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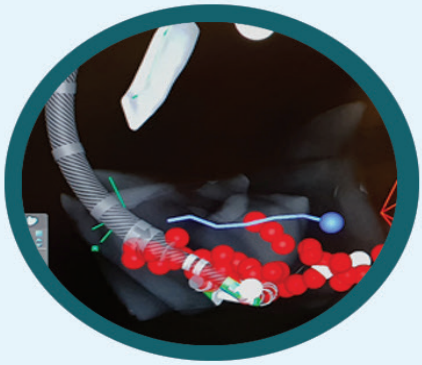

- Atrial Fibrillation and Atrial Flutter Ablation – an Unconventional Approach.
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Editorial

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Global Warming, Cricket World Cup and Atrial Fibrillation Awareness!

Dear Colleagues

Welcome to the Summer issue of the Journal of Atrial Fibrillation. Hope everyone had a great time with family and friends. Whoever wants the world to believe that Global Warming is an invention of over enthusiastic environmentalists, I say they are dead wrong. I had experienced the true impact of Global Warming this Summer during my trip to Europe with temperatures clearly in the record highs. For those of you who are Cricket nuts, the World Cup ended with a thrilling final. England faced off New Zealand in a nail biter that got extended into a super over. England took the World Cup home on a technicality dashing the hopes of 5 million Kiwis. The 4 sub-continent teams – India, Pakistan, Sri Lanka and Bangladesh exited at various stages. There were hundreds of millions of betting dollars lost and won with an unexpected loss of the tournament favorite India to New Zealand in the semi-final.

Kansas City Heart Rhythm Symposium marked its 11th year and the founding Editor-in-Chief of JAFIB was honored with the well-deserved "Pioneer in Cardiovascular Electrophysiology" Award. Dr. Natale is well known for his incredible contributions to the field, particularly developing real life practical approaches to several complex arrhythmias. Special shout out to the EP Live Foundation on successfully organizing EP Live Europe (Milan) and EP Live India (Bengaluru) a two-day case-based learning event where several live cases and recorded cases were showcased with robust discussion on clinical and technical aspects. They were very popular and especially India it ignited a significant interest in complex arrhythmia ablation in many budding young electrophysiologists.

Congratulations to the Global AF Alliance (GAFA) Foundation, Heart Rhythm Society (HRS) and ACC for launching a very effective AF awareness campaign last month It takes unfettered commitment from all fronts to fight this 21st century epidemic. Mellanie True Hills and group developed an AF awareness song as part of STOPAFIB.org's continued engagement in patient education. Several physicians and hospital systems across the world have organized many grass roots level events. ACC Electrophysiology Council and Heart Rhythm Society organized a Twittenar on life style management and risk factor modification as the main theme. It is refreshing to see the Eps systematically establishing a multipronged approach to the treatment of AF targeting obstructive sleep apnea, obesity, hypertension, diabetes and exercise.

This issue of the journal has several interesting original articles and case reports worth spending time on. One paper that caught my attention is the survey of Cardio-Thoracic surgery residents. The survey reflects a relative dearth of training, volume and dedicated arrhythmia surgery ablation training. As the field moves towards a heart team approach for the treatment of AF, Surgical training curriculums need special attention arrhythmia surgery. We once again appreciate your support to the journal and look forward to your contributions to the field.

Best wishes
DJ Lakkireddy

Dhanunjaya (DJ)Lakkireddy
MD, FACC, FHRS
Editor-in-Chief

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Intermittent Nonhabitual Coffee Consumption and Risk of Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background

Though it is a widely held belief that caffeinated beverages predispose individuals to arrhythmias, it is not clear whether regular coffee consumption is associated with development of atrial fibrillation (AF).

Objective

We examined the association between long-term coffee consumption and development of AF in both habitual (≥0.5 cups of daily coffee) and nonhabitual (<0.5 cups/day) drinkers.

Methods

A total of 5,972 men and women, aged 45-84 years and without a history of cardiovascular disease at baseline in the Multi-Ethnic Study of Atherosclerosis (MESA) were followed from 2000 to 2014 for incident AF with baseline coffee consumption assessed in 2000-2002 via a Food Frequency Questionnaire and divided into quartiles of 0 cups/day, >0 to <0.5 cups/day, ≥0.5 to <1 cups/day, and ≥1.5 cups/day.

Results

Out of the 828 incident cases of AF, intermittent coffee consumption (>0 to 0.5 cups of daily coffee) was associated with a greater risk of incident AF (HR=1.36, 95% CI 1.04-1.77) relative to 0 cups/day in multivariable Cox proportional hazards models after adjustment for numerous AF risk factors. Higher coffee consumption was not associated with AF risk (HR 1.03, 95%CI 0.93-1.14 for ≥0.5 to 1.5 cups/day and 1.05, 95%CI 0.97-1.13 for ≥1.5 cups/day).

Conclusions

While there appears to be no dose-response association between habitual coffee intake and AF risk, we found evidence that intermittent, but not habitual, coffee consumption is associated with a modestly increased risk of incident AF that deserves further study.

Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and causes substantial morbidity, mortality and socioeconomic burden [1]. Caffeine consumption is cited as a common trigger for AF episodes but it is not clear whether regular coffee consumption or consumption of large amounts of coffee is actually associated with development of AF [2]. Habitual coffee consumption has been established as having having neutral to beneficial effects on type 2 diabetes, coronary artery disease, congestive heart failure, and stroke [3-7]; furthermore, large observational studies suggest that, compared to non-drinkers, regular coffee drinkers have reduced mortality [8,9]. Interestingly, the effects of coffee have been suggested to be different in habitual drinkers (defined as those who consume more than a half cup of daily coffee) compared to nonhabitual drinkers. In caffeine-naïve subjects, coffee is associated with acute increases in blood pressure but does not affect blood pressure in habitual coffee drinkers [10]. The relationship of coffee to development of AF is not as well characterized. In total three meta-analyses have assessed the association between coffee consumption and development of AF and all have demonstrated no increased risk [11-13]. However, these studies are limited because the division of groups of coffee consumption is inconsistent and may not be able to identify nonhabitual consumers. With consideration of these controversial data, our objective was to clarify the relationship between coffee consumption and the development of AF in both habitual and nonhabitual drinkers from data in the Multi-Ethnic Study of Atherosclerosis (MESA), a large prospective cohort study in the United States.

Key Words

Coffee, Caffeine, Atrial Fibrillation, Epidemiology, Cardiovascular Disease.

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Materials and Methods

MESA is a prospective population study whose study methods have been described previously in detail [14]. In brief, between 2000 and 2002, MESA enrolled 6,814 individuals free of cardiovascular disease age 45-84 years from four different race/ethnicities (Caucasian, African-American, Hispanic, and Chinese) from six US field centers. Participants were free of cardiovascular disease at baseline (defined as physician-diagnosed myocardial infarction, angina or nitroglycerin use, stroke or transient ischemic attack, heart failure, current AF or having undergone cardiovascular procedures) and underwent follow-up from 2000 to 2014. Standardized MESA procedures required exclusion of subjects who reported any of these conditions or noninvasive testing indicating a concern for a condition requiring medical follow-up from the participant's baseline questionnaire.

