiology

The mechanisms that give rise to AF, whether paroxysmal or chronic have been investigated by many, yet there is still no consensus on many of the physiologic, structural, mechanical or electrical etiologies of AF. Disease of the SN has been implicated as one of the many underlying causes of AF. Table 2. The conceptual framework for understanding AF mechanisms has its groundwork in ideas developed in early twentieth century.[3] The

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concept of the "wavelength of re-entry" developed by Allessie et al emphasized the notion of the size of the wavelength on functional re-entry in his "leading circle" hypothesis.[4] This work experimentally confirmed the hypothesis of Moe et al. of the role of multiple re-entrant wavelets in the perpetuation of AF in animal models.[5] Other theories such as "focal source hypothesis" and "sustained re-entry"[6,7] have also been validated. A role for pulmonary veins drew attention when Haissaguerre et al. reported that rapid activations in the pulmonary veins may be triggering AF.[8] Electrical remodeling is believed to be a central point in perpetuation of AF.

How does SND cause AF?

Atrial extrasystoles:

Our knowledge of the formation of AF is far from complete, but work by Hudson and Laippestad in the early 1960's suggested that damage to the sino-atrial

(SA) node was an important factor.[9,10] When the sinus impulse formation is depressed in the presence of SND, an atrial extrasystole may occur during the slow atrial cycle. Most atrial extrasystoles are followed by a compensatory pause.If there is SND, the pause may be prolonged, allowing other atrial "escape" foci to fire. As stated by Ferrer: "If a dominant pacemaker ceases its activity, or slows its rate below that of a lower pacemaker, the latter will escape and control the cardiac rhythm." [1] In a substrate such as dilated or ischemic atria, any slowing of the SN, either via compensatory pause from extrasystoles or failure of sinus impulse formation, will allow sufficient time for multiple atrial foci to mature and fire. Since the foci are coming from an irritated atrial tissue, they may form frequent, multifocal, or "chaotic" atrial rhythms that frequently herald AF.[11] Early works by Killip and Bennet have shown that in some patients atrial extrasystoles are critical to the initiation of AF and AFL.[12,13]

Re-entry:

SND also may facilitate re-entry. In an atrium with SND early premature impulses originate from areas other than SN. Spach demonstrated regional differences of repolarization in the atrium.[14] He noted that the duration of the longest atrial action potential (ADP) occurs in the area of the SN, with stepwise decrease in ADP as the distance from SN increases. Thus, impulses originating from sites other than the SN lose the protective effect of the long action potential and may result in conduction block and re-entry.[14] Whether from a single circuit or multiple circuits, re-entry has been a dominant conceptual model of AF.[3]

Re-entry is also facilitated by an increase in the dispersion of excitability recovery during sinus bradycardia as reported by Han.[15] According to Han, AF results from non-uniform recovery of excitability.[16] AF may occur whenever there is dispersion of atrial refractoriness. Bradycardia further increases the dispersion of canine atrial refractoriness.[15] A study by Luck et al. confirms that prolonged non-uniform refractoriness and increased dispersion of refractoriness are features of SND in humans.[17] Unfortunately, these features persist even during atrial pacing, reflecting intrinsic atrial

Table 1 Some Causes of Sinus Node Dysfunction.

Some Causes of Sinus Node Dysfunction		
Underlying Heart Disease	**Other Predisposing Factors**	**Reversible Causes**
Coronary artery disease	Friedreich's ataxia	Atrial Fibrillation
Ischemic sino-atrial disease	Muscular Dystrophy	Atrial Flutter
Rheumatic heart disease	Collagen Disease	Acute Ischemia
Dilated cardiomyopathy	Amyloidosis	Pericarditis
Restrictive cardiomyopathy	Hemochromatosis	Myocarditis
Hypertrophic cardiomyopathy	Familial sinoatrial disease Muscular Dystrophy	Pneumonia

disease and possibly explaining why atrial pacing is relatively ineffective at preventing AF. [17]

SN ischemia:

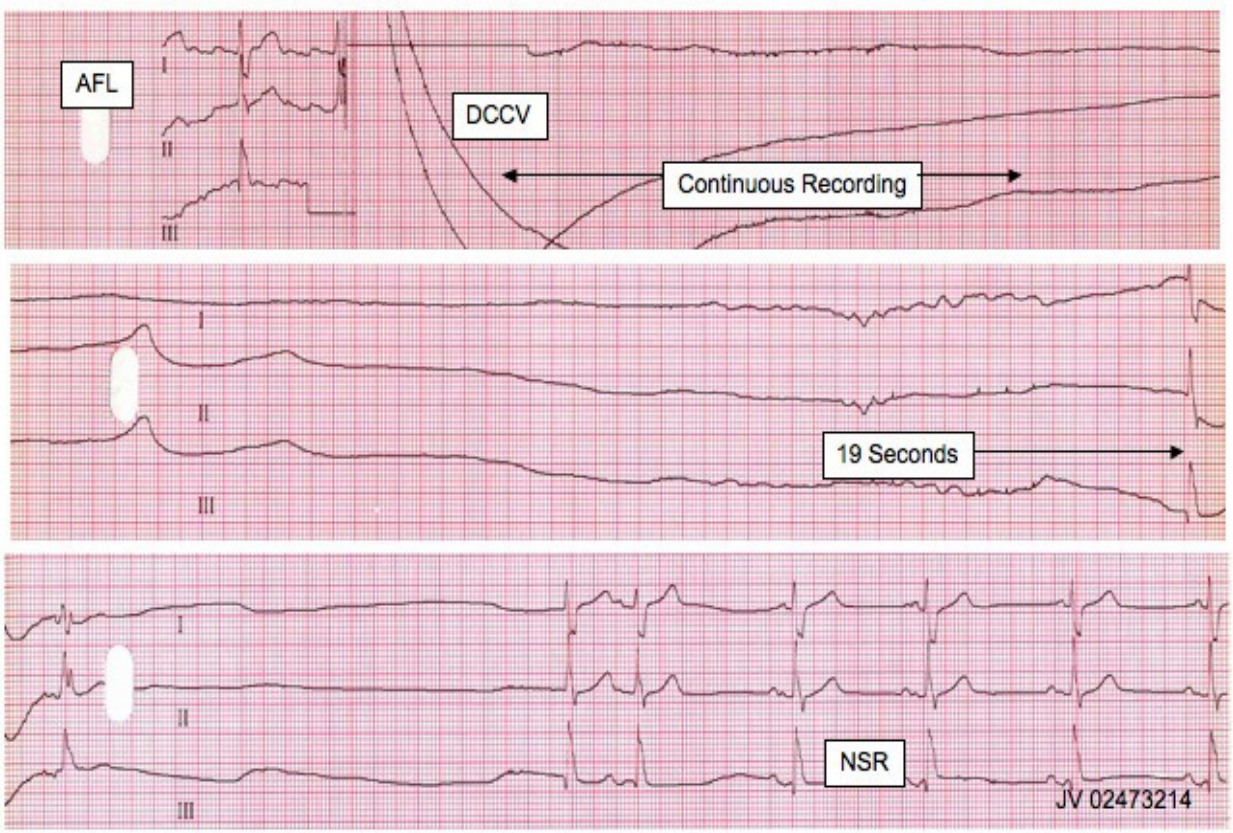
Ischemic damage to the SA node alone, with no other atrial wall disturbances such as fibrosis, stretch or muscle loss may result in chronic atrial fibrillation (CAF). In a pathologic analysis of hearts with chronic and short-term AF, Davies noted that stenosis in the sinus nodal artery was common in patients with CAF.[18] In a study of post CABG patients with AF and sinus rhythm (SR) angiograms showed SA nodal artery disease in 9 out of 25.[19]

Overall, a combination of atrial extrasystoles, shorter atrial ADP, dispersion of excitability recovery and ischemia to the SN itself are mechanisms by which SND may cause and promote AF.

Does AF cause SND?

Many have speculated on the concept that AF itself may alter a normal SN or promote preexisting SND. The concept of one pacemaker dominating the cardiac rhythm of the atria comes into play where AF is believed to shut down the SN by long term overdrive suppression of its activity. Hocini et al. found that patients with PAF and prolonged sinus pauses (>3sec), had improved SN function after ablation. Sinus pauses were thought to be due to long-term suppression of SN activity.[20] Turitto reported a series of patients that demonstrated atrial standstill for up to 12 hours following ablation of long-standing AFL and AF.[21] These findings suggest functional depression of sino-atrial activity. In 2/3 patients, depression was permanent and a pacemaker was needed. In contrast, Palma et al. noted to return to normal sinus function one day following ablation of chronic (25 years) atrial flutter.[22] Prolonged suppression of sino-atrial activity can be attributed to both molecular and cellular mechanisms. Electrical remodeling and AF induced changes in atrial substrate work in concert to alter SN function.

Figure 1: Prolonged asystole following cardioversion, followed by resumption of sinus rhythm. AFL: atrial flutter. DCCV: direct current cardioversion. NSR: normal sinus rhythm.



Atrial Electrical Remodeling

Calcium:

Electrical remodeling can be largely attributed to intracytoplasmic calcium overload within atrial myocytes.[3] Upon initiation of AF, intracellular calcium increases and results in subsequent down-regulation of inward calcium channel current and calcium channel alpha subunit production. Reduced inward calcium current during this electrical remodeling of the atrium also reduces SN impulse formation.[23,24] Ischemia and calcium: Many studies have shown that AF can produce transient myocardial ischemia. In a study by Knoll et al. on myocyte nuclei of ischemic hearts, increased transcriptional activity for sarcoplasmic Ca2+ ATPase, resulted in decreased cytoplasmic Ca2+ concentration, which in turn shortened the ADP.[25]

3 had partial recovery, and 3 had no recovery of diaphragmatic function.

Atrial rate effects:

SAF results in a tenfold increase in atrial rate, initially increasing cellular Ca2+ loading.[24] This threatens cell viability which triggers down regulation of the ICa channel, ultimately decreasing cytoplasmic Ca2+ concentration thereby promoting AF by decreasing the atrial effective refractory period (AERP) and negatively affecting SN impulse formation.[3] Marked reductions in the densities of ICa channel, transient outward K+ current, (Ito) and ultra rapid delayed rectifier K+ current (Ikur) in atrial myocytes from patients in CAF were found in a study by Wagoner.[26] These changes appear to be caused by a reduction in mRNA concentration of the respective channel alpha-subunits[27] and reduction of L-type Ca2+ channel, SR, Ca2+ ATPase mRNA levels in patients with established AF.[28]

SN Electrical Remodeling

BSN electrical remodeling was demonstrated in a dog model using chronic pacing to maintain AF by Elvan and Zipes.[29] In this model, 15 dogs were rapidly paced either in the ventricle or atrium for 2-6 weeks. As compared to controls, dogs with rapid atrial pacing were noted to have prolongation of P wave duration and sinus node recovery times (SNRT), indicating slowed conduction and depressed SN activity. In addition, shortening of AERP and reduced intrinsic heart rate were noted. These changes in the SN promote AF.Further, the duration of inducible AF was increased with atrial pacing compared with control dogs, and those paced only in the ventricle. Perhaps unexpectedly, the duration of AERPs became independent of basic drive cycle length. These findings suggest the existence of atrial memory in these models. We will revisit this concept later in this review. Suppression of SN function following initiation and maintenance of AF supports the notion that AF begets SND.

Table 2 | Causes of Atrial Fibrillation.

Causes of Atrial Fibrillation		
Underlying Heart Disease	**Other Predisposing Factors**	**Reversible Causes**
Coronary artery disease	Hyperthyroidism	ETOH intake
Valvular rheumatic disease	Genetic/Familial	Electrocution
Hypertensive heart disease	Bronchopulmonary disease	Surgery
Dilated cardiomyopathy	Diabetes	Myocardial Infarction
Hypertrophic cardiomyopathy	Congestive Heart Failure	Pericarditis
Restrictive cardiomyopathy	Familial sinoatrial disease Muscular Dystrophy	Pneumonia
Atrial ischemia	Increased left atrial size	Myocarditis
None ("Lone AF")	Autonomic nervous system	Drug-electrolyte abnormalities

There is a wealth of evidence supporting the idea that AF temporarily or permanently affects SN activity.On a short term basis, prolongation of SNRT has been demonstrated following overdrive atrial pacing and has been attributed to the interaction between sino-atrial conduction and recovery of automaticity.[30,31] Hadian et al. demonstrated SNRT prolongation occurring with 10-15 minutes of rapid atrial pacing, consistent with early SN electrical remodeling.[32] Patients with CAF who undergo cardioversion, have an increased prevalence of SND. Such patients were noted to have prolonged SNRTs and delayed intra-atrial conduction times, showing that prevalence of at least temporary sinus nodal dysfunction was high in these patients.[33] In addition, early recurrence of AF is frequently observed.[34]

AF is also associated with significant atrial structural changes.Atrial enlargement in CAF can cause structural changes to the SN affecting its activity. Increased atrial size combined with rapid heart rates predispose to atrial ischemia and further SND.[23,35,36] Rapid ventricular rates during periods of AF may cause transient hemodynamic changes, in turn affecting sympathetic tone. Elvan and Zipes suggest that since AF leads to an increased sympathetic tone ,[29] it in turn affects SN function, since autonomic tone is a major factor in regulation of sino-atrial conduction and SN automaticity.[37, 38, 39] Ischemia, stretch, increased atrial mass and changes in autonomic tone are associated with interstitial fibrosis, connexin disarray, cellular damage and apoptosis of atrial tissue.[23,36] Overall, AF can alter the structure and function of the SN via overdrive suppression, ion channel remodeling, cellular remodeling, transient myocardial ischemia, atrial enlargement and increased sympathetic tone.

CAF and PAF affect sinus nodal function differently

Remodeling:

Electrical remodeling of the atrium and SN may result from prolonged changes in atrial rate.[23] The "Four Time Domains in Adaptation to Heart Rate" proposed by Alessie represent the different adaptative processes by the atria in response to changes in heart rate.[4] Table 3. This simplified scheme describes various levels or remodeling that occur between short term (metabolic- i.e. ion concentrations) and very-long-term (years – i.e. anatomical remodeling, fibrosis and muscle loss) changes to atrial substrate. These time domains help to elucidate pathophysiological differences between atria with PAF and CAF.

Alessie prefers to avoid the term "remodeling" related to short-lived metabolic or electrical changes, and reserves "remodeling" for changes that occur after a period of time when there are changes to structure, cells and ion channels.[4] Others use the term "electrical remodeling" for changes that do not (yet) include structural changes.[25, 32, 40, 41, 42]

CAF:

Autopsy studies have revealed significant changes to atrial structure in patients with CAF consistent

Table 3 | Four Time Domains*.

Causes of Atrial Fibrillation	
Short term changes – metabolic	**Increased/decreased ion concentrations**
(lasts seconds – minutes)	Increased/decreased ion pump activity
Moderate-term changes expression (via electrical remodeling synthesis, hours to days)	Changes in ion channel gene
	Increased/decreased protein
	assembly
Long term –contractile Myocardium remodeling (weeks)	Hibernating myocardium (reversible damage)
Very long term – anatomical Remodeling (months-years)	Structural damage to myocardium (irreversible damage mostly) (scarring, fibrosis, fatty infiltration)

with those described in Alessie's fourth time domain. In a study by Davies, where the hearts of 100 deceased patients with AF were examined, clear pathologic differences between chronic and short-term AF were found.[45] Out of 74 patients with chronic AF 54 had SA node muscle loss. This was in contrast to patients with short-term AF where no muscle loss or damage to the SN, was noted.[46] Thus, in chronic AF, remodeling of the SN occurs at many different levels; altered ion channel gene expression,[25, 40] irreversible structural damage via atrial stretch with increased atrial volume,[35,43,44] and direct damage to the SN via increased metabolic demand accompanied by reduced coronary reserve to the SA nodal artery. [36]

PAF:

Paroxysmal AF has also been implicated as a cause of SN electrical remodeling. In a study by Hadian et al., short-term rapid atrial pacing significantly prolonged sino-atrial conduction time (SACT) and corrected SNRT.[32] A study by Goette et al demonstrated decreased AERP within 30 minutes of rapid pacing without atrial stretch. [41]AF can decrease AERP after ten minutes.[47] Decreases in AERP promote AF by decreasing the reentrant circuit wavelength (wavelength =AERP x CV (conduction velocity)), allowing the atria to accommodate a larger number of functional reentry circuits.[3] These findings were confirmed by Yue et al who noted a decrease in L-type Ca^2 current and Ca^2-independent transient outward current (Ito) in the atria during rapid atrial pacing.[48] Such short term changes in outward calcium current decrease atrial refractoriness and further promote AF.Dynamic decreases in atrial refractoriness were observed in all patients with PAF suggesting that electrical remodeling developed regardless of baseline AERPs.[42] These short term changes fall into Time Domains 1 and 2, and may be reversible over a short period of time.

Atrial memory and short term atrial electrical remodeling.

Memory has been described as a "specialized form of remodeling…induced by a preceding period of altered electrical activation." [49] One would then expect AF or rapid atrial pacing to induce atrial memory effects. In a study by Morillo, sustained AF could not be induced by electrical stimulation in dogs at baseline.[35] After rapid pacing (400 bpm) for 6 weeks, AF was readily inducible by 1-3 extrastimuli.These findings suggest that atrial memory or atrial electrical remodeling predispose to AF. [35] Duration of inducible AF was increased in paced dogs, while AERPs became independent of the basic drive cycle length.[29] Left atrial (LA) pacing in mongrel dogs was associated with a decreased atrial gradient (the root mean square of three P-Ta voltage time integrals) and with occurrence of atrial tachycardias during pacing, that persisted during recovery from pacing.[50] This suggests that altering the atrial activation sequence induces atrial memory, without altering the AERP. In another study by Herweg et al. displacement of the atrial gradient vector occurred during recovery from LA pacing, was more marked at rapid pacing rates, and manifested accumulation and resolution consistent with atrial cardiac memory. [51] Changes observed during recovery from LA pacing appeared to affect repolarization primarily and were expressed electrographically as an altered P-Ta voltage-time integral.[51] As stated by Goyal, changes in repolarizing currents and AP durations are elements of atrial memory.[52] After electrical or drug cardioversion, AF vulnerability remains high, with single premature beats re-inducing drug-cardioverted AF and frequent recurrence for 1-2 days after electrical cardioversion. [53,54] These observations of AF recurrence after cardioversion or short term pacing of the LA are all suggestive of atrial memory. Still, others doubt that atrial memory has been demonstrated, looking at AERP changes rather than P-Ta voltage-time integrals.[55]

Sinus node recovery: is it influenced by the duration of AF, reversible with arrhythmia termination, or doomed from the start of arrythmia?

While electrical remodeling has been shown to occur in both CAF and PAF, the SN has been studied for its propensity for reverse electrical remodeling. The duration of AF is an important predictor of the restoration of sinus rhythm by direct cardioversion.[56] Differences between SN electrical remodeling in chronic versus paroxysmal atrial fibrillation have been studied. In one paper, comparing patients undergoing left atrial catheter ablation for CAF and PAF, CAF was associated with slower reverse electrical remodeling.[42] Patients with PAF had shorter AERPs following AF termination as

compared to baseline. In this patient group AERP returned to baseline within five minutes. In patients with CAF, both AERP's and SNRT's were shortened, but it took up to three weeks to return to baseline duration.[42] Another study by Raitt et al. noted that AERP varies significantly at the lateral right atrium, as compared to the proximal and distal coronary sinus.[57] They concluded that electrical remodeling occurs at different rates in different regions of the atrium, which could be a possible trigger for future atrial arrhythmia.[57]

WAforementioned studies on canine atrial memory also noted differential findings between the left and right atria and demonstrated "memory" of atrial arrhythmia in the left atrium only. Also, it may be interpreted that the SN may be more likely to recover, as a RA structure, with less atrial memory/remodeling present than the LA. These findings may also explain why the left atrium is the major focus of catheter ablation in patients with recurrent AF. In a study by Hocini et al twenty patients with PAF and prolonged sinus pauses (>3 seconds) were ablated and resulted in significant reverse remodeling of SN function with increase in heart rate, heart rate range, maximal heart rate and decreased SNRT.[20] The extent of damage to the SN, whether from ischemia or chronic atrial arrhythmia may determine its reversibility of function. A study by Waris et al. showed that if the SN has sustained only partial damage to its structure, it is more likely to recover after DC cardioversion even after years of AF.[58]

In another study by Daoud et al., progressive recovery of SNRT and P wave amplitude T were observed in patients with chronic AF only after 14 days and much more after 3 months post ablation.[47] For some individuals, duration of AF/AFL may not be critical: in a case report by Palma et al. SN function was noted to return to normal one day following ablation of chronic (25 years) atrial flutter.[22] Finally, recovery of SN function has been demonstrated in patients with CAF following the surgical maze procedure, where SND disappeared after 12 months[59] and SN response to exercise returned after 6 months after Maze procedure.[60] The recovery of SN function again raises "chicken or the egg" questions. Is the SN more likely to recover if it was not damaged prior to the arrhythmia? Given that some AF terminations reveal SN dysfunction, can it be that AF developed as a "rescue" mechanism to SND and by terminating the AF, the underlying SN disease is now uncovered? We have seen that SN function normalizes in some patients after years of AF, so AF does not always cause lasting damage to the SN. Yet in others atrial enlargement in CAF causes irreversible structural changes to the SN.

Clinical Correlations

Studies of electrical remodeling and cardiac memory help to elucidate the relationship between AF and SSS. However more information is required to understand the link between these two entities. Evidence reviewed above supports the notion that AF results in SN remodeling on a cellular and molecular basis and may cause SND.[23, 25, 32,36, 40, 41] However not all patients with AF have SSS, and many present with SSS prior to developing AF. Animal models of SSS clearly demonstrate that SND can presage the onset of AF. [61] Ultimately, factors common to both conditions such as aging and interstitial atrial fibrosis, may explain their coexistence.

Treatment of patients presenting with both AF and SSS (tachycardia-bradycardia syndrome) is particularly challenging. One can divide patients into three main groups: 1) patients with AF and reversible SND; 2) patients with AF and permanent SND requiring pacemaker implantation, and 3) patients with AF who have reversible SND but are not candidates for rhythm control therapy. Patients with permanent SSS will clearly benefit from pacemaker (PPM) implantation and medical therapy. The difficult task will be predicting which patients have "permanent" SSS following eradication of AF.
Our review raises many unanswered questions that relate to patient management.

Conclusions:

1.Sinus node dysfunction in atrial fibrillation: cause or effect? Chicken or egg? Can be both or either.
2.Could it be that SND gives rise to PAF, and then via process of electrical remodeling or atrial memory, PAF promotes itself to CAF and in turn worsens the SN function? AF begets AF? Yes!

3.Could the two processes be coexistent, since many of the structural abnormalities and etiologies of both are similar? Yes!
4.Could AF be the rescue mechanism of SN after all? Yes!
5.Can management of one worsen the other? (maze, ablations that worsen SN function, antiarrhythmic medications, and pacemakers that may induce AF?). Yes!

References

1. Ferrer, MI. The Sick Sinus Syndrome. Futura Publishing Company, 1974. "
2. Ferrer MI. The sick sinus syndrome in arial disease. JAMA. 1968; 206: 645-646. CrossRef PubMed
3. Nattel S. New Ideas about atrial fibrillation 50 years on. Nature 2002; 415: 219-226. CrossRef PubMed
4. Allessie MA. Atrial electrophysiologic remodeling :Another vicious circle? J Cardiovasc Electrophysiol 1998; 9: 1378-1393. CrossRef PubMed
5. Moe G.K. Rheinboldt, WW.C. and Abildskov, J.A. A computer model of atrial fibrillation. Am Heart J 1964; 67: 200-220. CrossRef PubMed
6. Prinzmetal M, Corday E, Brill IC, Sellers AL, Oblath RW, Flieg WA, Kruger HE. Mechanism of the auricular arrhythmias. Circulation 1950; 1(2): 241-245."
7. Jalife J, Berenfeld O, Skanes A, Mandapati R. Mechanisms of atrial fibrillation: Mother rotors or multiple daughter wavelets, or both ? J Cardiovasc Electrophysiol 1998; 9: S2-S12. CrossRef CrossRef PubMed
8. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, LeMatayer P, Clementy J. Spontaneous initiation of atrial fibrillation by actopic beats originating in the pulmonary veins. N Engl J Med 1998; 339: 659-666. CrossRef PubMed
9. Hudson, RE B Cardiovascular Pathology. Edward Arnold, London, 1965."
10. Lippestad CT, Marton, PF. Sinus arrest in proximal right coronary artery occlusion. Am Heart J 1967; 74: 551-556. CrossRef PubMed
11. Topol EJ. Textbook of Cardiovascular Medicine. 3rd Ed., Lippincott Williams &Wilkins. Philadelphia. 2007; 37-44."
12. Killip T, Gault JH. Mode of onset of atrial fibrillation in man. Am Heart J 1965; 70: 172-179 CrossRef PubMed
13. Bennet MA, Pentecost BL. The pattern of onset and spontaneous cessation of atrial fibrillation in man. Circulation 1970; 41: 981-988."
14. Spach MS, Dolber PC, Aderson PS. Multiple regional differences in cellular properties that regulate repolarization and contraction in the right atrium of adult and newborn dogs. Circ Res 1989; 65(6): 1594-1611."
15. Han J, Miller D, Chizzonitti B, Moe GK. Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate. Am Heart J 1966; 71: 481-487. CrossRef PubMed
16. Han J. The concepts of reentrant activity responsible for ectopic rhythms. Am J Cardiol 1971; 28: 253-262. CrossRef PubMed
17. Luck JC, Engel TR. Dispersion of atrial refractoriness in patients with sinus node dysfunction. Circulation 1979; 60(2): 404-412."
18. Davies MJ, Pomerance A. Pathology of atrial fibrillation in man. Br Heart J 1972; 34: 520-525. 19. Kolvekar S., D'souza A, Akhtar P, Reek C, Garratt C, Spyt T. Role of atrial ischaemia in development of atrial fibrillation following coronary artery bypass surgery. Eur J Cardiothorac Surg 1997; 11(1): 70-75. CrossRef PubMed
20. Hocini M, Sanders P, Deisenhofer I, Jais P, Hsu LF, Scavee C, Weerasoriya R, Raybaud F, Macle L, Shah D, Garrigue S, LeMetayer P, Clementy J, Haissaguerre M. Reverse remodeling of sinus node function after catheter ablation of atrial fibrillation in patients with prolonged sinus pauses. Circulation 2003; 108: 1172-1175. CrossRef PubMed
21. Turitto G, Saponieri C, Onuora A, El-sherif N. Prolonged transient atrial electrical silence following termination of chronic atrial tachyarrhythmias. Pacing Clin Electrophysiol 2007; 30: 1311-1315. CrossRef PubMed
22. Palma EC, Pugazhendi V, Ferrick K, Gross J, Kim SG, Fisher JD. Sinus node recovery after 25 years of atrial flutter. Pacing Clin Electrophysiol 2001; 24: 1295-1296. CrossRef Kirchhof CJ, Dorland R, Allessie MA" . Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995; 92: 1954-1968.
23. Wijffels M, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995; 92: 1954-1968. "
24. Sun H, Chartier D, Leblanc N, Nattel S. Intracellular calcium changes and tachycardia-induced contractile dysfunction in canine atrial myocytes. Cardioavasc Res 2001; 49: 751-761. CrossRef PubMed
25. Knoll R, Arras M, Zimmerman R, Schaper J, Schaper W. Changes in gene expression following short coronary occlusions studied in porcine hearts with run-on assays. Cardiovasc Res 1994; 28: 1062–1069. CrossRef PubMed
26. Van Wagoner DR, Nerbonne JM. Molecular basis of electrical remodeling in atrial fibrillation. J Mol Cell Cardiol 2000; 32: 1101-1117. CrossRef PubMed, De Langen C, Van Gelder IC, de Kam PJ, Grandjean J, Bel KJ, Wijffels MC, Allessie MA, Crijns HJ. Verapamil reduces tachycardia-induced electrical remodeling of the atria. Circulation" 1997; 95(7): 1945-1953.
28.27. Tieleman RG, De Langen C, Van Gelder IC, de Kam PJ, Grandjean J, Bel KJ, Wijffels MC, Allessie MA, Crijns HJ. Verapamil reduces tachycardia-induced electrical remodeling of the atria. Circulation 1997; 95(7): 1945-1953. , Xu GJ, Shabiti Y, Yunus K, Abutirehemen M, Cheng ZH. Alterations in gene expression of calcium handling proteins in patients with chronic atrial fibrillation. Zhongguo Yi Xue Ke Xue Yuan Xue Bao (Yes, that is the journal name-au)." 2007; (5): 642-646.
28. Tang BP, Xu GJ, Shabiti Y, Yunus K, Abutirehemen M, Cheng ZH. Alterations in gene expression of calcium handling proteins in patients with chronic atrial fibrillation. Zhongguo Yi Xue Ke