At the baseline health examination, height, weight, and systolic and diastolic blood pressure were measured. Total cholesterol, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), and triglycerides were measured in nonfasting blood samples. MESA initially defined hypertension using JNC-6 criteria, but in light of recent modifications to the definition by ACC/AHA, hypertension was redefined as taking antihypertensives, systolic blood pressure (BP) ≥130, or diastolic BP ≥80. Participants completed a self-reported questionnaire on highest attained education, cigarette smoking status (never, former, current), total pack year smoking history, alcohol consumption habit (never, former, current), and assessed reported intake of alcoholic drinks (g/day), soda, diet soda, and tea (servings/day).

Baseline coffee consumption was assessed in 2000-2002 via a 120-item Food Frequency Questionnaire (FFQ) that assessed daily intake of foods, beverages, and nutrients in the past year. The questionnaire allowed nine responses that ranged from rare to never, 1-3 per month, once a week, 2-4 per week, 5-6 per week, once a day, 2-3 per day, 4-5 per day, 6+ per day. These responses were converted into daily servings of 0, 0.07, 0.14, 0.43, 0.79, 1, 2.5, 4.5, and 6 cups, respectively. Coffee intake was not differentiated by caffeinated or decaffeinated state and was reported by average serving size as small, medium, or large. A small serving size was characterized as a half cup of coffee, a medium serving was a full cup, and a large serving was 1.5 cups. Using these calculations, we divided average daily coffee consumption into quartiles of 0 cups/day, intermittent nonhabitual (<0.5 cups/day), ≥0.5 to <1.5 cups/day, and ≥1.5 cups/day.

MESA participants or a proxy were contacted by phone every 9 to 12 months to identify all new hospitalizations. Trained staff obtained medical records for all reported hospitalizations and discharge diagnosis International Classification of Diseases, Ninth Revision (ICD-9) codes. AF was identified by: (1) an ICD-9 code for AF (427.31) in any position assigned at hospital discharge, (2) an ICD-9 code for atrial flutter (427.32) in any position assigned at hospital discharge, (3) by study electrocardiogram at a single follow-up visit (2010-2012) (with electrocardiograms reviewed by the study events committee), or (4) for those enrolled in fee-for-service Medicare (55% of the cohort), by an inpatient or outpatient claim with an AF or atrial flutter ICD-9 diagnosis code in any position, using methods adapted from the Cardiovascular Health Study [15]. Hospital discharge diagnosis data and Medicare claims data were available through December 2014. The date of incident AF was defined as the first date AF was noted either by study electrocardiogram or a single ICD-9 code in any position in cohort hospitalization monitoring or Medicare inpatient or outpatient claims data. A review of 16 validation studies determined that the use of the ICD-9 codes to identify AF events has relatively good performance [16].

Participants with preexisting AF (66), incomplete FFQs with >70 questions left blank (282), and lacking clinical covariates (494) were excluded from the analyses leaving 5,972 eligible participants. Baseline characteristics were initially compared across quartiles of coffee consumption using analysis of variance or the Chi-square test of proportions for continuous and categorical variables, respectively.

Multivariable-adjusted Cox proportional hazards regression models were used incorporating time from baseline to incident AF or censoring at death, dropout, or end of the analysis period, December 2014. The lowest approximate quartile corresponding to participants who reported zero coffee consumption was used as the reference category. Nested models with progressive degrees of adjustment were constructed to account for various confounding factors. The first model adjusted for demographic data including age, gender, and race/ethnicity. The second model additionally adjusted for education (less than college degree, college degree, more than college degree), body mass index, systolic BP, diastolic BP, taking antihypertensive medication, diabetes mellitus, LDL-C, and HDL-C. The final model was further adjusted for possible lifestyle confounders including ever/former/current alcohol drinker, daily alcohol intake (g/day), ever/former/current cigarette smoker, pack year smoking history, moderate-vigorous physical activity, and total energy intake, which was calculated from the FFQ. This hierarchial model procedure allowed for examining whether age, gender, and race, first, standard risk factors second, or lifestyle confounders lastly might attenuate any relationships observed between coffee consumption and AF risk. We tested for heterogeneity by including age, gender, education, and race/ethnicity by including interaction of coffee consumption with each covariate, testing statistical significance using the Wald test. A full multivariable model is also provided showing all covariates and their relationships to risk of incident AF.

P-values less than 0.05 were considered statistically significant. All statistical analyses were conducted using Stata (version 12.0, StataCorp, College Station, TX, USA).

Results

Characteristics at baseline according to categories of coffee consumption are shown in [Table 1]. Participants were on average 63 ± 10 years old, 47% male, and 40% Caucasian. During 14 years of follow-up a total of 828 incident AF events were identified. The percentage of participants who developed AF in each quartile (0, <0.5, ≥0.5-1.5, and ≥1.5 cups per day of coffee) was 12.0%, 14.6%, 15.0%, and 14.1%, respectively. The frequency of AF episodes is consistent with prior studies that have looked at this population. Those who drank more coffee tended to be male, be of Caucasian race, and have higher education. They were more likely to be cigarette smokers and consumed more alcohol.

Table 1: Baseline characteristics of participants in the Multi-Ethnic Study of Atherosclerosis (MESA), by approximate quartile of daily coffee consumption

	0 cups coffee	Nonhabitual (<0.5 cups coffee)	≥0.5-1.5 cups coffee	≥1.5 cups coffee	
Total	1651	1508	1378	1435	
Number of AF events	198	221	207	202	
% AF events	12.0%	14.7%	15.0%	14.1%	
Gender					p <0.001
Male	46.4%	45.7%	43.2%	54.2%	
Female	53.6%	54.3%	56.8%	45.8%	
Age (years)	62 (10)	63 (10)	64 (10)	62 (10)	p=0.001
Race					p <0.001
Caucasian	29.1%	25.2%	42.5%	66.4%	
Chinese	19.6%	16.0%	5.2%	2.4%	
African American	34.5%	34.5%	26.6%	16.1%	
Hispanic	16.8%	24.3%	15.1%	16.2%	
Education					p <0.001
Less than Bachelor's	61.7%	59.1%	51.2%	52.4%	
Bachelor's	12.1%	16.9%	24.0%	18.8%	
Master's or doctorate	26.2%	24.0%	24.8%	28.8%	
BMI, kg/m2	27.8 (5.7)	28.3 (5.5)	28.6 (5.3)	28.6 (5.2)	p <0.001
Cigarette smoking					p <0.001
Never	61.5%	54.9%	46.3%	36.0%	
Former	29.9%	34.7%	40.6%	46.2%	
Current	8.6%	10.4%	13.1%	17.8%	
Smoking pack-years	8 (18)	9 (18)	11 (18)	19 (28)	p <0.001
Diabetes mellitus	12.5%	11.0%	10.2%	6.6%	p <0.001
Hypertension (taking antihypertensives, SBP/DBP ≥130 / ≥80 mmHg)	61.5%	62.9%	63.6%	54.9%	p <0.001
LDL cholesterol, mg/dL	116 (32)	118 (32)	118 (32)	118 (29)	p <0.001
Alcohol					p <0.001
Never	29.1%	22.1%	16.0%	9.3%	
Former	25.4%	23.8%	22.9%	21.2%	
Current	45.5%	54.1%	61.1%	69.5%	
Alcohol consumption (g/day)	2.5 (7.2)	4.3 (12.3)	5.4 (12.7)	9.1 (16.6)	p <0.001
Soda consumption (cans/day)	0.39 (1.08)	0.31 (0.76)	0.38 (0.85)	0.42 (0.94)	p <0.001
Diet soda consumption (cans/day)	0.39 (1.11)	0.34 (0.96)	0.44 (1.05)	0.60 (1.21)	p <0.001
Black tea consumption (cups/day)	0.40 (1.05)	0.30 (0.75)	0.25 (0.74)	0.25 (0.84)	p <0.001