Xue Yuan Xue Bao (Yes, that is the journal name-au). 2007; (5): 642-646. "
29. Elvan A, Wylie K, Zipes D. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs. Circulation 1996; 94: 2953-2960."
30. Steinbeck G, Haberl R, Luderitz B. Effects of atrial pacing on atrio-sinus conduction and overdrive suppression in the isolated rabbit sinus node. Circ Res 1980; 46: 859-869. 31 Gomes JA, Harlman RL, Chowdry IA. New application of direct sinus node recordings in man: assessment of sinus node recovery time. Circulation 1984; 70: 663-671."
32. Hadian D, Zipas DP, Olgin JE, Miller JM. Short-term rapid atrial pacing produces electrical remodeling of sinus node function in humans. J Cardiovasc Electrophysiol 2002; 13: 584-586. CrossRef PubMed
33. Kumagai K, Akimitsu S, Kawahira K, Kawanami F, Yamanouchi Y, Hiroki T, Arakawa K. Electrophysiological properties in chronic lone atrial fibrillation. Circulation 1991; 84: 1662-1668."
34. Akyurek O, Sayin T, Dincer I, Karaoguz R, Guldal M, Oral D. Lengthening of intraatrial conduction time in atrial fibrillation and its relation with early recurrence of atrial fibrillation. Jpn Heart J2001; 42(5): 575-84. CrossRef PubMed
35. Morillo CA, Klein GJ, Jones DL, Guiraudon CL. Chronic rapid atrial pacing: Structural, functional and electrophysiologic characteristics of a new model of sustained atrial fibrillation. Circulation 1995; 91: 1588-1595."
36. White C, Holida M, Marcus M. Effects of acute atrial fibrillation on the vasodilator reserve of the canine atrium. Cardiovasc Res 1986; 20: 683-689. CrossRef PubMed
37. Zipes DP, Mihalick M, Robbins GT. Effects of selective vagal and stellate ganglion stimulation on atrial refractoriness. Cardiovasc Res 1974; 8: 647-655 CrossRef PubMed
38. Schuessler RB, Bromberg BI, Boineau JP. Effect of neurotransmitters on the activation sequence of the isolated right atrium. Am J Physiol 1990; 258: H1632-H1641."
39. Smeets JLRM, Allessie MA, Lammers WJEP, Bonke FIM, Hollen J. The wavelength of the cardiac impulse and reentrant arrhythmias in isolated rabbit atrium. Circ Res 1986; 58: 96-108."
40. Akao M, Otani H, Horie M, Takano M, Kuniyasu A, Nakayama H, Kouchi I, Murakami T, Sasayama S. Myocardial ischemia induces differential regulation of KATP channel gene expression in rat hearts. J Clin Invest 1997; 100: 3053–3059. CrossRef PubMed, Kuniyasu A, Nakayama H, Kouchi I, Murakami T, Sasayama S" . Myocardial ischemia induces differential regulation of KATP channel gene expression in rat hearts. J Clin Invest 1997; 100: 3053–3059.
41. Goette A, Honeycutt C, Langberg JJ. Electrical remodeling in atrial fibrillation. Time course and mechanisms. Circulation 1996; 94(11): 2968-2975."
42. Sparks PB, Jayaprakash S, Vohra JK, Kalman JM. Electrical remodeling of the atria associated with paroxysmal and chronic atrial flutter. Circulation 2000; 102: 1807-1813."
43. Boyden PA, Hoffman BF. The effects of atrial electrophysiology and structure of surgically induced right atrial enlargement in dogs. Circ Res 1981; 49: 1319-1331."
44. Boyden PA, Tilley LR, Pham D, Liu SK, Fenoglic JJ Jr, Wit AL. Effects of left atrial enlargement on atrial transmembrane potentials and structure in dogs with mitral valve fibrosis. Am J Cardiol 1982; 49: 1896-1908. CrossRef PubMed, Fenoglic JJ Jr, Wit AL" . Effects of left atrial enlargement on atrial transmembrane potentials and structure in dogs with mitral valve fibrosis. Am J Cardiol 1982; 49: 1896-1908.
45. Davies M.J. and Pomerance A. Pathology of atrial fibrillation in man. Br Heart J 1972; 34: 520-525. CrossRef
46. Sih HJ, Zipes DP, Berbari EJ, Adams DE, Olgin JE. Differences in organization between acute and chronic atrial fibrillation in dogs. J Am Coll Cardiol 2000; 36(3): 924-931. CrossRef PubMed, Zipes DP, Berbari EJ, Adams DE, Olgin JE" . Differences in organization between acute and chronic atrial fibrillation in dogs. J Am Coll Cardiol 2000; 36(3): 924-931.
47. Daoud EG, Weiss R, Augostini RS, Kalbfleisch SJ, Schroeder J, Polsinelli G, Hummel JD. Remodeling of sinus node function after catheter ablation of right atrial flutter. J Cardiovasc Electrophysiol 2002; 13: 20-24. CrossRef PubMed
48. Yue L, Feng J, Gaspo R, Li GR, Wang Z, Nattel S. Ionic remodeling underlying action potential changes in canine model of atrial fibrillation. Circ Res 1997; 81: 512-525."
49. Patberg KW, Shvilkin A, Plotnikov AN, Chandra P, Josephson M, Rosen MR. Cardiac memory: Mechanisms and clinical implications. Heart Rhythm 2005; 2(12): 1376-1382. CrossRef PubMed
50. Chandra P, Rosen TS, Herweg B, Danilo P, Rosen MR. Left atrial pacing induces memory and is associated with atrial tachyarrhythmias. Card Res 2003; 60: 307-314. CrossRef PubMed
51. Herweg B, Chang F, Chandra P, Danilo P, Rosen M. Cardiac memory in canine atrium. Identification and implications. Carculation 2001; 103: 455-461."
52. Goyal R, Morady F. Atrial cardiac memory: Fact or Fiction? J Electrocardiol 1998; 30: 27. CrossRef PubMed
53. Allessie MA, Wijffels MC, Dorland R. Mechanisms of pharmacologic cardioversion of atrial fibrillation by Class I drugs. J Cardiovasc Electrophysiol 1998; 9(8 Suppl): S69-77., Wijffels MC, Dorland R. Mechanisms of pharmacologic cardioversion of atrial fibrillation by Class I drugs. J Cardiovasc Electrophysiol" 1998; 9(8 Suppl): S69-77.
54. Tieleman RG, Man Gelder I, Crijns HJGM Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodeling of the atria? J Am Coll Cardiol 1998; 31: 167-173. CrossRef PubMed
55. Vollmann D, Blaauw Y, Neuberger HR, Schotten U, Llessie M. Long-term changes in sequence of atrial activation and refractory periods: NO evidence for "atrial memory". Heart Rhythm 2005; 2: 155-161. CrossRef PubMed
56. Van Gelder IC, Crijns HJ, Verwer R, Lie KI. Prediction of uneventful cardioversion and maintenance of sinus rhythm from direct-current electrical cardioversion of chronic atrial fibrillation and flutter. Am J Cardiol 1991; 68: 41-46. CrossRef PubMed
57. Raitt MH, Kusumoto W, Giraud G, McAnulty GH. Reversal of electrical remodeling after cardioversion of persistent atrial fibrillation. J Cardiovasc Electrophysiol 2004; 15: 507-512."
58. Waris E., Kreus K. E., and Salokannel J. Factors influencing persistence of sinus rhythm after DC shock treatment of atrial fibrillation. Acta Med Scand, 1971; 189: 161-166."

59. Pasic M, Musci M, Niniawski H, Edelmann B, Tediriya T, Hetzer R. Transient sinus node dysfunction after the cox-maze III procedure in patients with organic heart disease and chronic fixed atrial fibrillation. J Am Coll of Cardiol 1998; 32(4): 1040-1047. CrossRef PubMed
60. Tamai J, Kosakai Y, Yoshioka T, Ohnishi E, Takaki H, Okano Y, Kawashima Y. Delayed improvement in exercise capacity with restoration of sinoatrial node response in patients after combined treatment with surgical repair for organic heart disease and the Maze procedure for atrial fibrillation. Circulation. 1995; 91(9): 2392-2399., Kosakai Y, Yoshioka T, Ohnishi E, Takaki H, Okano Y, Kawashima Y. Delayed improvement in exercise capacity with restoration of sinoatrial node response in patients after combined treatment with surgical repair for organic heart disease and the Maze procedure for atrial fibrillation. 1995; 91(9): 2392-2399.
61. Stieber J, Wieland K, Stockl G, Ludwig A, Hofmann F. Bradycardic and proarrhythmic properties of sinus node inhibitors. Mol Pharm 2006; 69(4): 1328-1337. CrossRef PubMed

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Impact of Smoking on the Atrial Substrate Characteristics in Patients with Atrial Fibrillation

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Introduction

Cigarette smoking is a common health issue throughout the world. It can cause the development of various major diseases, such as chronic obstructive pulmonary disease (COPD),[1] most cardiovascular diseases and many types of cancer. Thus, people with a tobacco habit can produce devastating health consequences for themselves. At present, there are about five million people that die annually, which can be attributed to cigarette smoking, and half of those deaths, which are mortalities from smoking, always occur in middle age.[2] Therefore, how to reduce cigarette smoking remains the most important work to avoid the causes of health disabilities and premature death.

Cardiopulmonary Effect of Smoking

It is well known that smoking is an important risk factor for chronic bronchitis, COPD[3] and can accelerate the decline in the pulmonary function.[4] The incidence of atrial flutter (AFL) increased 1.9 times in those with COPD.[5] On the other hand; many studies have well established the evidence of smoking's effect on coronary risk. Smoking, even at a light level, can have a major impact on coronary and peripheral vascular disease.[6] Cigarette smoke is a complex mixture containing several ingredients that have the adverse effects of accelerating atherosclerotic progression and atherothrombosis, by increasing the platelet adhesiveness[7] and serum fibrinogen levels,[8] and decreasing the high density lipoprotein cholesterol levels.[9] It also increases the heart rate, blood pressure, sympathetic tone and consumption of oxygen by the heart muscle. When a healthy person smokes a cigarette, the coronary blood flow must increase to meet the increased demand.[10] In the presence of coronary-artery stenosis, the coronary flow can not increase and ischemia may develop, with resultant angina pectoris or myocardial dysfunction.[11,12] Recently, Barua RS, et al. demonstrated that smoking could cause dysfunction of the nitric oxide biosynthesis in endothelium cells by oxdative stress[9] and that mechanism may further impair the endothelium-dependent coronary artery dilatation capability and reduce the myocardial oxygen supply.

Smoking and Cardiac Arrhythmias

Nicotine may be a precipitating factor of cardiac arrhythmias due to a marked elevation in the serum catecholamine concentration, heart rate, and blood pressure; production of coronary spasms; and increased myocardial oxygen consumption with a reduction in the myocardial oxygen supply.[10-14] Cigarette consumption is directly related to increased rates of sudden cardiac death (SCD), mainly through its direct toxic effects. Recently, the impact of the smoking status on SCD was studied in patients with established coronary artery

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disease (CAD).[15] In that study, current cigarette smoking was a powerful independent predictor of the SCD risk and those that quit smoking experienced a significant reduction in the SCD risk. Other studies, such as The CAST experience[16] also had the same results, which showed a marked reduction in arrhythmic death and overall mortality with the cessation of smoking.

In 1997, Mehta et al. reported that high levels of serum nicotine may be a possible cause of cardiac arrhythmias in dogs with a dose-dependent arrhythmogenicity.[17] There were only three sporadic case reports in humans[19-20] and suggested that high serum nicotine levels at the time the patient developed his first episode of atrial fibrillation may have had a causal relationship. Recently, one substudy of the Multicenter Automatic Defibrillator Implantation Trial-II revealed continued cigarette smoking was associated with an increased risk of rapid supraventricular arrhythmias.[21] Other studies have shown that nicotine administration could produce action potential alterations that could predispose to decremental conduction and hence, to a conduction disturbance.[22] Nicotine administration, in addition, can also enhance the automaticity. A combination of enhanced automaticity with a simultaneous depression of the conduction favors the initiation of a number of arrhythmias. A previous study demonstrated that chronic exposure to nicotine promotes the occurrence of atrial flutter (AFL) in dogs with a myocardial infarction (MI).[23] They also found a nicotine-induced increase in the atrial interstitial fibrosis in dogs with an MI. The occurrence of increased atrial interstitial fibrosis and a flattened electrical restitution are important substrates for AFL.

Impact of Smoking on Atrial Substrates

Our previous study and other investigators have demonstrated a wide area of low voltage zones (LVZs) in patients with atrial fibrillation (AF) and AFL.[24,25] Previous studies have found that the prolonged administration of nicotine was associated with a loss of intracellular K+ and the new appearance of cardiac necrosis.[26] So, smoking may theoretically change the substrate properties causing an attenuation of the atrial voltage and perpetuate the atrial tachycardia, especially in patients with typical AFL. This concept had been proven in animal study by Chen PS et al. who reported nicotine could increase the atrial interstitial fibrosis in dogs with a myocardial infarction.[23] In humans, one recent report had demonstrated that cigarette smoking contributed to the development of atrial fibrosis via nicotine in patients with CAD.[27] Previous studies had shown that atrial fibrosis can provide an arrhythmogenic substrate, which may increase the likelihood of the occurrence of atrial arrhythmias. Our group first reported the impact of smoking on the right and left atrial (RA, LA) substrates.[28] We found that the mean peak-to-peak bipolar voltage of the RA was lower in the patients with a previous history of smoking than in those without a history of smoking, but there was a similar mean peak-to-peak bipolar voltage in the LA. Further, the total activation time of the RA was longer in the patients with a previous history of smoking, than in those without a history of smoking, but that was not the case in the LA. Furthermore, the voltage reduction in the RA was related to the smoking intensity-duration in the patients with a history of smoking. In contrast to the mean peak-to-peak voltage, the voltage reduction in the LA was weakly correlated to the smoking intensity-duration.

Clinical Implications concerning the Management of AF

Several studies have clearly demonstrated that the atrial substrate is an important factor for perpetuating atrial arrhythmias.[24,25,29] Substrate changes themselves may increase the difficulty in successfully terminating AF during radiofrequency catheter ablation. Thus, more delicate procedures during AF ablation may be needed in patients that smoke and have large substrate changes. Second, continuing smoking has been proven to be an important risk factor for increasing SCD[15,16] and tachyarrhythmias in patients with implantable cardiovector defibrillators. Therefore, cessation of smoking should be encouraged in patient with AF, no matter whether they receive an invasive procedure to treat their AF or not.

Conclusion

Cigarette smoking can change the atrial substrate with a dose dependent effect, especially in the RA and that substrate change may perpetuate atrial tachyarrhythmias. However, the risk of smoking in patients with AF was low, as reported in the

Framingham Heart Study.[30] Thus, the causal relationship between smoking and AF still remains unclear. The mechanism involved in that deserves further study.

References

1. UA Surgeon General. The health consequences of smoking: Chronic obstructive pulmonary disease. Washington, DC: US department of health and Human services, 1984, Pub. No 84-50205.

2. Benowitz NL. Clinical Pharmacology of Nicotine: Implications for Understanding, Preventing, and Treating Tobacco Addiction. Clin Pharmacol Ther. 2008;83(4):531-41. Epub 2008 Feb 27. PubMed

3. Fletcher CM, peto R. The natural history of chronic airflow obstruction. BMJ 1977; 1:1645-1648.

4. Pelkonen M, Notkola I-L, Tukiainen H ea al. Smoking cessation, decline in pulmonary function and total mortality: a 30 year follow up study among the Finish cohorts of Seven Countries Study. Thorax 2001; 56:703-707.CrossRef PubMed

5. Granada J, Uribe W, Chyou PH, Massen K, Vierkant R, Snith PN, Hayes J, Eaker E, and Vidaillet H. Incidence and predictors of atrial flutter in the general population. J Am Coll Cardiol 2000; 36:2242-2246.(2)

6. Prescott E, Scharling H, Osler M, Schnohr P: Important of light smoking and inhalation habits on risk of myocardial infarction and all cause mortality: A 22 year follow up of 12,149 men and women in The Copenhagen City Heart Study. J Epidemiol Community Health 2002; 56:702-706.PubMed

7. Fuster V, Chesebro JH, Frye RL, Elveback LR. Platelet survival and the development of coronary disease in the young adult: effects of cigarette smoking, strong family history and medical therapy. Circulation 1981; 63:546-551.

8. Billimoria J, Pozner H, Metselaar B, Best FW, James DC. Effect of cigarette smoking on lipids, lipoproteins, blood coagulation, fibrinolysis and cellular components of human blood. Atherosclerosis 1975; 21:61-76.CrossRef PubMed

9. Criqui MH, Wallace RB, Heiss G, Mishkel M, Schonfeld MD, Jones GTL. Cigarette smoking and plasma high-density liproportein cholesterol: the Lipid Research Clinics Program prevalence study. Circulation 1980; 62 Suppl IV:70-76.

10. Nicod P, Rehr R, Winniford MD, Campell WB, firth BG, Hillis LD. Acute systemic and coronary hemodynamic and serologic responses to cigarette smoking in long-term smokers with atherosclerotic coronary artery disease. J Am Coll Cardiol 1984; 4:964-971.

11. Aronow WS, Cassidy J, Vangrow JS, March H, Kern JC, Goldsmith JR, Khemka M, Pagano J, Vawter M. Effect of cigarette smoking and breathing carbon monoxide on cardiovascular hemodynamics in anginal patients. Circulation 1974; 50:340-347.