Entries are N (%) for categorical variables and mean (± standard deviation) for continuous variables. Differences between groups were analyzed by analysis of variance (ANOVA) for continuous variables, and by $\chi 2$ test for categorical variables.

In an unadjusted model looking at the cumulative incidence of AF over time [Figure 1], a Kaplan Meier curve demonstrated an increased risk of AF development in both nonhabitual (<0.5 cups/day) and habitual users (≥0.5 cups/day) compared to participants who drank no coffee.

After adjustment for demographics, participants in the second (nonhabitual, <0.5 cups/day) quartile had a statistically significant

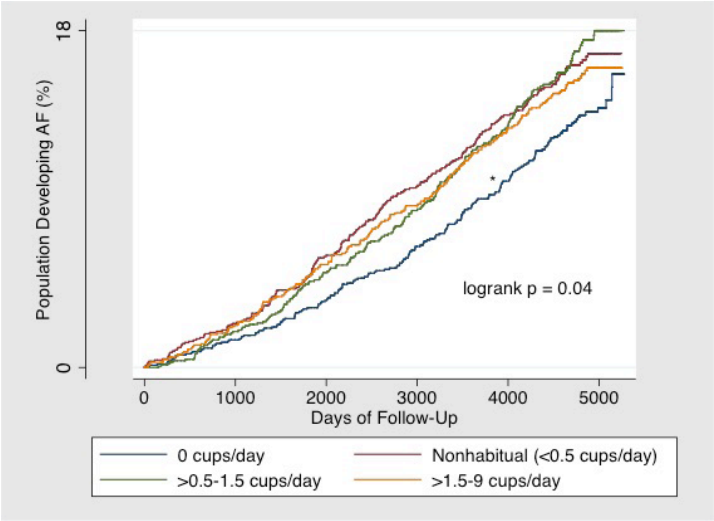

Figure 1: Kaplan-Meier estimates of the percentages of participants who developed AF.

Table 2: Risk of atrial fibrillation by quartile of coffee consumption in MESA

Coffee intake (cups/day)	Total	0 cups/day	Nonhabitual (<0.5 cups/day	≥0.5-1.5 cups/day	≥1.5 cups/day
Total AF events/n (%)	828/5972 (13.9)	198/1651 (12.0)	221/1508 (14.6)	207/1378 (15.0)	202/1435 (14.1)
Model 1 HR (95% CI)		1 (referent)	1.23* (1.01-1.49)	1.06 (0.96-1.17)	1.07* (1.00-1.15)
Model 2 HR (95% CI)		1 (referent)	1.23* (1.01-1.49)	1.06 (0.96-1.17)	1.07* (1.00-1.15)
Model 3 HR (95% CI)		1 (referent)	1.22* (1.01-1.48)	1.03 (0.93-1.14)	1.05 (0.97-1.13)

*p < 0.05
Model 1: adjusted for sex, age, and race/ethnicity
Model 2: as model 1 and education, BMI, SBP, DBP, taking antihypertensives, diabetes, LDL, HDL
Model 3: as model 2 and never/former/current alcohol drinker, daily alcohol intake, never/former/current tobacco user, pack years, daily soda intake, daily diet soda intake, daily tea intake

increased risk of AF (HR 1.23, 95% CI 1.01-1.49) The association in the nonhabitual group persisted after adjustment for various cardiovascular and dietary risk factors in three hierarchical models (HR 1.22, 95% CI 1.01-1.48)[Table 2]. The association was not dose-dependent as there was no significant difference in AF risk from zero coffee consumption if daily coffee consumption exceeded half a cup per day.

No significant heterogeneity in the association of coffee intake with AF was observed among subgroups defined by age, gender, education, or race/ethnicity (p >0.05 for each interaction). The risk of AF in the nonhabitual group appeared particularly pronounced in males with a HR of 1.36 (95% CI 1.04-1.77) after adjustment for risk factors.

In our full multivariable model [Table 3], in addition to the low dose coffee consumption relation previously noted, age, male sex, body mass index, current smoking, and pack years of smoking were all significantly associated with higher risks for incident AF, while African-American ethnicity and daily tea intake were associated with lower risks for incident AF.

Discussion

In this large prospective study, nonhabitual intermittent coffee consumption, which we defined as less than a half cup of daily coffee, was associated with a modest increase in the risk of AF, a finding which persisted in fully-adjusted models. However, there was no increased AF risk if daily coffee consumption exceeded a half cup per day. We have built on the findings of the previous cohort studies, which did not identify a dose-dependent relationship of increasing coffee intake to risk of AF and were encapsulated in a recent review [17]. In 1976, Klatsky et al administered a survey of coffee and tea consumption to 130,000 patients in the Kaiser Permanente health system and followed them until 2008. The study revealed that consumption of four or more cups of coffee per day was associated with an 18% reduction in the risk of hospitalization for arrhythmias, including AF [18]. However, this finding has not been consistent across all studies examining AF incidence and coffee consumption. The Danish Diet, Cancer, and Health cohort study demonstrated that there was no increased risk of AF with consumption of coffee across increasing sextiles of coffee intake in 57,053 participants after a follow-up of 13.5 years until consumption exceeded >6 cups [19].

Table 3: Multivariate analysis of demographic, cardiovascular, and dietary risk factors in relation to incident atrial fibrillation

	Odds ratio	p-value
Age (years)	1.09 (1.08-1.10)	<0.001
Gender (M vs. F)	1.5 (1.26-1.79)	<0.001
Coffee consumption		
<0.5 cups/day vs. none	1.22 (1.01-1.48)	0.04
≥0.5-<1.5 cups/day vs. none	1.03 (0.93-1.14)	0.54
≥1.5 cups/day vs. none	1.05 (0.97-1.13)	0.24
Race		
Chinese vs. Caucasian	1.02 (0.78-1.34)	0.87
African American vs. Caucasian	0.81 (0.73-0.90)	<0.001
Hispanic vs. Caucasian	0.93 (0.86-1.002)	0.06
Education		
Bachelor's vs. less than Bachelor's	1.08 (0.89-1.31)	0.44
more than Bachelor's vs. less than Bachelor's	1.02 (0.93-1.12)	0.69
Per Unit BMI (kg/m2)	1.1 (1.01-1.21)	0.01
Cigarette smoking		
former vs. never	0.97 (0.79-1.18)	0.74
current vs. never	1.23 (1.04-1.45)	0.02
Smoking pack-years	1.005 (1.001-1.008)	0.002
Diabetes mellitus (yes vs. no)	1.03 (0.96-1.11)	0.36
LDL cholesterol (per 10 mg/dL)	0.98 (0.96-1.01)	0.18
HDL cholesterol (per 10 mg/dL)	1.03 (0.98-1.08)	0.29
Alcohol		
former vs. never	1.02 (0.81-1.29)	0.85
current vs. never	0.94 (0.85-1.04)	0.24
Alcohol consumption (g/day)	1.001 (0.996-1.01)	0.67
Daily soda intake (cans/day)	1.001 (0.91-1.10)	0.97
Daily diet soda intake (cans/day)	0.99 (0.93-1.07)	0.87
Daily tea intake (cups/day)	0.89 (0.81-0.99)	0.03

The Women's Health Study confirmed these findings in a selected population of healthy 33,738 middle-aged women after a median follow-up of 14.4 years [20]. The Physician's Health Study was the most recent cohort study that examined this relationship, and found that out of 18,960 male physicians, there was a slight decrease in incident atrial fibrillation in those who drank 1-3 cups of coffee per day after a follow-up of 9 years [21]. It should be noted, also, that the Women's Health Study analyzed exclusively caffeinated coffee, while the Danish study and the Physician's Health Study did not distinguish between whether the coffee was caffeinated or decaffeinated. In meta-analyses, cohort studies did not support an association between coffee consumption and development of AF [11-13].

To our knowledge our study is the first to investigate effects of coffee consumption in the nonhabitual group, as prior studies characterize the lowest group of coffee consumption as ranging from less than 1 to 1-4 cups per day [11-13].

Many patients with paroxysmal AF indicate coffee intake and vagal activity as triggering factors for arrhythmia [22,23]. However, the cohort studies mentioned above as well as direct electrophysiologic monitoring indicate that this effect not does appear to be sustained with long-term use. In a study consisting of 1,388 participants undergoing 24-hour Holter monitoring, there was no association noted between higher caffeine intake and atrial or ventricular premature beats [24].

A proposed mechanism for this finding is the development of increased tolerance to the effects of coffee in the acute setting. Caffeine acts on the heart by binding to the A1 and A2 subtypes of the adenosine receptor. In intermittent doses, endogenously released adenosine may shorten atrial refractoriness and predispose to arrhythmias. However, it is possible that habituation could develop with long-term use. Coffee could theoretically confer cardioprotection from AF with habitual intake by attenuating the effects of endogenous adenosine. A controlled trial in dogs found that escalating doses of caffeine decreased propensity for atrial fibrillation [25], and a study of 68 patients in the emergency department who ingested caffeine had decreased responsiveness to a 6 mg bolus of adenosine in the treatment of supraventricular tachycardias [26]. Additionally, coffee has been recently demonstrated to attenuate the affect of coronary vasodilation as detected on myocardial perfusion scintigraphy [27].

There is evidence to suggest that coffee has different effects on cardiac physiology in habitual drinkers compared to nonhabitual drinkers [28]. In a study conducted in Switzerland, nonhabitual coffee drinkers developed acute increases in systolic BP 30-60 minutes after drinking a triple espresso coffee; habitual drinkers did not demonstrate similar findings despite undergoing similar increases in heart rate and sympathetic muscle tone [10]. In the same population, the authors also demonstrated that coffee blunted the blood pressure response to mental stress in habitual, but not in nonhabitual, drinkers [29]. Similar findings have been demonstrated in a study conducted on a Japanese population [30]. There is also evidence to suggest that transient exposure to coffee has an increased risk of triggering myocardial infarction in those with occasional coffee intake compared to nondrinkers; this effect is attenuated with increasing cups [31]. While the definition of "nonhabitual" is not standardized for

the time being, most studies characterize it as between the range of less than one cup a day to less than two cups a week.

Our study has strengths and limitations. An important strength is the consistent standardized assessment of coffee intake as well as evaluation of AF. Our study includes both genders, encompasses a broad range of racial and ethnic diversity, and adjusts for additional risk categories related to smoking and alcohol consumption (pack-years and g of alcohol intake) compared to previous cohort studies. Ours is also the first to utilize the modified definition of hypertension of systolic blood pressure (BP) ≥130 mmHg and/or diastolic BP ≥80 mmHg as defined by the ACC/AHA guidelines established in 2017 [32]. With this in mind, prospective studies such as ours cannot infer causality between coffee consumption and risk of AF. FFQs by nature are subject to recall bias and underreporting, and the limitations of nutritional epidemiology have been addressed in many editorials [33,34]. AF events were not classified by duration (paroxysmal versus persistent versus permanent), and the AF incidence is likely underestimated as regular EKGs were not performed in this cohort to determine the presence of asymptomatic AF, which is common in the older population; however, there is no reason to believe any underreporting of AF would be different according to coffee consumption status. Furthermore, because coffee consumption was assessed only at baseline, our study may not reflect long-term behavioral patterns or the effects of changes in coffee consumption. Other limitations include potential residual confounders such as presence of obstructive sleep apnea and sleep patterns, for which data in this cohort was only collected in a limited subset, as well as outcome ascertainment bias in patients with limited access to health care.

We did not directly quantify total caffeine intake in this study. This is because the FFQ did not draw a distinction between decaffeinated and caffeinated coffee, although even had the survey parsed the two, quantifying total caffeine content would be problematical. The caffeine content in a cup of coffee is variable, even if brewed from the same outlet; a standard 8-oz cup of coffee can contain anywhere between 95-200 mg of caffeine [35,36]. Furthermore, it is important to emphasize that caffeine and coffee are not synonymous, and conflation of the two oversimplifies the effect coffee may have on cardiovascular health. In a study of 15 volunteers, intravenous caffeine infusion induced similar increases in muscle sympathetic activity and blood pressure in both habitual and nonhabitual coffee drinkers. However, drinking a cup of coffee increased blood pressure in only the nonhabitual drinkers despite comparable increases of muscle sympathetic activity and plasma caffeine levels in both populations [10].

Conflicts of Interest

Drs. Xu, Fan, Heckbert, Amsterdam, Alonso, and Wong have no disclosures to declare. Dr. Budoff is funded by the National Institutes of Health and GE Healthcare, Chicago, IL.