12. Jain AC, Bowyer AF, Marshall RJ, Asato H. Left ventricular function after cigarette smoking by chronic smokers: comparison of normal subjects and patients with coronary artery disease. Am J Cardiol 1977; 39:27-31CrossRef PubMed

13. Barua RS, Ambrose JA, Srivastava S, DeVoe MC, Eales-Reynolds L-J. Reactive oxygen species are involved in smoking-induced dysfunction of nitric oxide biosynthesis and upregulation of endothelial cells. Circulation 2003; 107:2342-2347.CrossRef PubMed

14. Sugishi M, Faminaro T. Cigarette smoking is a major risk for coronary spasm. Circulation. 1993; 87:76-79.

15. Goldenberg I, Jonas M, Tenenbaum A, Boyko V, Matetzky S, Shotan A, Behar S, Reicher-Reiss H, for the Bezafibrate Infarction Prevention Study Group. Arch Intern Med. 2003; 163:2301-2305. CrossRef PubMed

16. Feters RW, Brooks MM, Todd L, Liebson PR, Wilhelmsen L, for the Cardiac Arrhythmia Supression Trial (CAST) investigators. Smoking cessation and arrhythmic death: the CAST experience. J Am Coll Cardiol. 1995; 26:1287-1292.CrossRef PubMed

17. Mehta MC, Jain AC, Mehta A, Billie M. Cardiac arrhythmias following intravenous nicotine: experimental study in dogs. J cardiovasc Pharmacol Ther 1997; 2:291-298.CrossRef PubMed

18. Stewart PM, Catterall JR. Chronic nicotine ingestion and atrial fibrillation. Br Heart J 1985; 54:222-223.CrossRef

19. Rigotti NA, Eagle KA. Atrial fibrillation while chewing nicotine gum [letter] JAMA 1986; 255:1018.CrossRef PubMed

20. Choragudi NL, Aronow WS, DeLuca AJ. Nicotine Gum-induced atrial fibrillation. Heart Dis 2003; 5:100-101.CrossRef PubMed

21. Goldenberg I,Moss AJ,McNitt S,Zareba W,Daubert JP,Hall WJ,Andrews ML,Multicenter Automatic Defibrillator Implantation Trial-II Investigators. Cigarette Smoking and the Risk of Supraventricular and Ventricular Tachyarrhythmias in High-Risk Cardiac Patients with Implantable Cardioverter Defibrillators. J Cardiovasc Electrophysiol 2006; 17:931-6.CrossRef PubMed

22. Greenspan K, Edmands RE, Knoebeb SB, Fisch C. Some effect of nicotine on cardiac automaticity, conduction, and inotropy. Arch Intern Med 1969; 123:707-712.CrossRef PubMed

23. Miyauchi M, Qu Z, Miyauchi Y, Zhou SM, Pak H, Mandel WJ, Fihbein FP, Chen PS and Karagueuzian HS. Chronic nicotine in hearts with healed ventricular myocardial infarction promotes atrial flutter that resembles typical atrial flutter. Am J Physiol Heart circ Physio 2005; 288:H2878-H2886.(3)

24. Lin YJ, Tai CT, Huang JL, Lee KT, Lee PC, Hsieh MH, Lee SH, Higa S, Yuniadi Y, Liu TY, Chen SA. Characterization of right atrial substrate in patients with supraventricular tachyarrhythmias. J Cardiovasc Electrophysiol 2005; 16:173-180.CrossRef PubMed

25. Verma A, Wazni OM, Marrouche NF, Martin DO, Kilicaslan F, Minor S, Schweikert RA, Saliba W, Cummings J, Burkhardt JD, Bhargava M, Besden WA, Abdul-Karim A, Natale A. Pre-Existent left atrial scarring in patients undergoing pulmonary vein antrum isolation. J Am Coll Cardiol 2005; 45:285-292.CrossRef PubMed

26. Wenzel DG, Stark LG. Effect of nicotine on cardiac necrosis induced by isoproterenol. Am Heart J 1966; 71:368-370.CrossRef PubMed

27. Goette A, Lendeckel U, Kuchenbecker A, Bukowska A, Peters B, Klein HU, Huth C, Rocken C. Cigarette smoking induces atrial fibrosis in humans via nicotine. Heart 2007; 93:1056-1063.CrossRef PubMed

28. Tuan TC,Chang SL,Tai CT,Lin YJ,Hu YF,Lo LW,Wongcharoen W,Udyavar AR,Chiang SJ,Chen YJ,Tsao HM,Ueng KC,Chen SA. Impairment of the atrial substrates by chronic cigarette smoking in patients with atrial fibrillation. J Cardiovasc Electrophysio. 2008; 19(3):259-265.CrossRef PubMed

29. Sanders P, Morton JB, Kistler SJ, Spence SJ, Davidson NC, Hussin A, Vohra JK, Sparke PB, Kalman JM. Electrophysiological and electroanatomic characterization if the atria in sinus node disease: evidence of diffuse atrial remodeling. Circulation 2004; 109:1514-1522.CrossRef PubMed

30. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ and Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994; 271:840-844.CrossRef PubMed

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Atrial Septal Defect and Atrial Fibrillation: The Known and Unknown

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Abstract

Atrial fibrillation (AF) is a common complication in patients with atrial septal defects (ASDs). The link between AF and ASD is fairly complex and entails modifications in electrophysiologic, contractile and structural properties, at the cellular and tissue level, of both atria, mainly due to chronic atrial stretch and dilation. Surgical repair or percutaneous closure of ASDs are equally effective in reducing mortality and symptoms but limited in preventing or curbing AF, unless combined with an arrhythmia-specific procedure. Transesophageal echocardiography (TEE) and intracardiac echocardiography (ICE) have improved the safety and success of the above procedures. Finally, clearer understanding of the pathophysiology of AF in patients with ASD (and CHF, in general) has led to target-specific advances in medical management.

Introduction

AF is the most common sustained arrhythmia in clinical practice currently affecting approximately 2.2 million people in the United States with an estimate of more than 5.6 million, 50% of which aged 80 years or older, by the year 2050. The prevalence of AF directly correlates with age, with only 0.1% of adults younger than 55 years but 9.0% of adults 80 years or older affected.[1] Age-standardized prevalence of AF is higher among men than women and among patients with essential hypertension, ischemic or valvular heart disease, left atrial (LA) enlargement, congestive heart failure and diabetes, with cardiac failure and rheumatic heart disease being the most powerful predictive precursors.[2-13] AF is a very costly disease with significant impact on public health. The number of hospitalizations for AF has dramatically increased in the recent years with a subsequent rise in health care costs.[14-16] The development of AF places patients at significant risk for cardioembolic strokes, steadily increasing with age from 6.7% for ages 50 to 59 years to 36.2% for ages 80-89 years[5] and doubles their overall mortality.[8] In the subgroup of patients with ASD the incidence of atrial flutter (AFL) and AF has been reported to be as high as 15-40% in the 30-35 year olds and carries ominous prognosis[7,17] ASDs are quite common representing 10% of all cardiac malformations at birth, 12% in children and 15% at clinics for children and adults.[18] There are 3 major types of ASDs: ostium secundum, ostium primum and sinus venosus defects. The ostium secundum is a true defect of the atrial septum and is located in the region of the fossa ovalis. The ostium primum defect belongs to the atrioventricular (AV) septal defects (also known as endocardial cushion defects), which may include a large ventricular septal defect and a common AV valve

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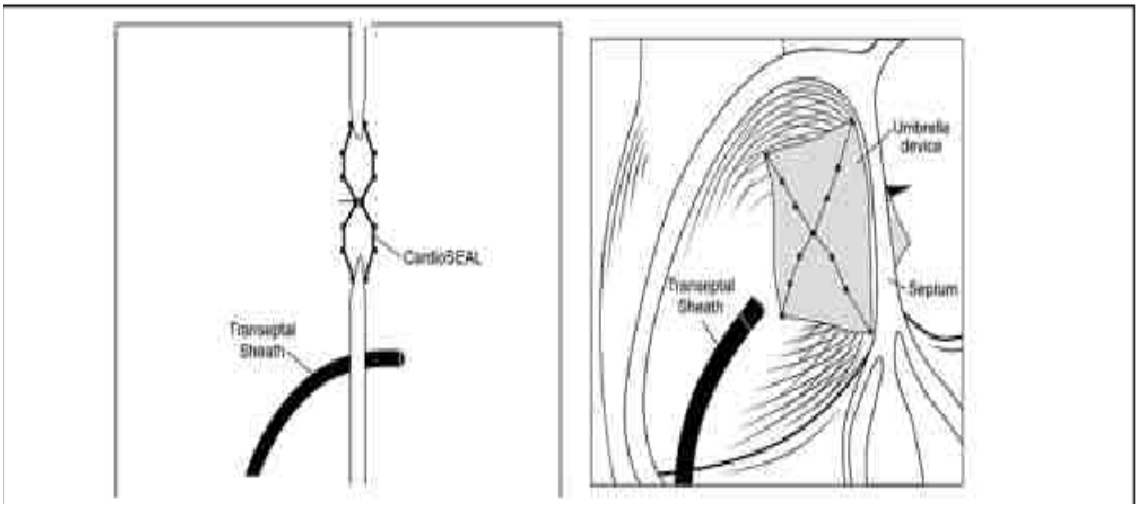
in its complete form. The sinus venosus defect is usually located at the junction of the right atrium (RA) and superior vena cava and almost always associated with partial anomalous pulmonary venous return. Two less common types of ASDs include the inferior vena cava form of sinus venosus defect and the coronary sinus septal defect.[19] With any ASD, the direction and amount of flow across the defect depends on the size of the defect and the diastolic properties of the two ventricles, which at birth are approximately equal and hence there is minimal net flow across the defect. As pulmonary arterial pressure falls, the right ventricle (RV) atrophies and becomes more distensible, while the left ventricle (LV) hypertrophies and becomes less compliant, due to increased systemic vascular resistance. This is the time when shunting of blood from the LA to the RA begins overloading the RV and shifting the interventricular septum to the left, decreasing the LV preload. The renis-angiotensin-aldosterone (RAA) system is thus activated increasing the intravascular volume and further increasing the pulmonary blood flow, eventually causing RA, LA and RV dilatation, pulmonary hypertension, right heart failure and flow reversal across the interatrial defect with significant hypoxia and cyanosis (Eisenmenger syndrome).[20] The most common initial presenting symptoms of ASD are exertional dyspnea or fatigue. Patients may then develop AF, decompensated right heart failure, occasionally, paradoxical embolus or transient ischemic attack, and finally, cyanosis (especially with inferior sinus venosus defect or right-to-left shunts).[19,21-25] Roesler in 1934 was the first to describe the natural history and clinical features of the disease based on 62 post mortem cases. Mean age of death was 36 years and usually resulted from heart failure, often associated with AF.[26] Campbell noticed that the mortality rates were quite low for the first two decades of life (0.6 to 0.7% per year) but rose significantly with subsequent decades (2.7% to 4.5% to 5.4% to 7.5% per year).[18] ASDs are quite common representing 10% of all cardiac malformations at birth, 12% in children and 15% at clinics for children and adults.[18] There are 3 major types of ASDs: ostium secundum, ostium primum and sinus venosus defects. The ostium secundum is a true defect of the atrial septum and is located in the region of the fossa ovalis. The ostium primum defect belongs to the atrioventricular (AV) septal defects (also known as endocardial cushion defects), which may include a large ventricular septal defect and a common AV valve in its complete form. The sinus venosus defect is usually located at the junction of the right atrium (RA) and superior vena cava and almost always associated with partial anomalous pulmonary venous return. Two less common types of ASDs include the inferior vena cava form of sinus venosus defect and the coronary sinus septal defect.[19] With any ASD, the direction and amount of flow across the defect depends on the size of the de-

Figure 1: Cross section interatrial septum showing the transseptal sheath inferior and posterior to the closure device (courtesy of Lakkireddy D, Patel D, Mlcochova H, Thal S, Wazni O, Kanj M, Arruda M, Prasad S, Bhargava M, Cummings J. Feasibility of transeptal puncture in radiofrequency catheter ablation of atrial fibrillation in patients with atrial septal defect (ASD) repair. Heart Rhythm. 2006; 3(5):s282-3 [Abstract])

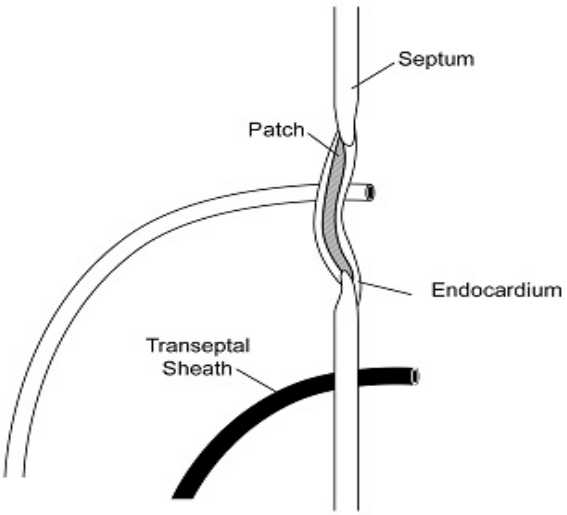


fect and the diastolic properties of the two ventricles, which at birth are approximately equal and hence there is minimal net flow across the defect. As pulmonary arterial pressure falls, the right ventricle (RV) atrophies and becomes more distensible, while the left ventricle (LV) hypertrophies and becomes less compliant, due to increased systemic vascular resistance. This is the time when shunting of blood from the LA to the RA begins overloading the RV and shifting the interventricular septum to the left, decreasing the LV preload. The renis-angiotensin-aldosterone (RAA) system is thus activated increasing the intravascular volume and further increasing the pulmonary blood flow, eventually causing RA, LA and RV dilatation, pulmonary hypertension, right heart failure and flow reversal across the interatrial defect with significant hypoxia and cyanosis (Eisenmenger syndrome).[20] The most common initial presenting symptoms of ASD are exertional dyspnea or fatigue. Patients may then develop AF, decompensated right heart failure, occasionally, paradoxical embolus or transient ischemic attack, and finally, cyanosis (especially with inferior sinus venosus defect or right-to-left shunts).[19,21-25] Roesler in 1934 was the first to describe the natural history and clinical features of the disease based on 62 post mortem cases. Mean age of death was 36 years and usually resulted from heart failure, often associated with AF.[26] Campbell noticed that the mortality rates were quite low for the first two decades of life (0.6 to 0.7% per year) but rose significantly with subsequent decades (2.7% to 4.5% to 5.4% to 7.5% per year).[18]

AF induction and maintenance in ASD patients

The link between AF and ASD is relatively complex. Changes in atrial size and pressures have been shown to induce and maintain atrial tachyarrhythmias by various mechanisms. The effects of acute atrial stretch on atrial electrophysiology are widely divergent. Sideris et al found that an increase in right atrial pressure by acute volume overload significantly prolonged right atrial effective refractory period (AERP), interatrial conduction time and increased the propensity of the atria to fibrillate by rapid atrial pacing (RAP).[27] Other investigators, however, concluded that acute atrial stretch highly correlated with shortening of AERP and increased vulnerability for AF by single premature stimuli.[28-29] Chronic atrial stretch and/or enlargement on the other hand (as in patients with ASD), have consistently been associated with a significant increase in AERP and susceptibility to AF with single extrastimulus. A number of

Figure 2: IInteratrial septum with surgical closure patch through which a transseptal sheath was placed. Note an additional sheath that was placed at a more posterior and inferior location. (courtesy of Lakkireddy D, Patel D, Mlcochova H, Thal S, Wazni O, Kanj M, Arruda M, Prasad S, Bhargava M, Cummings J. Feasibility of transeptal puncture in radiofrequency catheter ablation of atrial fibrillation in patients with atrial septal defect (ASD) repair. Heart Rhythm. 2006; 3(5):s282-3 [Abstract])



studies have shown that significant (at least 40%, by some[30]) atrial enlargement is associated with AERP prolongation, increased p-wave duration and extended sinus node recovery time (SNRT).[31-35] Biatrial enlargement due to AV dysynchrony by long-term VVI pacing has similarly been associated with prolongation of the AERP[36-37]

Electrical remodeling due to atrial enlargement contrasts the type of remodeling observed after RAP or AF. For the first time in an animal model, Wijffels et al[38] discovered that (artificially-induced and maintained) AF produced significant electrophysiologic changes in the atrial myocytes, namely a decrease in AERP, which caused AF to become sustained and unable to terminate spontaneously (hence, "AF begets AF").[38] Subsequent studies have confirmed the association of AF (and RAP) with marked decrease in AERP, as well as with significantly increased atrial impulse wavelength, loss of rate adaptation of the refractory period, sinus node dysfunction and accelerated conduction velocity, thus supporting the clinical experience that the success rate of chemical or electrical cardioversion of AF is higher when AF has lasted only a short time.[39-51]

Changes in atrial refractoriness has been explained at the atrial myocyte level by the concept of "ionic current remodeling" in the presence of congestive heart failure (CHF) and RAP. More specifically, with chronic atrial enlargement, there is a modest decrease in both L-type Ca2+ currents and transient outward (Ito) and slow delayed-rectifier (IKs) K+-currents, no change in inward rectifier, ultrarapid and rapid delayed rectifier, and T-type Ca2+ currents, and an increase in the Na+, Ca2+-exchanger (NCX) current. The net result is an increase in action potential duration (APD) at faster rates, paralleling AERP prolongation noted in vivo.[52-53] RAP on the other hand, has been associated with a significant reduction in the densities of Ito and Ica with subsequent reductions in APD and APD adaptation to rate and shorter atrial refractoriness.[54-56]