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Conclusion

Our findings support the previously reported studies in which there appears to be no dose-response association between coffee intake and AF risk. However, our study finds evidence that intermittent, but not habitual, coffee consumption, which is defined as <0.5 cups of daily coffee, might be associated with a modestly increased risk of incident AF in a healthy population free of cardiovascular disease. Further research is needed to clarify the relationship of coffee consumption, especially intermittent use, with the risk of incident and recurrent AF in regard to the biological mechanism and subgroups in which the effect is particularly pronounced.

References

1. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. J. Am. Coll. Cardiol. 2001;37 (2):371–8.
2. Groh CA, Faulkner M, Getabecha S, Taffe V, Nah G, Sigona K, Mc CD, Hills MT, Sciarappa K, Pletcher MJ, Olgin JE, Marcus GM. Patient-reported triggers of paroxysmal atrial fibrillation. Heart Rhythm. 2019;16 (7):996–1002.
3. NCA USA. National coffee drinking trends 2012. New York, NY: National Coffee Association USA. 2012;
4. Huxley R, Lee CMY, Barzi F, Timmermeister L, Czernichow S, Perkovic V, Grobbee DE, Batty D, Woodward M. Coffee, decaffeinated coffee, and tea consumption in relation to incident type 2 diabetes mellitus: a systematic review with meta-analysis. Arch. Intern. Med. 2009;169 (22):2053–63.
5. Wu J, Ho SC, Zhou C, Ling W, Chen W, Wang C, Chen Y. Coffee consumption and risk of coronary heart diseases: a meta-analysis of 21 prospective cohort studies. Int. J. Cardiol. 2009;137 (3):216–25.
6. Mostofsky E, Rice MS, Levitan EB, Mittleman MA. Habitual coffee consumption and risk of heart failure: a dose-response meta-analysis. Circ Heart Fail. 2012;5 (4):401–5.
7. D'Elia L, Cairella G, Garbagnati F, Scalfi L, Strazzullo P. Moderate coffee consumption is associated with lower risk of stroke: meta-analysis of prospective studies. J Hypertens. 2012;
8. Greenberg JA, Dunbar CC, Schnoll R, Kokolis R, Kokolis S, Kassotis J. Caffeinated beverage intake and the risk of heart disease mortality in the elderly: a prospective analysis. Am. J. Clin. Nutr. 2007;85 (2):392–8.
9. Lopez-Garcia E, van Dam RM, Li TY, Rodriguez-Artalejo F, Hu FB. The relationship of coffee consumption with mortality. Ann. Intern. Med. 2008;148 (12):904–14.
10. Corti R, Binggeli C, Sudano I, Spieker L, Hänseler E, Ruschitzka F, Chaplin WF, Lüscher TF, Noll G. Coffee acutely increases sympathetic nerve activity and blood pressure independently of caffeine content: role of habitual versus nonhabitual drinking. Circulation. 2002;106 (23):2935–40.
11. Cheng M, Hu Z, Lu X, Huang J, Gu D. Caffeine intake and atrial fibrillation incidence: dose response meta-analysis of prospective cohort studies. Can J Cardiol. 2014;30 (4):448–54.

12. Caldeira D, Martins C, Alves LB, Pereira H, Ferreira JJ, Costa J. Caffeine does not increase the risk of atrial fibrillation: a systematic review and meta-analysis of observational studies. Heart. 2013;99 (19):1383–9.
13. Johansson MK, Fegraeus KJ, Lindgren G, Ekesten B. Erratum to: The refractive state of the eye in Icelandic horses with the Silver mutation. BMC Vet. Res. 2017;13 (1).
14. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez RAV, Folsom AR, Greenland P, Jacob DR, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am. J. Epidemiol. 2002;156 (9):871–81.
15. Wallace ER, Siscovick DS, Sitlani CM, Dublin S, Mitchell PH, Odden MC, Hirsch CH, Thielke S, Heckbert SR. Incident Atrial Fibrillation and Disability-Free Survival in the Cardiovascular Health Study. J Am Geriatr Soc. 2016;64 (4):838–43.
16. Jensen PN, Johnson K, Floyd J, Heckbert SR, Carnahan R, Dublin S. A systematic review of validated methods for identifying atrial fibrillation using administrative data. Pharmacoepidemiol Drug Saf. 2012;21 Suppl 1 ():141–7. [PubMed]
17. Voskoboinik Aleksandr, PrabhuSandeep, SugumarHariharan, KistlerPeter M. Effect of Dietary Factors on Cardiac Rhythm. Am. J. Cardiol. 2018;122 (7):1265–1271.
18. Klatsky AL, Hasan AS, Armstrong MA, Udaltsova N, Morton C. Coffee, caffeine, and risk of hospitalization for arrhythmias. Perm J. 2011;15 (3):19–25.
19. Mostofsky E, Johansen MB, Lundbye-Christensen S, Tjønneland A, Mittleman MA, Overvad K. Risk of atrial fibrillation associated with coffee intake: Findings from the Danish Diet, Cancer, and Health study. Eur J Prev Cardiol. 2016;23 (9):922–30.
20. Conen D, Chiuve SE, Everett BM, Zhang SM, Buring JE, Albert CM. Caffeine consumption and incident atrial fibrillation in women. Am. J. Clin. Nutr. 2010;92 (3):509–14.
21. Bodar V, Chen J, Gaziano JM, Albert C, Djoussé L. Coffee Consumption and Risk of Atrial Fibrillation in the Physicians' Health Study. J Am Heart Assoc. 2019;8 (15).
22. Hansson A, Madsen-Härdig , Olsson SB. Arrhythmia-provoking factors and symptoms at the onset of paroxysmal atrial fibrillation: a study based on interviews with 100 patients seeking hospital assistance. BMC Cardiovasc Disord. 2004;4 ();
23. Mandyam MC, VedanthamV, Scheinman MM, Tseng ZH, Badhwar N, Lee BK, Lee RJ, Gerstenfeld EP, Olgin JE, Marcus GM. Alcohol and vagal tone as triggers for paroxysmal atrial fibrillation. Am. J. Cardiol. 2012;110 (3):364–8.
24. Dixit S, Stein PK, Dewland TA, Dukes JW, Vittinghoff E, Heckbert SR, Marcus GM. Consumption of Caffeinated Products and Cardiac Ectopy. J Am Heart Assoc. 2016;5 (1);
25. Rashid A, Hines M, Scherlag BJ, Yamanashi WS, Lovallo W. The effects of caffeine on the inducibility of atrial fibrillation. J Electrocardiol. 2006;39 (4):421–5.
26. Cabalag MS, Taylor DMD, Knott JC, Buntine P, Smit DV, Meyer A. Recent caffeine ingestion reduces adenosine efficacy in the treatment of paroxysmal supraventricular tachycardia. Acad Emerg Med. 2010;17 (1):44–9.
27. Reyes E, Loong CY, Harbinson M, Donovan J, Anagnostopoulos C, Underwood SR. High-dose adenosine overcomes the attenuation of myocardial perfusion reserve caused by caffeine. J. Am. Coll. Cardiol. 2008;52 (24):2008–16.
28. Mattioli AV. Beverages Of Daily Life: Impact Of Caffeine On Atrial Fibrillation. J Atr Fibrillation. 2014;7 (2);
29. Sudano I, Spieker L, Binggeli C, Ruschitzka F, Lüscher TF, Noll G, Corti R. Coffee blunts mental stress-induced blood pressure increase in habitual but not in nonhabitual coffee drinkers. Hypertension. 2005;46 (3):521–6.
30. Hara A, Ohide H, Miyagawa K, Takeuchi T, Nakatani Y, Yokoyama H, Amano T. Acute effects of caffeine on blood pressure and heart rate in habitual and non-habitual consumers: a randomized, double-blind, placebo-controlled study. Jpn J Pharm Healthcare Sci. 2014;0:383–388.
31. Baylin A, Hernandez-Diaz S, Kabagambe EK, Siles X, Campos H. Transient exposure to coffee as a trigger of a first nonfatal myocardial infarction. Epidemiology. 2006;17 (5):506–11.
32. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison HC, De PSM, Gidding S, Jamerson KA, JonesDW, Mac LEJ, Muntner P, Ovbiagele B, Smith SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Williamson JD, Wright JT. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J. Am. Coll. Cardiol. 2018;71 (19):e127–e248.
33. Ioannidis JPA. The Challenge of Reforming Nutritional Epidemiologic Research. JAMA. 2018;320 (10):969–970.
34. Cainzos-Achirica M, Bilal U, Kapoor K, Ayala RQ, McEvoy JW, Pladevall-Vila M, Blumenthal RS, Blaha MJ. Methodological issues in nutritional epidemiology research--sorting through the confusion. Curr Cardiovasc Risk Rep . 2018;
35. McCusker RR, Fuehrlein B, Goldberger BA, Gold MS, Cone EJ. Caffeine content of decaffeinated coffee. J Anal Toxicol. 2006;30 (8):611–3.
36. McCusker RR, Goldberger BA, Cone EJ. Caffeine content of specialty coffees. J Anal Toxicol. 2003;27 (7):520–2.