While shortening of the AERP has clearly been shown to predispose and sustain AF, lengthening of the AERP (as present in ASD patients with chronic atrial enlargement) may still increase atrial susceptibility to fibrillate by a different mechanism. Atrial refractoriness appears to be heterogeneously dispersed across key anatomic areas of the right and left atrium, most notably the crista terminalis (CT) and the posterior wall of the left atrium (PLA), respectively.[57] Ultrastructural analysis of the CT reveals a simple end-to-end communication between the myocytes with numerous gap junctions in intercalated disks and minimal connections between laterally apposed cells, hence the propagation velocity in the CT is approximately 10 times greater in the longitudinal than in the transverse direction leading to anisotropic conduction preferentially along the anatomic LoB.[58] The increase in atrial refractoriness observed with atrial dilatation is unequally distributed across the RA (anisotropic dispersion of AERP), with AERP significantly prolonged along the thin free wall compared to the thick CT (functional LoB).[32-33] The combination of both anatomical and functional LoB's predisposes the RA to re-entrant tachyarrhythmias presenting as atrial flutter or atrial fibrillation, depending on the length of the overall LoB. A shorter LoB is more likely to "short-circuit" and become unstable, degenerating into AF. RAP and spontaneous atrial tachyarrhythmias have already been shown to produce a functional LoB between the vena cavae and its length was found to be critical for the maintenance of AFL and in preventing its degradation into AF.[59-61] The PLA is another key site where a line of anatomic LoB can be drawn perpendicularly between the superior and inferior pulmonary veins, correlating well with a region of change in subendocardial fiber orientation. This line is responsible for the breakup of wave fronts into multiple wavelets during the initiation of AF from the pulmonary vein foci.[62] In the presence of chronic LA dilation, conduction along the anatomic LoB of the PLA becomes more anisotropic due to heterogeneous dispersion of atrial refractoriness (functional LoB) creating a favorable substrate for re-entry and fibrillatory activity.[57,63]

However, even after prolonged periods of AF (months or years), electrical remodeling appears to be completely reversible and atrial refractoriness becomes normal within a few days of sinus rhythm. Allessie et al[46] suggested that a "second factor" was responsible for persistent AF. Good candidates included "atrial stunnig" (loss of atrial contractility, contractile remodeling) and atrial interstitial fibrosis (structural remodeling). Down-regulation of ICaL, pronounced reduction of Ca2+ -transient current and Ca overload intra-

cellularly were shown experimentally to cause atrial stunning.[55,64-65] The duration of contractile dysfunction correlated well with the duration of AF and could take months prior to full recovery.[66] Still, atrial fibrosis is the hallmark of AF "domestication" by maintaining an arrhythmogenic substrate. Atrial fibrosis is the convergent pathologic end point of a variety of cardiac insults, including chronic atrial stretching (such as with an ASD), and a reparative process to replace degenerating myocardial cells.[67-68] Mechanical stretch induces increased angiotensin II (AngII) and transforming growth factor (TGF) –beta 1 expression and collagen synthesis in cardiac fibroblasts. It also stimulates cardiomyocyte signaling via activation of the angiotensin II type 1 (AT1) receptors and mitogen-activated protein kinase, with direct fibroblast-activating effects.[69-73] A lower percentage of atrial cardiomyocytes (compared to the ventricles, 45% vs 76%), and thus, a larger concentration of fibroblasts, inevitably leads to pronounced atrial extracellular matrix accumulation and remodeling.[74-75] Fibrosis has significant electrophysiologic effects, namely, it creates localized areas of muscle fiber disarray and thinning causing conduction slowing, increased conduction heterogeneity, unidirectional conduction blocks and smaller and more numerous reentrant circuits, a necessary substrate for AF.[76-80] Atrial myocytes, on the other hand, assume a more fetal phenotype (dedifferentiation), which resembles the changes in ventricular myocytes due to chronic ischemia (hibernation); such changes are initially reversible and heterogeneously distributed, however, in dilated atria (especially the RA), progression to DNA cleavage, programmed cell death and replacement with fibrous tissue, have been observed.[46,81]

ASD repair and AF

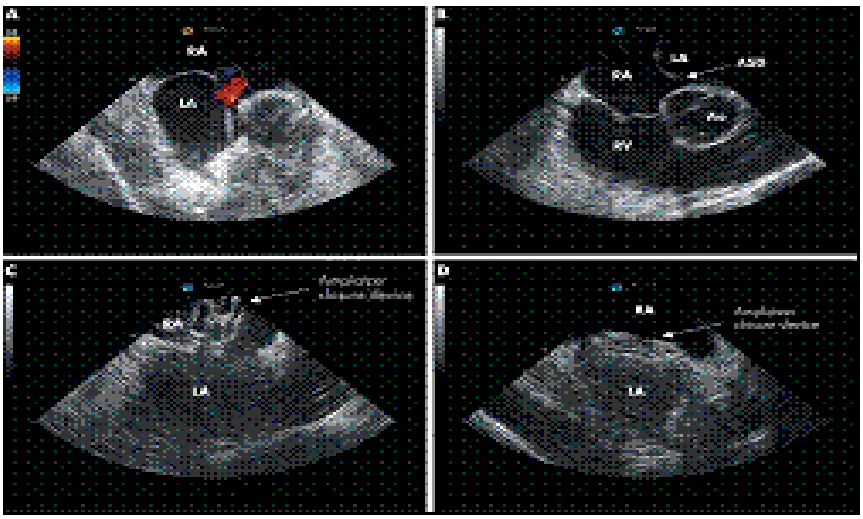
Therefore, patients with significant ASDs should be offered elective closure once the diagnosis is made. Current indications for ASD closure include right atrial and ventricular dilation by echocardiography, MRI or CT associated with ASD minimum diameter > 10mm on echocardiography and/or Qp:Qs > 1.5:1.0 by echocardiographic or cardiac MRI flow assessment or from oxygen saturation runs, when cardiac catheterization is performed. Treatment includes surgical repair of the ostium primum and sinus venosus ASDs, as well as of the ostium secundum ASDs, which are unsuitable for percutaneous device closure (defect > 36mm, inadequate atrial septal rims for stable device deployment, or proximity of the defect to the AV valves, the coronary sinus or the vena cavae) [19,82]. Mortality and symptoms are significantly improved after surgical repair of ASDs, regardless of age, pulmonary arterial pressure (PAP) or pre-operative functional class.[22,83-84] On the other hand, the incidence of atrial tachyarrhythmias (most notably AF and AFL) is significantly age-dependent, with a higher incidence of AF and AFL among patients undergoing surgical closure in adulthood. Multiple studies have shown that preoperative, persistent and new-onset (i.e. postsurgical) AF or AFL are significantly more common among older patients.[21,23-25,83,85-92] For instance, Gosh et al observed a lower incidence of preoperative AF (23.5% vs 43.6%, $p < 0.05$) among patients 35-50 years old than among patients older than 50 years and a lower incidence of new AF (7.8% vs 34%, $p < 0.05$) in the former than the latter group.[93] The reported incidence of AF and AFL after surgical closure of ASD at adult age was indeed comparable to the incidence of these arrhythmias in natural history studies of ASD patients, namely, 15-40% in 30-35 year-olds.[7,18] Some studies even claimed a higher incidence of new onset supraventricular arrhythmias in surgical patients than in patients receiving medical management (39% vs 14%, $p=0.01$).[89,94] These numbers are significantly different from the 3% incidence reported by Roos et al for ASD patients operated in childhood.[95] The etiology of persistent or new-onset atrial arrhythmias following surgical repair of ASD in adults in not completely understood, however, the extent of residual RA dilatation after ASD closure appears to play a critical role. Indexed RA area remains increased after ASD repairs in adults compared to that in control subjects (still relatively decreased over time) and the decrease in RA area is inversely proportional to the patient's age at the time of the ASD closure .[96] As shown earlier, persistent atrial dilatation is essential for the initiation and domestication of AF and AFL. In addition, surgical scars (from the ASD repair) in the RA free wall act as anatomical LoB allowing either re-entry phenomena and AFL or scattered atrial electrical activity and AF to take place depending on the length of the LoB.[59-61,97-99] Finally, parameters such as the use of cardioplegia, type of cannulation, location of the defect and the presence of abnormal pulmonary

venous drainage have been associated with sinus node injury or dysfunction and atrial arrhythmias .[21-24] The unacceptably high rates of persistent or new AF and AFL after adult ASD surgery (with their associated risks of stroke and chronic drug therapy) in conjunction to the small added risk of performing an AF surgical procedure, such as the modified Cox-Maze procedure, support their combination in such high risk patients.[100-101] The combination of the two surgical procedures has been associated with an approximately 85% rate of restoring sinus rhythm, a 90% rate of maintaining sinus rhythm and a significant improvement in New York Heart Association classification 8 months after combined surgery [102-103] with rates heavily dependent on the pre-operative size of the left atrium and the magnitude of the atrial fibrillatory wave[103]

Nevertheless, surgical repair of ASDs carries significant morbidity and mortality.[23,89,99,104] Percutaneous closure has recently emerged as an attractive alternative to the traditional open-chest procedures. The new modality has been associated with significant hemodynamic and electrophysiologic improvements in cardiac function. RV volumes are significantly decreased in < 24 hours after the procedure and continue to improve for up to 6 months (-not observed with surgical ASD repair due to the detrimental effects of cardioplegia.[108-110]). Improvement in RV filling pressures and function after percutaneous ASD repair have been associated (via the principle of ventricular interdependence) with an improved LV diastolic function, as suggested by normalization of the LV isovolumic relaxation time and LV end-diastolic dimension, and systolic function, as suggested by a statistically significant increase in LV ejection fraction.[84,109,111-112] Improved ventricular filling and atrial preload parameters may lead to noticeable reductions in indexed RA and LA areas (though, without complete resolution) over time in an age-dependent fashion.[96,106,113] Early percutaneous repair of ASDs has been associated with a decreased incidence of atrial tachyarrhythmias and ectopy compared to surgical closure.[105,114]

At any rate, patients who develop AF after ASD repair or PFO closure maintain the option of AF ablation irrespective of the closure (surgical or percutaneous) modality chosen. Concerns regarding gaining access to the LA via a transeptal puncture (TSP) under fluoroscopic guidance in the presence of an intra-atrial patch closure device initially led to reasonable hesitations in percutaneously treating AF. Alterations in the septal anatomy after repair and the potential for mechanical dislodgement and damage to the closure apparatus made the complexity of the procedure, risks of complications and the fluoroscopy time prohibitive to many operators. Nevertheless, a few studies have shown that TSP under these conditions can be performed with low risk of complications. In a study of 39 pediatric patients with congenital heart disease requiring intra-atrial patch (IAP), the IAP was successfully punctured in 97.5% of

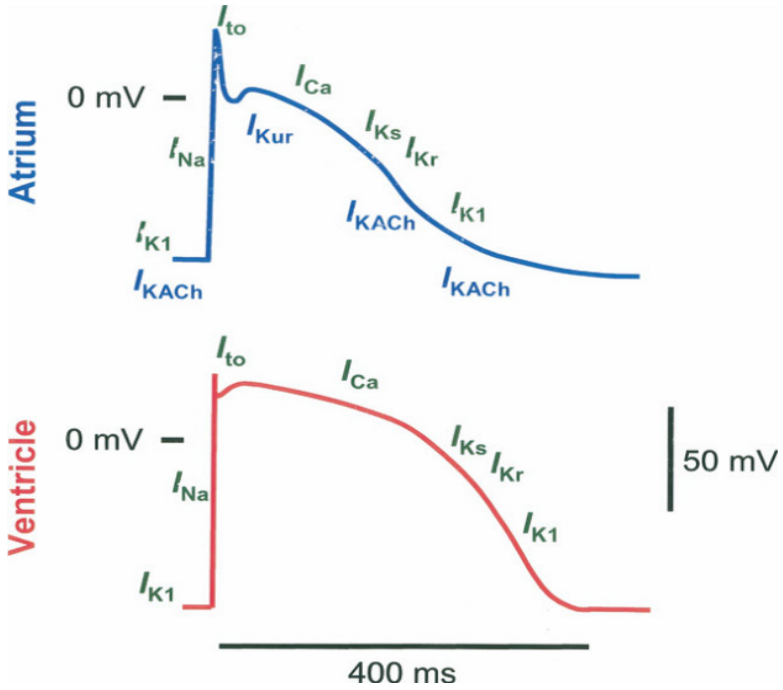
Figure 3: Closure of an atrial septal defect (ASD) under ICE guidance. (A) Colour Doppler demonstrating an ASD located in the inferior part of the atrial septum. (B) Relation of the ASD (arrow) to intracardiac structures. (C) Positioning of the Amplatzer closure device. (D) After several minutes, flattening of the closure device occurs. The device is positioned stable in between the right and left atria. Ao, aorta; LA, left atrium; RA, right atrium; RV, right ventricle



the patients (38/39) with no complications; follow-up echocardiography in 79% of the patients revealed no residual shunting across the atrial septum except for two cases of atrial baffle, which were intentionally fenestrated.[115] Double TSP for AF ablation was successfully (95%) performed under the guidance of intracardiac echocardiography (ICE) in a prospective study of 20 post-ASD/PFO repair patients, age- and gender-matched with 20 control patients. Lakkireddy et al showed that surgical repairs with synthetic materials like Dacron (but not Gore-Tex) can safely be punctured to gain access to the LA, while most ASD or PFO closure devices typically occlude the anteroseptal portion of the interatrial septum, leaving a relatively wide posteroinferior area for TSP [figures 1-2]. No acute or long-term complications were noted and echocardiographic follow-up at 3 months showed residual interatrial communication in only 1 patient, which resolved in 12 months.[116]

Overall, percutaneous ASD closure is a safe and efficient procedure with only rare (less than 1%) serious complications in experienced centers. Case reports of device failure to deploy, malfunction, fracture or embolization, myocardial perforation and hemopericardium (with or without tamponade), residual shunts, thrombus formation on the device and aortic sinus-to-left atrial fistula formation have been reported.[117-122] In an effort to improve the safety and success of percutaneous (and surgical) ASD procedures, cardiac imaging such as transesophageal echocardiography (TEE) and ICE have been incorporated in all ASD closure procedures. TEE has been helpful in the selection of patients for surgical or percutaneous repair, in assessing the morphology, dimensions and relationship of ASD to the other intracardiac structures, in guiding the operator during the procedure and in early detection of any ensuing complications. Although the risks of TEE are minimal (< 0.02%), insertion of the TEE probe can potentially result in oral, esophageal or pharyngeal trauma, arrhythmias and patient discomfort. General anesthesia is usually required and additional staff (anesthesiologist, TEE operator) need to be present in the lab throughout the procedure. Experienced TEE operators are crucial for acquisition of quality images and reducing procedure and fluoroscopy times.[123-125] ICE has emerged as the preferred alternative to TEE. It provides accurate visualization of

Figure 4: Regional Difference in Ionic Current Contribution to APs. Differences in key ion currents between atrial (blue) and ventricular (red) action potentials (APs). Atrial APs have smaller AP amplitude and less negative resting membrane potential. Currents (green) identified above the line illustrating the APs are present in both regions; atrially expressed ionic currents are illustrated below the AP schematic (blue). IKACh _ acetylcholine-regulated potassium current; IKur _ ultrarapid delayed-rectifier potassium current; INa _sodium current (courtesy of Ehrlich JR, Biliczki P, Hohnloser SH, Nattel S. Atrial-selective approaches for the treatment of atrial fibrillation. J Am Coll Cardiol. 2008 Feb 26;51(8):787-92)



the intracardiac anatomic structures, defect(s) and closure devices or patches and guides the operator in interventions, such as TSPs and placement of closure devices, thus preventing complications associated with the procedure [figure 3]. It also helps in microbubble monitoring for power adjustment during radiofrequency ablation and in visualization of thrombus formation on catheters and sheaths.[126-132] In contrast to TEE though, it avoids esophageal probe insertion (and its associated risks), patient discomfort and general anesthesia.