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Characteristics of Atrial Fibrillation Patients with a Family History of Atrial Fibrillation

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Abstract

Background

Family history has been shown to be associated with increased risk of atrial fibrillation (AF). However, the specific AF characteristics that travel with a family history have not yet been elucidated. The purpose of this study was to determine whether a family history of AF is associated with specific patient characteristics in a worldwide, remote cohort.

Methods

From the Health eHeart Study, an internet-based prospective cohort, we performed a cross-sectional analysis of AF participants who reported their family history and completed questionnaires regarding their medical conditions and AF symptoms. We assessed demographics, cardiovascular comorbidities, and AF symptom characteristics in AF participants with and without a family history of AF.

Results

In multivariable analysis of 5,884 participants with AF (mean age 59.9 ± 14.5, 59% male, 92% white), female sex (odds ratio [OR]=1.35, 95% CI, 1.17-1.54, p<0.0001) and birth in the U.S. (OR=2.54, 95% CI, 2.12-3.05, p<0.0001) were independently associated with having a family history of AF. Having a family history of AF was also more commonly associated with symptoms of shortness of breath (OR=1.40, 95% CI, 1.07-1.82, p=0.014), chest pain, pressure, or discomfort (OR=1.95, 95% CI, 1.22-3.13, p=0.0052), and feeling generally "off" about oneself (OR=1.84, 95% CI, 1.27-2.67, p=0.0013).

Conclusions

Patients with a family history of AF are more likely to be female, be US-born, and experience symptoms of AF, suggesting underlying mechanistic differences between those with and without family history of AF.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, affecting millions of Americans and rapidly increasing in both incidence and prevalence [1-4]. AF doubles mortality and is a common cause of stroke [1,2]. Though the mechanisms underlying AF remain largely unknown, established risk factors, such as age, male sex, white race, hypertension, and other comorbidities, have been identified [5,6]. A family history of AF has similarly emerged as a well-established risk factor for the disease [5-9]. Several common genetic variants have been associated with an increased susceptibility to AF [8,10,11], but the mechanisms underlying those associations remain unclear. One previous registry-based study in the US suggested that patients with a family history of AF develop the disease at a younger age, have less comorbidities, and are more symptomatic [12], but no additional studies have examined these relationships. We therefore sought to compare the characteristics of AF patients with and without a family history of the disease in a worldwide, remote cohort.

Key Words

Atrial fibrillation, Family history, Genetics, Heritability, Phenotype.

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Methods

Study design

We utilized data collected between March 8, 2013 and October 25, 2017 from the Health eHeart Study (www.health-eheartstudy.org), an online-based prospective, longitudinal cohort study. English-speaking adults each with an active email were recruited through academic institutions, lay press, social media and promotional events. Upon enrollment, all participants provided informed consent electronically and were asked to complete a series of online questionnaires regarding demographics, personal and family medical history, habits, symptoms, and quality of life [Supplementary Table 1]. The Health eHeart Study was approved by the UCSF Institutional Review Board.

Assessment of atrial fibrillation and family history

AF was determined by responses to the question, "Have you ever been told by a doctor or nurse that you have, or have been treated for, atrial fibrillation (in the past or currently)?" with response options "Yes", "No" and "Don't know." We included only participants who responded "yes" and treated those who responded as "Don't know" as missing. This approach was previously validated using medical record data among 42 patients [13]. To identify those with any family history of AF, we included participants who reported any family member

Table 1: Baseline characteristics of atrial fibrillation participants with and without any family history of the disease.