Medical management of AF in ASD patients

Atrial extrasystoles:

Since AF is so common in the group of ASD (and especially, the unrepaired or adult-repaired ASD) patients, medical management remains essential. Pharmacologic agents to convert AF and prevent relapses have traditionally included antiarrhythmic drugs of the Vaughan-Williams class I and III. However, these agents are notorious for their proarrhythmic effects and poor tolerability. Latest breakthroughs in the understanding of the pathophysiologic mechanisms behind the initiation and maintenance of AF (and other atrial tachyarrhythmias) have inspired rigorous interest in the pharmacologic targeting of the various steps. The concept of electrical remodeling in AF has led research efforts towards "atrial-selective" drugs, that is, modulators targeting ion-specific-channels [figure 4] (most notably Ikur[133] and IkAch,[134]), stretch-activated nonselective cation channels (SACs)[135] and atrial structures (such as atrially expressed connexins[136]), to affect atrial electrophysiologic activity.

Most of the currently investigated modulators though are not in strict terms "specific", but rather one or two orders of magnitude more selective in inhibiting the target(s) of interest compared to other potential targets.[137] Structural remodeling due to interstitial fibrosing is another potential target of pharmacotherapy and important feature of AF substrate. Several profibrotic factors have been discovered, most notably, AngII, TGF-b1, PDGF and connective tissue growth factor, and the renin – angiotensin – aldosterone pathway has extensively been implicated in the process.[73] Recent therapeutic agents such as ACE inhibitors, angiotensin II type 1 receptor blockers and antialdosterone therapies specifically target the latter and have been shown in multiple studies to substantially reduce fibroting changes and AF.[140-141] Similarly, 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors[142-143] and omega-3 polyunsaturated fatty acids were found to delay tissue fibrosis and thus prevent AF.[144] Gene therapy remains the last frontier in AF therapy with the most promise for atrial selectivity but is still lacking clinical applications.

Conclusions:

In conclusion, AF in ASD patients is mainly the by-product of RA and LA dilation. Changes in atrial refractoriness, ionic currents and atrial conduction properties (electrical remodeling), along with tissue remodeling due to atrial fibrosis (structural remodeling) generate a favorable substrate for the initiation and domestication of AF (and other atrial tachyarrhythmias). Surgical repair of ASD remains the standard therapeutic modality except for a selective population of patients, for which a percutaneous approach is preferred. Adult repair is associated with similar rates of AF in comparison to unrepaired ASD, partly due to residual RA dilation with fibrotic changes. Current AF treatment in ASD patients includes the modified Cox-Maze procedure (usually concomitantly with the ASD repair), percutaneous AF ablation via TSP and pharmacologic modalities, currently focusing on atrially expressed targets and pathophysiologic steps in atrial remodeling. Genetic manipulation is a promising research field in AF.

References

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer ED. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001 May 9;285(18):2370-5CrossRef PubMed

2. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation. 1995 Aug 15;92(4):835-41.

3.Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). Am J Cardiol. 1994 Aug 1;74(3):236-

41.CrossRef PubMed
4. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG.Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications.Arch Intern Med. 1995 Mar 13;155(5):469-73.CrossRef PubMed
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med. 1987 Sep;147(9):1561-4.CrossRef PubMed
6. Friberg J, Buch P, Scharling H, Gadsbphioll N, Jensen GB. Rising rates of hospital admissions for atrial fibrillation. Epidemiology. 2003 Nov;14(6):666-72.CrossRef PubMed
7. Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart. 2001 Nov;86(5):516-21.CrossRef PubMed
8. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med. 1982 Apr 29;306(17):1018-22.
9. Petersen P, Godtfredsen J.Atrial fibrillation-a review of course and prognosis.Acta Med Scand.1984;216(1):5-9. 10. Alpert JS, Petersen P, Godtfredsen J. Atrial fibrillation: natural history, complications, and management. Annu Rev Med. 1988;39:41-52. CrossRef PubMed
11. Brand FN, Abbott RD, Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation. 30-year follow-up in the Framingham Study. JAMA. 1985 Dec 27;254(24):3449-53.CrossRef PubMed
12. Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes DR Jr, Ilstrup DM, Frye RL. The natural history of lone atrial fibrillation. A population-based study over three decades. N Engl J Med. 1987 Sep 10;317(11):669-74.
13. Davidson E, Rotenberg Z, Weinberger I, Fuchs J, Agmon J. Diagnosis and characteristics of lone atrial fibrillation. Chest. 1989 May;95(5):1048-50.CrossRef PubMed
14. Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. Circulation. 2003 Aug 12;108(6):711-6. Epub 2003 Jul 28.CrossRef PubMed
15. Stewart S, Murphy NF, Walker A, McGuire A, McMurray JJ. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. Heart. 2004 Mar;90(3):286-92.CrossRef PubMed
16. Le Heuzey JY, Paziaud O, Piot O, Said MA, Copie X, Lavergne T, Guize L. Cost of care distribution in atrial fibrillation patients: the COCAF study. Am Heart J. 2004 Jan;147(1):121-6.CrossRef PubMed
17. Campbell M, Neill C, Suzman S. The prognosis of atrial septal defect. Br Med J. 1957 Jun 15;1(5032):1375-83.
18. Campbell M. Natural history of atrial septal defect. Br Heart J. 1970 Nov;32(6):820-6.PubMed
19. Webb G, Gatzoulis MA. Atrial septal defects in the adult: recent progress and overview. Circulation. 2006 Oct 10;114(15):1645-53. CrossRef PubMed
20. Ward C. Secundum atrial septal defect: routine surgical treatment is not of proven benefit. Br Heart J. 1994 Mar;71(3):219-23. PubMed
21. McNamara DG, Latson LA.Long-term follow-up of patients with malformations for which definitive surgical repair has been available for 25 years or more. Am J Cardiol. 1982 Sep;50(3):560-8. CrossRef PubMed
22. Rostad H, Sørland SJ. Atrial septal defects of secundum type in patients less than 40 years of age. A follow-up study. Acta Med Scand Suppl. 1981;645:29-35.
23. Bink-Boelkens MT, Velvis H, van der Heide JJ, Eygelaar A, Hardjowijono RA. Dysrhythmias after atrial surgery in children. Am Heart J. 1983 Jul;106(1 Pt 1):125-30.CrossRef PubMed
24. Meyer RA, Korfhagen JC, Covitz W, Kaplan S. Long-term follow-up study after closure of secundum atrial septal defect in children: an echocardiographic study. Am J Cardiol. 1982 Jul;50(1):143-8.CrossRef PubMed
25. Konstantinides S, Geibel A, Olschewski M, Görnandt L, Roskamm H, Spillner G, Just H, Kasper W. A comparison of surgical and medical therapy for atrial septal defect in adults. N Engl J Med. 1995 Aug 24;333(8):469-73.CrossRef PubMed
26. Roesler, H. Interatrial Septal Defect. Arch Int Med 1934;54:339-80.
27. Sideris DA, Toumanidis ST, Thodorakis M, Kostopoulos K, Tselepatiotis E, Langoura C, Stringli T, Moulopoulos SD. Some observations on the mechanism of pressure related atrial fibrillation. Eur Heart J. 1994 Nov;15(11):1585-9.
28. Tse HF, Pelosi F, Oral H, Knight BP, Strickberger SA, Morady F. Effects of simultaneous atrioventricular pacing on atrial refractoriness and atrial fibrillation inducibility: role of atrial mechanoelectrical feedback. J Cardiovasc Electrophysiol. 2001 Jan;12(1):43-50.CrossRef PubMed
29. Ravelli F, Allessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. Circulation. 1997 Sep 2;96(5):1686-95.
30. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation. 1995 Mar 1;91(5):1588-95.
31. Morton JB, Sanders P, Vohra JK, Sparks PB, Morgan JG, Spence SJ, Grigg LE, Kalman JM. Effect of chronic right atrial stretch on atrial electrical remodeling in patients with an atrial septal defect. Circulation. 2003 Apr 8;107(13):1775-82. Epub 2003 Mar 10.CrossRef PubMed
32. Satoh T, Zipes DP. Unequal atrial stretch in dogs increases dispersion of refractoriness conducive to developing atrial fibrillation. J Cardiovasc Electrophysiol. 1996 Sep;7(9):833-42.CrossRef PubMed
33. Chen YJ, Chen SA, Tai CT, Yu WC, Feng AN, Ding YA, Chang MS. Electrophysiologic characteristics of a dilated atrium in patients with paroxysmal atrial fibrillation and atrial flutter. J Interv Card Electrophysiol. 1998 Jun;2(2):181-6.CrossRef PubMed
34. Power JM, Beacom GA, Alferness CA, Raman J, Wijffels M, Farish SJ, Burrell LM, Tonkin AM. Susceptibility to atrial fibrillation: a study in an ovine model of pacing-induced early heart failure. J Cardiovasc Electrophysiol. 1998 Apr;9(4):423-35.CrossRef PubMed
35. Oliver JM, Gallego P, González A, Benito F, Mesa JM, Sobrino

JA. Predisposing conditions for atrial fibrillation in atrial septal defect with and without operative closure. Am J Cardiol. 2002 Jan 1;89(1):39-43.CrossRef PubMed
36. Sparks PB, Mond HG, Vohra JK, Jayaprakash S, Kalman JM. Electrical remodeling of the atria following loss of atrioventricular synchrony: a long-term study in humans. Circulation. 1999 Nov 2;100(18):1894-900.
37. Sparks PB, Mond HG, Vohra JK, Yapanis AG, Grigg LE, Kalman JM. Mechanical remodeling of the left atrium after loss of atrioventricular synchrony. A long-term study in humans. Circulation. 1999 Oct 19;100(16):1714-21.
38. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995 Oct 1;92(7):1954-68.
39. Suttorp MJ, Kingma JH, Jessurun ER, Lie-A-Huen L, van Hemel NM, Lie KI. The value of class IC antiarrhythmic drugs for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. J Am Coll Cardiol. 1990 Dec;16(7):1722-7.
40. Gold RL, Haffajee CI, Charos G, Sloan K, Baker S, Alpert JS. Amiodarone for refractory atrial fibrillation. Am J Cardiol. 1986 Jan 1;57(1):124-7.CrossRef PubMed
41. Waris E, Kreus KE, Salokannel J. Factors influencing persistence of sinus rhythm after DC shock treatment of atrial fibrillation. Acta Med Scand. 1971 Mar;189(3):161-6.
42. Bjerkelund C, Orning OM. An evaluation of DC shock treatment of atrial arrhythmias. Acta Med Scand. 1968 Dec;184(6):481-91.
43. Crijns HJ, van Wijk LM, van Gilst WH, Kingma JH, van Gelder IC, Lie KI. Acute conversion of atrial fibrillation to sinus rhythm: clinical efficacy of flecainide acetate. Comparison of two regimens. Eur Heart J. 1988 Jun;9(6):634-8.
44. Suttorp MJ, Kingma JH, Lie-A-Huen L, Mast EG. Intravenous flecainide versus verapamil for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. Am J Cardiol. 1989 Mar 15;63(11):693-6.CrossRef PubMed
45. Crozier IG, Ikram H, Kenealy M, Levy L. Flecainide acetate for conversion of acute supraventricular tachycardia to sinus rhythm. Am J Cardiol. 1987 Mar 1;59(6):607-9.CrossRef PubMed
46. Allessie M, Ausma J, Schotten U.Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res. 2002 May;54(2):230-46.CrossRef PubMed
47. Elvan A, Wylie K, Zipes DP. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs. Electrophysiological remodeling. Circulation. 1996 Dec 1;94(11):2953-60.
48. Bolens M, Friedli B. Sinus node function and conduction system before and after surgery for secundum atrial septal defect: an electrophysiologic study. Am J Cardiol. 1984 May 15;53(10):1415-20.CrossRef PubMed
49. Gaspo R, Bosch RF, Talajic M, Nattel S. Functional mechanisms underlying tachycardia-induced sustained atrial fibrillation in a chronic dog model. Circulation. 1997 Dec 2;96(11):4027-35.
50. Fareh S, Villemaire C, Nattel S. Importance of refractoriness heterogeneity in the enhanced vulnerability to atrial fibrillation induction caused by tachycardia-induced atrial electrical remodeling. Circulation. 1998 Nov 17;98(20):2202-9.
51. Sparks PB, Jayaprakash S, Vohra JK, Kalman JM. Electrical remodeling of the atria associated with paroxysmal and chronic atrial flutter. Circulation. 2000 Oct 10;102(15):1807-13.
52. Shinagawa K, Li D, Leung TK, Nattel S. Consequences of atrial tachycardia-induced remodeling depend on the preexisting atrial substrate. Circulation. 2002 Jan 15;105(2):251-7.CrossRef PubMed
53. Li D, Melnyk P, Feng J, Wang Z, Petrecca K, Shrier A, Nattel S. Effects of experimental heart failure on atrial cellular and ionic electrophysiology. Circulation. 2000 Jun 6;101(22):2631-8.
54. Nattel S, Li D. Ionic remodeling in the heart: pathophysiological significance and new therapeutic opportunities for atrial fibrillation. Circ Res. 2000 Sep 15;87(6):440-7.
55. Yue L, Feng J, Gaspo R, Li GR, Wang Z, Nattel S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. Circ Res. 1997 Oct;81(4):512-25.
56. Yu WC, Lee SH, Tai CT, Tsai CF, Hsieh MH, Chen CC, Ding YA, Chang MS, Chen SA. Reversal of atrial electrical remodeling following cardioversion of long-standing atrial fibrillation in man. Cardiovasc Res. 1999 May;42(2):470-6.CrossRef PubMed
57. Roberts-Thomson KC, Stevenson IH, Kistler PM, Haqqani HM, Goldblatt JC, Sanders P, Kalman JM. Anatomically determined functional conduction delay in the posterior left atrium relationship to structural heart disease. J Am Coll Cardiol. 2008 Feb 26;51(8):856-62.CrossRef PubMed
58. Saffitz JE, Kanter HL, Green KG, Tolley TK, Beyer EC. Tissue-specific determinants of anisotropic conduction velocity in canine atrial and ventricular myocardium. Circ Res. 1994 Jun;74(6):1065-70.
59. Waldo AL, Feld GK. Inter-relationships of atrial fibrillation and atrial flutter mechanisms and clinical implications. J Am Coll Cardiol. 2008 Feb 26;51(8):779-86.CrossRef PubMed
60. Ortiz J, Niwano S, Abe H, Rudy Y, Johnson NJ, Waldo AL. Mapping the conversion of atrial flutter to atrial fibrillation and atrial fibrillation to atrial flutter. Insights into mechanisms. Circ Res. 1994 May;74(5):882-94.
61. Cox JL, Canavan TE, Schuessler RB, Cain ME, Lindsay BD, Stone C, Smith PK, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation. J Thorac Cardiovasc Surg. 1991 Mar;101(3):406-26.
62. Markides V, Schilling RJ, Ho SY, Chow AW, Davies DW, Peters NS. Characterization of left atrial activation in the intact human heart. Circulation. 2003 Feb 11;107(5):733-9.CrossRef PubMed
63. Gerstenfeld EP.Functional block in the posterior left atrium another piece in the puzzle of atrial fibrillation initiation. J Am Coll Cardiol. 2008 Feb 26;51(8):863-4.CrossRef PubMed
64. Manning WJ, Silverman DI, Katz SE, Riley MF, Come PC, Doherty RM, Munson JT, Douglas PS. Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. J Am Coll Cardiol. 1994 Jun;23(7):1535-40.
65. Sun H, Gaspo R, Leblanc N, Nattel S. Cellular mechanisms of atrial contractile dysfunction caused by sustained atrial tachycardia. Circulation. 1998 Aug 18;98(7):719-27.