	No Family History of AF (n = 4600)	Family History of AF (n = 1284)	p-value
Basic demographics			
Age, mean ± SD, years	56.9 ± 15.4	60.4 ± 11.2	<0.0001
Sex			<0.0001
Male	2009 (61%)	647 (52%)	
Female	1269 (39%)	607 (48%)	
Country of birth			<0.0001
USA	2336 (71%)	1085 (87%)	
Other	939 (29%)	169 (13%)	
Race/Ethnicity, n (%)			0.17
Black	50 (1%)	20 (2%)	
White	2998 (92%)	1144 (91%)	
Asian	89 (3%)	29 (2%)	
Native Hawaiian	4 (0.1%)	0 (0%)	
American Indian	8 (0.2%)	9 (0.7%)	
Other	51 (2%)	15 (1%)	
Don't know	**3 (0.09%)**	**1 (0.08%)**	
Hispanic (ethnicity)	170 (5%)	50 (4%)	0.09
Medical history			
Hypertension	2357 (51%)	676 (53%)	0.38
Diabetes	589 (13%)	155 (12%)	0.48
Coronary artery disease	1029 (22%)	245 (19%)	0.011
Heart attack	583 (13%)	151 (12%)	0.38
Congestive heart failure	734 (16%)	187 (15%)	0.22
Stroke or TIA	533 (12%)	120 (9%)	0.023
Congenital heart disease	433 (9%)	102 (8%)	0.10
Obstructive sleep apnea	1238 (27%)	346 (27%)	0.85
COPD	354 (8%)	104 (8%)	0.70
Asthma	544 (12%)	155 (12%)	0.91
Cardiac arrest	316 (7%)	81 (6%)	0.43
Implantable device	3802 (84%)	1088 (85%)	0.33
Smoking history			
History of smoking regularly	910 (53%)	707 (56%)	0.05
Current smoker	63 (4%)	46 (4%)	0.99
Alcohol Use			
Did you drink alcoholic beverages in the past year?	1334 (77%)	971 (77%)	0.93
Did you drink alcohol more than once or twice in the past?	248 (63%)	186 (66%)	0.54
Drinks of wine/week	4.2 ± 28.1	3.4 ± 5.9	0.38
Drinks of beer/week	1.9 ± 9.5	1.3 ± 3.4	0.061
Drinks of hard liquor/week	1.4 ± 4.2	1.4 ± 4.4	0.098
Drinks in the past 24 hours	0.9 ± 2.6	0.9 ± 1.7	0.071
Approximately how many years ago did you stop drinking?	56.3 ± 289.4	46.2 ± 243.5	0.70
What is the usual number of drinks you consumed per week before you stopped?	13.3 ± 35.9	10.2 ± 19.6	0.29
Atrial fibrillation history			
Symptoms when first diagnosed?	3092 (76%)	1005 (80%)	0.006
Paroxysmal AF	1953 (48%)	627 (50%)	0.29
Hx of cardioversion	1286 (32%)	394 (31%)	0.80
Hx of AF ablation	976 (24%)	330 (26%)	0.12
Atrial fibrillation symptoms (check all that apply)			
Never have symptoms	540 (12%)	138 (11%)	0.33
Palpitations	2675 (58%)	807 (63%)	0.0025
SOB	364 (8%)	152 (12%)	<0.0001
Difficulty exercising	94 (2%)	25 (2%)	0.83
Chest pain/pressure/ discomfort	78 (2%)	36 (3%)	0.01
Dizziness	85 (2%)	16 (1%)	0.14
Feeling generally tired	69 (2%)	21 (2%)	0.73
Feeling generally "off" your normal self	117 (3%)	57 (4%)	0.0004
Other	45 (1%)	12 (1%)	0.89
Don't know	540 (12%)	139 (11%)	0.14

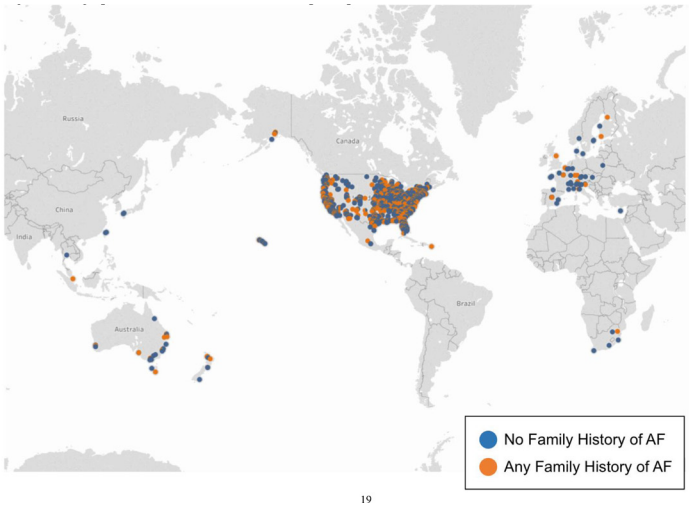

Figure 1: Geographical distribution of Health eHeart participants with atrial fibrillation.

Each dot represents at least one participant in a given zipcode. Blue dots indicate those with a family history of atrial fibrillation, while orange dots indicate those without a family history of atrial fibrillation.

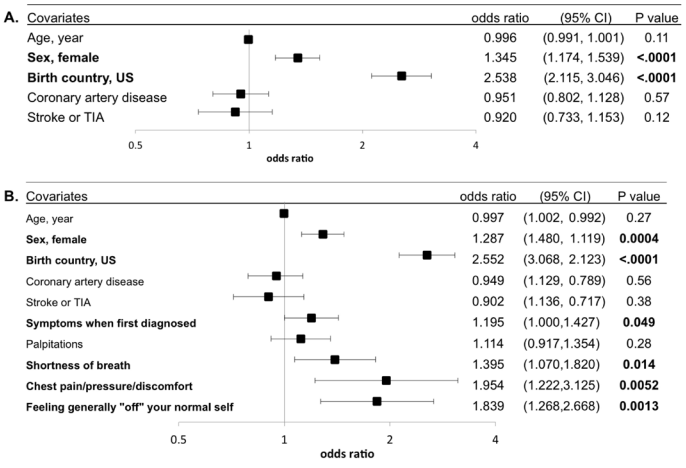

Figure 2: Multivariable adjusted relationships between participant characteristics and any family history of AF.

(A) Adjusted for relevant demographics, medical history and habits. (B) Additionally adjusted for relevant AF- and symptom-related history. Models were adjusted for all covariates listed. Statistically significant relationships are in bold. Y error bars denote 95% confidence intervals.

Table 2: Baseline characteristics of atrial fibrillation participants with and without a first-degree family history of the disease.