66. Daoud EG, Marcovitz P, Knight BP, Goyal R, Man KC, Strickberger SA, Armstrong WF, Morady F. Short-term effect of atrial fibrillation on atrial contractile function in humans. Circulation. 1999 Jun 15;99(23):3024-7.
67. Boyden PA, Tilley LP, Pham TD, Liu SK, Fenoglic JJ Jr, Wit AL. Effects of left atrial enlargement on atrial transmembrane potentials and structure in dogs with mitral valve fibrosis. Am J Cardiol. 1982 Jun;49(8):1896-908.CrossRef PubMed
68. Boyden PA, Tilley LP, Albala A, Liu SK, Fenoglio JJ Jr, Wit AL. Mechanisms for atrial arrhythmias associated with cardiomyopathy: a study of feline hearts with primary myocardial disease. Circulation. 1984 May;69(5):1036-47.
69. Carver W, Nagpal ML, Nachtigal M, Borg TK, Terracio L. Collagen expression in mechanically stimulated cardiac fibroblasts. Circ Res. 1991 Jul;69(1):116-22.
70. Riser BL, Cortes P, Heilig C, Grondin J, Ladson-Wofford S, Patterson D, Narins RG. Cyclic stretching force selectively upregulates transforming growth factor-beta isoforms in cultured rat mesangial cells. Am J Pathol. 1996 Jun;148(6):1915-23.
71. Zou Y, Akazawa H, Qin Y, Sano M, Takano H, Minamino T, Makita N, Iwanaga K, Zhu W, Kudoh S, Toko H, Tamura K, Kihara M, Nagai T, Fukamizu A, Umemura S, Iiri T, Fujita T, Komuro I. Mechanical stress activates angiotensin II type 1 receptor without the involvement of angiotensin II. Nat Cell Biol. 2004 Jun;6(6):499-506. Epub 2004 May 16.CrossRef PubMed
72. Malhotra R, Sadoshima J, Brosius FC 3rd, Izumo S. Mechanical stretch and angiotensin II differentially upregulate the renin-angiotensin system in cardiac myocytes In vitro. Circ Res. 1999 Jul 23;85(2):137-46.
73. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol. 2008 Feb 26;51(8):802-9.CrossRef PubMed
74. Hinescu ME, Gherghiceanu M, Mandache E, Ciontea SM, Popescu LM. Interstitial Cajal-like cells (ICLC) in atrial myocardium: ultrastructural and immunohistochemical characterization. J Cell Mol Med. 2006 Jan-Mar;10(1):243-57.CrossRef PubMed
75. Popescu LM, Gherghiceanu M, Hinescu ME, Cretoiu D, Ceafalan L, Regalia T, Popescu AC, Ardeleanu C, Mandache E. Insights into the interstitium of ventricular myocardium: interstitial Cajal-like cells (ICLC). J Cell Mol Med. 2006 Apr-Jun;10(2):429-58.CrossRef PubMed
76. Boyden PA, Hoffman BF. The effects on atrial electrophysiology and structure of surgically induced right atrial enlargement in dogs. Circ Res. 1981 Dec;49(6):1319-31.
77. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation. 1999 Jul 6;100(1):87-95.
78. Kalman JM, Sparks PB. Electrical remodeling of the atria as a consequence of atrial stretch. J Cardiovasc Electrophysiol. 2001 Jan;12(1):51-5.CrossRef PubMed
79. Spach MS, Dolber PC. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle. Evidence for electrical uncoupling of side-to-side fiber connections with increasing age. Circ Res. 1986 Mar;58(3):356-71.
80. Lammers WJ, Schalij MJ, Kirchhof CJ, Allessie MA. Quantification of spatial inhomogeneity in conduction and initiation of reentrant atrial arrhythmias. Am J Physiol. 1990 Oct;259(4 Pt 2):H1254-63.
81. Everett TH 4th, Li H, Mangrum JM, McRury ID, Mitchell MA, Redick JA, Haines DE. Electrical, morphological, and ultrastructural remodeling and reverse remodeling in a canine model of chronic atrial fibrillation. Circulation. 2000 Sep 19;102(12):1454-60.
82. Saxena A, Divekar A, Soni NR. Natural history of secundum atrial septal defect revisited in the era of transcatheter closure. Indian Heart J. 2005 Jan-Feb;57(1):35-8.
83. John Sutton MG, Tajik AJ, McGoon DC. Atrial septal defect in patients ages 60 years or older: operative results and long-term postoperative follow-up. Circulation. 1981 Aug;64(2):402-9.
84. Satoh A, Katayama K, Hiro T, Yano M, Miura T, Kohno M, Fujii T, Matsuzaki M. Effect of right ventricular volume overload on left ventricular diastolic function in patients with atrial septal defect. Jpn Circ J. 1996 Oct;60(10):758-66.CrossRef PubMed
85. Murphy JG, Gersh BJ, McGoon MD, Mair DD, Porter CJ, Ilstrup DM, McGoon DC, Puga FJ, Kirklin JW, Danielson GK. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. N Engl J Med. 1990 Dec 13;323(24):1645-50.
86. Gatzoulis MA, Freeman MA, Siu SC, Webb GD, Harris L. Atrial arrhythmia after surgical closure of atrial septal defects in adults. N Engl J Med. 1999 Mar 18;340(11):839-46.CrossRef PubMed
87. Medeiros A, Iturralde P, Márquez M, Ramírez S, de Micheli A, Guevara M, Buendía A. Permanent rhythm and conduction disorders in patients surgically treated for atrial septal defect. Arch Inst Cardiol Mex. 2000 Jan-Feb;70(1):46-54.
88. Shah D, Azhar M, Oakley CM, Cleland JG, Nihoyannopoulos P. Natural history of secundum atrial septal defect in adults after medical or surgical treatment: a historical prospective study. Br Heart J. 1994 Mar;71(3):224-7; discussion 228.PubMed
89. Favilli S, Zuppiroli A, Mori F, Santoro G, Manetti A, Dolara A. Should the patient with an interatrial defect recognized in adulthood always be operated on? G Ital Cardiol. 1999 Nov;29(11):1302-7.
90. Thilén U, Berlind S, Varnauskas E. Atrial septal defect in adults. Thirty-eight-year follow-up of a surgically and a conservatively managed group. Scand Cardiovasc J. 2000;34(1):79-83. CrossRef PubMed
91. Meijboom F, Hess J, Szatmari A, Utens EM, McGhie J, Deckers JW, Roelandt JR, Bos E. Long-term follow-up (9 to 20 years) after surgical closure of atrial septal defect at a young age. Am J Cardiol. 1993 Dec 15;72(18):1431-4.CrossRef PubMed
92. Perloff JK. Surgical closure of atrial septal defect in adults. N Engl J Med. 1995 Aug 24;333(8):513-4.CrossRef PubMed
93. Ghosh S, Chatterjee S, Black E, Firmin RK. Surgical closure of atrial septal defects in adults: effect of age at operation on outcome. Heart. 2002 Nov;88(5):485-7.CrossRef PubMed
94. Horvath KA, Burke RP, Collins JJ Jr, Cohn LH. Surgical treatment of adult atrial septal defect: early and long-term results. J Am Coll Cardiol. 1992 Nov 1;20(5):1156-9.
95. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, Bogers AJ, Simoons ML. Excellent survival and low incidence of arrhythmias, stroke and

heart failure long-term after surgical ASD closure at young age. A prospective follow-up study of 21-33 years. Eur Heart J. 2003 Jan;24(2):190-7.CrossRef PubMed
96. Kort HW, Balzer DT, Johnson MC. Resolution of right heart enlargement after closure of secundum atrial septal defect with transcatheter technique. J Am Coll Cardiol. 2001 Nov 1;38(5):1528-32.CrossRef PubMed
97. Waldo AL. Pathogenesis of atrial flutter. J Cardiovasc Electrophysiol. 1998 Aug;9(8 Suppl):S18-25.
98. Feld GK, Shahandeh-Rad F. Mechanism of double potentials recorded during sustained atrial flutter in the canine right atrial crush-injury model. Circulation. 1992 Aug;86(2):628-41.
99. Tomita Y, Matsuo K, Sahadevan J, Khrestian CM, Waldo AL. Role of functional block extension in lesion-related atrial flutter. Circulation. 2001 Feb 20;103(7):1025-30.
100. Cox JL, Jaquiss RD, Schuessler RB, Boineau JP. Modification of the maze procedure for atrial flutter and atrial fibrillation. II. Surgical technique of the maze III procedure. J Thorac Cardiovasc Surg. 1995 Aug;110(2):485-95.CrossRef PubMed
101. Bonchek LI, Burlingame MW, Worley SJ, Vazales BE, Lundy EF. Cox/maze procedure for atrial septal defect with atrial fibrillation: management strategies. Ann Thorac Surg. 1993 Mar;55(3):607-10.
102. Sandoval N, Velasco VM, Orjuela H, Caicedo V, Santos H, Rosas F, Carrea JR, Melgarejo I, Morillo CA. Concomitant mitral valve or atrial septal defect surgery and the modified Cox-maze procedure. Am J Cardiol. 1996 Mar 15;77(8):591-6.CrossRef PubMed
103. Kamata J, Kawazoe K, Izumoto H, Kitahara H, Shiina Y, Sato Y, Nakai K, Ohkubo T, Tsuji I, Hiramori K. Predictors of sinus rhythm restoration after Cox maze procedure concomitant with other cardiac operations. Ann Thorac Surg. 1997 Aug;(2):394-8. CrossRef PubMed
104. Galal MO, Wobst A, Halees Z, Hatle L, Schmaltz AA, Khougeer F, De Vol E, Fawzy ME, Abbag F, Fadley F, et al. Peri-operative complications following surgical closure of atrial septal defect type II in 232 patients--a baseline study. Eur Heart J. 1994 Oct;15(10):1381-4.
105. Santoro G, Pascotto M, Sarubbi B, Cappelli Bigazzi M, Calvanese R, Iacono C, Pisacane C, Palladino MT, Pacileo G, Russo MG, Calabrò R. Early electrical and geometric changes after percutaneous closure of large atrial septal defect. Am J Cardiol. 2004 Apr 1;93(7):876-80.CrossRef PubMed
106. Salehian O, Horlick E, Schwerzmann M, Haberer K, McLaughlin P, Siu SC, Webb G, Therrien J. Improvements in cardiac form and function after transcatheter closure of secundum atrial septal defects. J Am Coll Cardiol. 2005 Feb 15;45(4):499-504. CrossRef PubMed
107. Du ZD, Cao QL, Koenig P, Heitschmidt M, Hijazi ZM. Speed of normalization of right ventricular volume overload after transcatheter closure of atrial septal defect in children and adults. Am J Cardiol. 2001 Dec 15;88(12):1450-3, A9.
108. Eidem BW, O'Leary PW, Tei C, Seward JB. Usefulness of the myocardial performance index for assessing right ventricular function in congenital heart disease. Am J Cardiol. 2000 Sep 15;86(6):654-8.CrossRef PubMed
109. Dhillon R, Josen M, Henein M, Redington A. Transcatheter closure of atrial septal defect preserves right ventricular function. Heart. 2002 May;87(5):461-5.CrossRef PubMed
110. Shaheen J, Alper L, Rosenmann D, Klutstein MW, Falkowsky G, Bitran D, Tzivoni D. Effect of surgical repair of secundum-type atrial septal defect on right atrial, right ventricular, and left ventricular volumes in adults. Am J Cardiol. 2000 Dec 15;86(12):1395-7, A6.
111. Walker RE, Moran AM, Gauvreau K, Colan SD. Evidence of adverse ventricular interdependence in patients with atrial septal defects. Am J Cardiol. 2004 Jun 1;93(11):1374-7, A6.
112. Giardini A, Donti A, Formigari R, Specchia S, Prandstraller D, Bronzetti G, Bonvicini M, Picchio FM. Determinants of cardiopulmonary functional improvement after transcatheter atrial septal defect closure in asymptomatic adults. J Am Coll Cardiol. 2004 May 19;43(10):1886-91.CrossRef PubMed
113. Schussler JM, Anwar A, Phillips SD, Roberts BJ, Vallabhan RC, Grayburn PA. Effect on right ventricular volume of percutaneous Amplatzer closure of atrial septal defect in adults. Am J Cardiol. 2005 Apr 15;95(8):993-5.CrossRef PubMed
114. Schenck MH, Sterba R, Foreman CK, Latson LA. Improvement in noninvasive electrophysiologic findings in children after transcatheter atrial septal defect closure. Am J Cardiol. 1995 Oct 1;76(10):695-8.CrossRef PubMed
115. El-Said HG, Ing FF, Grifka RG, Nihill MR, Morris C, Getty-Houswright D, Mullins CE. 18-year experience with transseptal procedures through baffles, conduits, and other intra-atrial patches. Catheter Cardiovasc Interv. 2000 Aug;50(4):434-9; discussion 440.CrossRef PubMed
116. Lakkireddy D, Patel D, Mlcochova H, Thal S, Wazni O, Kanj M, Arruda M, Prasad S, Bhargava M, Cummings J. Feasibility of transeptal puncture in radiofrequency catheter ablation of atrial fibrillation in patients with atrial septal defect (ASD) repair. Heart Rhythm. 2006; 3(5):s282-3 [Abstract].PubMed
117. Rickers C, Hamm C, Stern H, Hofmann T, Franzen O, Schräder R, Sievert H, Schranz D, Michel-Behnke I, Vogt J, Kececioglu D, Sebening W, Eicken A, Meyer H, Matthies W, Kleber F, Hug J, Weil J. Percutaneous closure of secundum atrial septal defect with a new self centering device ("angel wings"). Heart. 1998 Nov;80(5):517-21.
118. Mashman WE, King SB, Jacobs WC, Ballard WL. Two cases of late embolization of Amplatzer septal occluder devices to the pulmonary artery following closure of secundum atrial septal defects. Catheter Cardiovasc Interv. 2005 Aug;65(4):588-92. CrossRef PubMed
119. Ruge H, Wildhirt SM, Libera P, Vogt M, Holper K, Lange R. Images in cardiovascular medicine. Left atrial thrombus on atrial septal defect closure device as a source of cerebral emboli 3 years after implantation. Circulation. 2005 Sep 6;112(10):e130-1.CrossRef PubMed
120. Knirsch W, Dodge-Khatami A, Balmer C, Peuster M, Kadner A, Weiss M, Prêtre R, Berger F. Aortic sinus-left atrial fistula after interventional closure of atrial septal defect. Catheter Cardiovasc Interv. 2005 Sep;66(1):10-3.CrossRef PubMed
121. Costache V, Chavanon O, Thony F, Blin D. Aortic arch embolization of an Amplatzer occluder after an atrial septal defect closure: hybrid operative approach without circulatory arrest. Eur J Cardiothorac Surg. 2005 Aug;28(2):340-2.CrossRef

PubMed
122. Sievert H, Babic UU, Ensslen R, Merle H, Osypka P, Rubel C, Scherer D, Spies H, Wiederspahn T, Zeplin HE. Occlusion of atrial septal defect with a new occlusive device. Z Kardiol. 1996 Feb;85(2):97-103.
123. Peterson GE, Brickner ME, Reimold SC. Transesophageal echocardiography: clinical indications and applications. Circulation. 2003 May 20;107(19):2398-402.CrossRef PubMed
124. Brochu MC, Baril JF, Dore A, Juneau M, De Guise P, Mercier LA. Improvement in exercise capacity in asymptomatic and mildly symptomatic adults after atrial septal defect percutaneous closure. Circulation. 2002 Oct 1;106(14):1821-6.CrossRef PubMed
125. Figueroa MI, Balaguru D, McClure C, Kline CH, Radtke WA, Shirali GS. Experience with use of multiplane transesophageal echocardiography to guide closure of atrial septal defects using the amplatzer device. Pediatr Cardiol. 2002 Jul-Aug;23(4):430-6. CrossRef PubMed
126. Jongbloed MR, Schalij MJ, Zeppenfeld K, Oemrawsingh PV, van der Wall EE, Bax JJ. Clinical applications of intracardiac echocardiography in interventional procedures. Heart. 2005 Jul;91(7):981-90.CrossRef PubMed
127. Bartel T, Konorza T, Arjumand J, Ebradlidze T, Eggebrecht H, Caspari G, Neudorf U, Erbel R. Intracardiac echocardiography is superior to conventional monitoring for guiding device closure of interatrial communications. Circulation. 2003 Feb 18;107(6):795-7.CrossRef PubMed
128. Earing MG, Cabalka AK, Seward JB, Bruce CJ, Reeder GS, Hagler DJ. Intracardiac echocardiographic guidance during transcatheter device closure of atrial septal defect and patent foramen ovale. Mayo Clin Proc. 2004 Jan;79(1):24-34.
129. Miyamoto N, Kyo S, Motoyama T, Hung JS, Suzuki S, Aihara S, Matsumura M, Omoto R, Dohi Y, Matsuo H. Usefulness of intracardiac echocardiography for guidance of transseptal puncture procedure. J Cardiol. 1995 Jan;25(1):29-35.
130. Epstein LM, Smith T, TenHoff H. Nonfluoroscopic transseptal catheterization: safety and efficacy of intracardiac echocardiographic guidance. J Cardiovasc Electrophysiol. 1998 Jun;9(6):625-30.CrossRef PubMed
131. Szili-Torok T, Kimman G, Theuns D, Res J, Roelandt JR, Jordaens LJ. Transseptal left heart catheterisation guided by intracardiac echocardiography. Heart. 2001 Nov;86(5):E11.PubMed
132. Citro R, Ducceschi V, Salustri A, Santoro M, Salierno M, Gregorio G. Intracardiac echocardiography to guide transseptal catheterization for radiofrequency catheter ablation of left-sided accessory pathways: two case reports. Cardiovasc Ultrasound. 2004 Oct 8;2:20.CrossRef PubMed
133. Wettwer E, Hála O, Christ T, Heubach JF, Dobrev D, Knaut M, Varró A, Ravens U. Role of IKur in controlling action potential shape and contractility in the human atrium: influence of chronic atrial fibrillation. Circulation. 2004 Oct 19;110(16):2299-306. Epub 2004 Oct 11.CrossRef PubMed
134. Cha TJ, Ehrlich JR, Chartier D, Qi XY, Xiao L, Nattel S. Kir3-based inward rectifier potassium current: potential role in atrial tachycardia remodeling effects on atrial repolarization and arrhythmias. Circulation. 2006 Apr 11;113(14):1730-7. Epub 2006 Apr 3.CrossRef PubMed
135. Bode F, Sachs F, Franz MR. Tarantula peptide inhibits atrial fibrillation.Nature. 2001 Jan 4;409(6816):35-6.CrossRef PubMed
136. Hagendorff A, Schumacher B, Kirchhoff S, Lüderitz B, Willecke K. Conduction disturbances and increased atrial vulnerability in Connexin40-deficient mice analyzed by transesophageal stimulation. Circulation.1999 Mar 23;99(11):1508-15.
137. Ehrlich JR, Biliczki P, Hohnloser SH, Nattel S. Atrial-selective approaches for the treatment of atrial fibrillation. J Am Coll Cardiol. 2008 Feb 26;51(8):787-92.CrossRef PubMed
138. Cardin S, Li D, Thorin-Trescases N, Leung TK, Thorin E, Nattel S. Evolution of the atrial fibrillation substrate in experimental congestive heart failure: angiotensin-dependent and -independent pathways. Cardiovasc Res. 2003 Nov 1;60(2):315-25.CrossRef PubMed
139. Li D, Shinagawa K, Pang L, Leung TK, Cardin S, Wang Z, Nattel S. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. Circulation. 2001 Nov 20;104(21):2608-14.CrossRef PubMed
<p class="Manuscript-Body"/>140. Sakabe M, Fujiki A, Nishida K, Sugao M, Nagasawa H, Tsuneda T, Mizumaki K, Inoue H. Enalapril prevents perpetuation of atrial fibrillation by suppressing atrial fibrosis and over-expression of connexin43 in a canine model of atrial pacing-induced left ventricular dysfunction. J Cardiovasc Pharmacol. 2004 Jun;43(6):851-9.CrossRef PubMed
141. Shi Y, Li D, Tardif JC, Nattel S. Enalapril effects on atrial remodeling and atrial fibrillation in experimental congestive heart failure. Cardiovasc Res. 2002 May;54(2):456-61.CrossRef PubMed
142. Fauchier L, Pierre B, de Labriolle A, Grimard C, Zannad N, Babuty D. Antiarrhythmic effect of statin therapy and atrial fibrillation a meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2008 Feb 26;51(8):828-35.CrossRef PubMed
143. Shiroshita-Takeshita A, Brundel BJ, Burstein B, Leung TK, Mitamura H, Ogawa S, Nattel S. Effects of simvastatin on the development of the atrial fibrillation substrate in dogs with congestive heart failure. Cardiovasc Res. 2007 Apr 1;74(1):75-84. Epub 2007 Jan 11.CrossRef PubMed
144. Sakabe M, Shiroshita-Takeshita A, Maguy A, Dumesnil C, Nigam A, Leung TK, Nattel S. Omega-3 polyunsaturated fatty acids prevent atrial fibrillation associated with heart failure but not atrial tachycardia remodeling. Circulation. 2007 Nov 6;116(19):2101-9. Epub 2007 Oct

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Physical Activity and Incidence of Atrial Fibrillation in Older Adults: The Cardiovascular Health Study

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Introduction

Retrospective case-control studies and case series of younger athletes and middle-aged adults have suggested an adverse association between physical activity and development of atrial fibrillation. However, these studies have evaluated subjects engaged in either vigorous exertion or endurance training. On the other hand, habitual physical activity might be expected through salutatory effects on blood pressure, vascular compliance, coronary disease, and heart failure to reduce the incidence of atrial fibrillation in the general population. The aim of this study was to assess the effect of habitual light to moderate physical activity on the incidence of atrial fibrillation among older adults.

Methods

IThe authors evaluated 5446 patients (58% female) = 65 years of age (72.8 ± 5.6 years) who were followed prospectively in The Cardiovascular Health Study, which was a National Heart, Lung, and Blood Institute sponsored prospective cohort study of determinants of cardiovascular risk among older subjects. Various measures of physical activity were assessed. Usual leisure-time activity (kcal/week) was assessed at baseline and at the third and seventh annual visits by use of a modified Minnesota Leisure-Time Activities questionnaire. This evaluates the frequency and duration of 15 different activities during the prior 2 weeks. The findings were quantified in quintiles. Usual exercise intensity was defined as no exercise or low, medium, or high intensity exercise. Finally, information on blocks walked (quintiles) and usual pace walked (< 2, 2-3, >3 mph) was obtained. Cases of atrial fibrillation were identified on the basis of either annual ECGs obtained on study participants or from hospital discharge diagnoses.

Our Experience

WDuring 12 years of follow-up, 1061 new cases of atrial fibrillation were documented, yielding an incidence rate of 22.4 cases per 1000 person-years. After adjustment for age and gender, both leisure-time activity and exercise intensity were associated with lower incidence of atrial fibrillation. Compared with the lowest quintile, individuals in quintiles 3,4, and 5 for leisure-time activity had 25%, 22%, and 36% lower risk, respectively of developing atrial fibrillation ($p < 0.001$). For exercise intensity, a U-shaped curve was observed.

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Compared with no regular exercise, patients engaged in moderate intensity exercise had a 28% lower risk of atrial fibrillation; however, those engaged in high-intensity exercise faired no better than individuals with a lifestyle of either no exercise or only low intensity exercise. A protective effect against atrial fibrillation was also observed in individuals who walked longer distances and at a brisker pace.

The authors repeated the analysis after excluding 1150 patients with a significant co-morbidity that could affect physical activity, such as claudication, angina, limited vision, and abnormal FEV1. However, the findings of the study were not significantly altered. In a novel analysis, the authors also calculated the proportion of new atrial fibrillation cases attributable to the lack of moderate physical activity (leisure-time activity below the median of 616 kcal/week, walking fewer than 12 blocks a week, or walking at a pace less than 2 mph). Overall, 26% (95% CI: 7-43%) of new atrial fibrillation cases were attributable to a lack of moderate level physical activity.

Conclusions

Atrial fibrillation continues to be an important clinical problem. In this study, 1 in 5 adults = 65 years of age developed atrial fibrillation during a 12-year follow-up period. This is an underestimate of the true incidence as many cases of paroxysmal atrial fibrillation (especially if asymptomatic) were likely missed based on the study design. The finding that engagement in only moderate leisure-time activity and regular walking at a moderate distance and pace may attenuate this risk in a quarter of the population is particularly impressive. These data highlight the need for public health policies that encourage participation in regular physical activity as part of our society's day-to-day lifestyle.

(accessed November 2012)
19. Wood S. Poetry, prayers, and pranayama: A low-tech therapy for heart failure. http://www.theheart.org/article/741763.do (accessed November 2012)
20. O' Riordan M. Tai chi movement therapy improves functional capacity and quality of life in patients with stable HF. http://www.theheart.org/article/240039.do (accessed November 2012)
21. Nainggolan L. More than 70% of ACS patients use alternative medicine. http://www.theheart.org/article/274935.do (accessed November 2012)
22. Bernardi L, Spadacini G, Bellwon J, Hajric R, Roskamm H, Frey AW. Effect of breathing rate on oxygen saturation and exercise performance in chronic heart failure. Lancet 1998;351:1308-1311
23. Radzievsky SA, Lebedeva OD, Fisenko LA, Majskaja SA. Function of myocardial contraction and relaxation in essential hypertension in dynamics of acupuncture therapy. Am J Chinese Med 1989;17:111-117
24. Suk Lee M, Soo Lee M, Choi ES, Chung HT. Effects of Qigong on Blood Pressure, Blood Pressure Determinants and Ventilatory Function in Middle-Aged Patients with Essential Hypertension. Am J Chinese Med 2003;31:489-497
25. Soo Lee M, Jeong Huh H, Gi Kim B, Ryu H, Lee HS, Kim JM, Chung HT. Effects of Qi-Training on Heart Rate Variability. Am J Chinese Med 2002;30:463-470
26. Lan C, Chen SY, Lai JS, Wong MK. Heart Rate Responses and Oxygen Consumption during Tai Chi Chuan Practice. Am J Chinese Med 2001;29:403-410
27. Effects of Qigong on Cardiorespiratory Changes: A Preliminary Study. Am J Chinese Med 1993;21:1-6
28. Dharmananda S. Neiguan (pericardium-6). http://www.itmonline.org/arts/pc6.htm (accessed November 2012)
29. Maciocia G. Diagnosis in Chinese Medicine, a comprehensive guide. 2nd Ed., London, Churchill Livingstone. 2005;457-458
30. Liu S, Chen Z, Hou J, Wang J, Wang J, Zhang X. Magnetic disk applied on Neiguan point for prevention and treatment of cisplatin-induced nausea and vomiting. J Tradit Chin Med 1991; 11: 181-183
31. Lin H. Specific therapeutic effect of Neiguan on heart disease. Int J of Clinical Acupuncture 1998; 9: 303-305.
32. Chiu YJ, Chi A, Reid IA. Cardiovascular and endocrine effects of acupuncture in hypertensive patients. Clin Exp Hypertens 1997; 19: 1047-1063
33. Lai Z, Cao Q, Chen S, Han Z. Role of amygdaloid nucleus in the correlation between the heart and the acupoint neiguan in rabbits. J Tradit Chin Med 1991; 11: 128-138
34. Syuu Y, Matsubara H, Kiyooka T, Hosogi S, Mohri S, Araki J, Ohe T, Suga H. Cardiovascular beneficial effects ofelectroacupuncture at Neiguan (PC-6) acupoint in anesthetized open-chest dog. Jpn J Physiol 2001; 51: 231-238
35. Kong SM, Li SX, Han YA, Zang YW, Li CX. Heart rate power spectral analysis during homeostatic action of neiguan acupoint--role played by the cardial vagus nerve. J Tradit Chin Med 1988; 8: 271-276
36. Lee S, Lee MS, Choi JY, Lee SW, Jeong SY, Ernst E. Acupuncture and heart rate variability: a systematic review. Auton Neurosci 2010; 155: 5-13
37. Li Z, Wang C, Mak AF, Chow DH. Effects of acupuncture on heart rate variability in normal subjects under fatigue and non-fatigue state. Eur J Appl Physiol 2005; 94: 633-640
38. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. Circulation 2002; 105: 2753-2759
39. Lombardi F, Tarricone D, Tundo F, Colombo F, Belletti S, Fiorentini C. Autonomic nervous system and paroxysmal atrial fibrillation: a study based on the analysis of RR interval changes before, during and after paroxysmal atrial fibrillation. Eur Heart

J 2004; 25: 1242-1248
40. Danik S, Neuzil P, d'Avila A, Malchano ZJ, Kralovec S, Ruskin JN, Reddy VY. Evaluation of catheter ablation of peri-atrial ganglionic plexi in patients with atrial fibrillation. Am J Cardiol 2008; 102: 578-583
41. Lu Z, Scherlag BJ, Lin J, Yu L, Guo JH, Niu G, Jackman WM, Lazzara R, Jiang H, Po SS. Autonomic mechanism for initiation of rapid firing from atria and pulmonary veins: evidence by ablation of ganglionated plexi. Cardiovasc Res 2009; 84: 245-252
42. Li S, Scherlag BJ, Yu L, Sheng X, Zhang Y, Ali R, Dong Y, Ghias M, Po SS. Low-level vagosympathetic stimulation: a paradox and potential new modality for the treatment of focal atrial fibrillation. Circ Arrhythm Electrophysiol 2009; 2: 645-651
43. Tai CT, Chiou CW, Wen ZC, Hsieh MH, Tsai CF, Lin WS, Chen CC, Lin YK, Yu WC, Ding YA, Chang MS, Chen SA. Effect of phenylephrine on focal atrial fibrillation originating in the pulmonary veins and superior vena cava. J Am Coll Cardiol 2000; 36: 788-793
44. Zhang Y, Scherlag BJ, Lu Z, Niu GD, Yamanashi WS, Hogan C, Fields J, Ghias M, Lazzara R, Jackman WM, Po S. Comparison of atrial fibrillation inducibility by electrical stimulation of either the extrinsic or the intrinsic autonomic nervous systems. J Interv Card Electrophysiol 2009; 24: 5-10
45. Lomuscio A, Belletti S, Battezzati PM, Lombardi F. Efficacy of Acupuncture in Preventing Atrial Fibrillation Recurrences After Electrical Cardioversion . J Cardiovasc Electrophysiol 2011; 22: 241-247
46. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagnè P, Nattel S, Thibault B, for the Canadian Trial of Atrial Fibrillation Investigators. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. N Engl J Med 2000;342:913-920
47. Hongwu L. Specific therapeutic effect of Neiguan on heart disease. Int J of Clinical Acupuncture 1998;9:303-305.
48. Van Gelder IC, Crijns HJ, Van GilstWH, Verwer R, Lie KI. Prediction of uneventful cardioversion and maintenance of sinus rhythm from direct-current electrical cardioversion of chronic atrial fibrillation and flutter. Am J Cardiol 1991;68:41-46
49. Lombardi F, Colombo A, Basilico B, Ravaglia R, Garbin M, Vergani D, Battezzati PM, Fiorentini C. Heart rate variability and early recurrence of atrial fibrillation after electrical cardioversion. J Am Coll Cardiol 2001;37:157-162
50. Lombardi F, Belletti S, Battezzati PM, Lomuscio A. Acupuncture for paroxysmal and persistent atrial fibrillation: An effective non-pharmacological tool? World J Cardiol 2012; 4(3): 60-65
51. Hughes S. Yoga found to reduce AF episodes. http://www.theheart.org/article/1204423.do (Accessed November 2012)
52. Baccetti S. Aritmie e medicina tradizionale cinese. http://www.regione.toscana.it/regione/multimedia/RT/documents/2012/04/02/3ff8113667e305fd0cb8cfdf3eef89ba_fiordiprugna.pdf (Accessed Novemer 2012)
53. Maciocia G. Diagnosis in Chinese Medicine, a comprehensive guide. 2nd Ed., London, Churchill Livingstone. 2005;19-40