	No First-Degree Family History of AF (n = 5136)	First-Degree Family History of AF (n = 748)	p-value
Basic demographics			
Age, mean ± SD, years	57.0 ± 15.5	58.7 ± 12.8	0.0003
Sex			
Male	2266 (60%)	390 (54%)	0.004
Female	1540 (40%)	336 (46%)	
Country of birth			
USA	2801 (74%)	620 (85%)	<0.0001
Other	1002 (26%)	106 (15%)	
Race/Ethnicity, n (%)			
Black	64 (2%)	6 (0.83%)	0.076
White	3458 (91%)	684 (94.34%)	
Asian	103 (3%)	15 (2.07%)	
Native Hawaiian	4 (0.1%)	0 (0.00%)	
American Indian	17 (0.5%)	0 (0.00%)	
Other Don't know	61 (2%) 3 (0.08%)	5 (0.69%) 1 (0.1%)	
Hispanic (ethnicity)	198 (5%)	22 (3%)	0.012
Medical history			
Hypertension	2657 (52%)	376 (50%)	0.45
Diabetes	667 (13%)	77 (10%)	0.038
Coronary artery disease	1148 (22%)	126 (17%)	0.0006
Heart attack	662 (13%)	72 (10%)	0.011
Congestive heart failure	818 (16%)	103 (14%)	0.13
Stroke or TIA	583 (11%)	70 (9%)	0.10
Congenital heart disease	488 (10%)	47 (6%)	0.0041
Obstructive sleep apnea	1376 (27%)	208 (28%)	0.68
COPD	398 (8%)	60 (8%)	0.85
Asthma	617 (12%)	82 (11%)	0.36
Cardiac arrest	357 (7%)	40 (5%)	0.090
Implantable device	832 (16%)	105 (14%)	0.10
Smoking history			
History of smoking regularly	1047 (46%)	324 (44%)	0.35
Current smoker	86 (4%)	23 (3%)	0.41
Alcohol Use			
Did you drink alcoholic beverages in the past year?	1732 (77%)	573 (79%)	0.29
Did you drink alcohol more than once or twice in the past?	336 (65%)	98 (64%)	0.82
Drinks of wine/week	4.0 ± 24.9	3.6 ± 5.3	0.76
Drinks of beer/week	1.7 ± 8.1	1.5 ± 5.6	0.76
Drinks of hard liquor/week	1.4 ± 4.0	1.4 ± 5.0	0.77
Drinks in the past 24 hours	0.8 ± 2.4	1.0 ± 1.5	0.25
Approximately how many years ago did you stop drinking?	57.7 ± 291.4	32.5 ± 181.1	0.42
What is the usual number of drinks you consumed per week before you stopped?	12.4 ± 32.5	10.4 ± 19.2	0.55
Atrial fibrillation history			
Symptoms when first diagnosed?	3517 (75%)	580 (78%)	0.20
Paroxysmal AF	2215 (48%)	365 (49%)	0.53
Hx of cardioversion	1448 (31%)	232 (31%)	0.96
Hx of AF ablation	1098 (24%)	208 (28%)	0.012
Atrial fibrillation symptoms (check all that apply)			
Never have symptoms	610 (12%)	68 (0.09%)	0.026
Palpitations	3008 (59%)	474 (63%)	0.012
SOB	432 (8%)	84 (11%)	0.011
Difficulty exercising	103 (2%)	16 (2%)	0.81
Chest pain/pressure/ discomfort	89 (2%)	25 (3%)	0.0029
Dizziness	93 (2%)	8 (1%)	0.15
Feeling generally tired	79 (2%)	11 (1%)	0.89
Feeling generally "off" your normal self	133 (3%)	41 (5%)	<0.0001
Other	45 (1%)	12 (2%)	0.58
Don't know	610 (12%)	68 (9%)	0.026

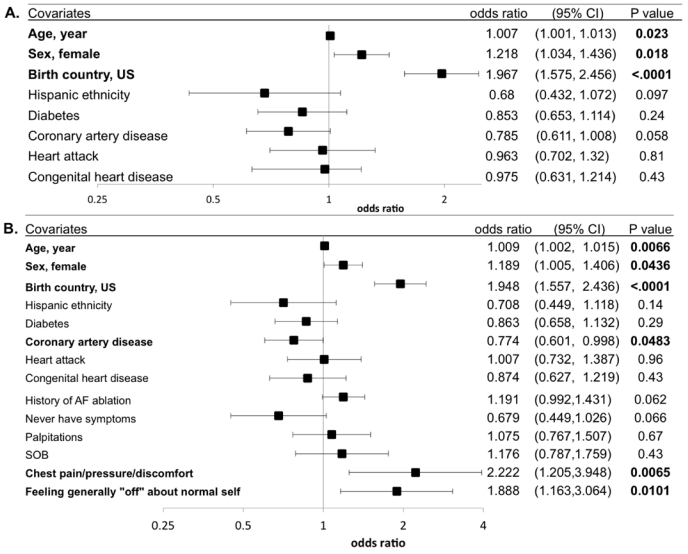

Figure 3: Multivariable adjusted relationships between participant characteristics and a first-degree family history of AF.

(A)Adjusted for relevant demographics, medical history and habits. (B) Additionally adjusted for relevant AF- and symptom-related history. Models were adjusted for all covariates listed. Statistically significant relationships are in bold. Y error bars denote 95% confidence intervals.

(either immediate or extended) with AF. If participants were unsure, the answer was considered negative. Participants were considered to have a first-degree family history of AF if they self-reported at least one biological sister, brother, father, or mother with AF.

Covariate ascertainment

Self-identified race was categorized as white, black, Asian, Native Hawaiian/Pacific Islander, American Indian, or other. Hispanic ethnicity was also assessed. Smoking status was ascertained as never, past, or current smoker, with regular use defined as at least 1 cigarette per day or a total of 100 cigarettes in one's lifetime. Alcohol use was assessed through self-report of consumption over the past year and number of drinks a week. Medical history was determined by participant report that they had specifically received a diagnosis of one of the following from a healthcare professional [Supplementary Table 1]: hypertension, diabetes, coronary artery disease, heart attack, congestive heart failure, cerebrovascular accident (stroke or transient ischemia attack), congenital heart disease, and obstructive sleep apnea. Participants with AF were also asked specific questions regarding their AF history and associated symptoms.

Statistical analysis

Normally distributed continuous variables are presented as means ± SD and were compared using unpaired t-tests. Non-normally distributed continuous variables are presented as medians and interquartile ranges and were compared using Wilcoxon rank-sum tests. Categorical variables were compared using x^2 tests. Multivariable analysis was performed with logistic regression analysis, including only co-variates that exhibited p values < 0.05 in unadjusted analyses. We first performed an analysis to assess relationships between demographics, medical comorbidities, habits and a family history of AF; we then analyzed relationships between a family history and characteristics of the participant's AF itself (such as AF type and associated symptoms) after adjusting for relevant demographics, medical conditions and habits. All analyses were performed using SAS Version 9.4. Two-tailed p values < 0.05 were considered statistically significant.

Results

Any family history of atrial fibrillation

At the time of study analysis, 76,973 of 137,648 Health eHeart participants (49.4%) had completed the survey for medical conditions. Of those, 5,884 (7.6%) reported a diagnosis of AF. Of those with AF, 1,284 (21.8%) had a family history of AF [Figure 1] and [Supplementary Figure 1]. [Table 1] shows the baseline characteristics among those with and without a family history of AF. Those with a family history of AF tended to be older, female, more often from the US, and less often with a history of coronary artery disease or a history of a cerebrovascular accident [Table 1]. In addition, those with a family history were more likely to experience symptomatic AF when they were first diagnosed and continued to manifest more symptoms of AF than AF patients without a family history.

In a multivariable adjusted analysis including relevant demographics, past medical history and habits, those with a family history of AF had a statistically significant 35% greater odds of being female and also had more than 2-fold greater odds of being born in the US [Figure 2]. After including AF-related history and symptoms that met criteria for inclusion in the multivariate model, being female and being born in the US remained significantly associated with a family history of AF [Figure 2]. In addition, AF patients with a family history of AF were more likely to report AF-related shortness of breath, chest pain, pressure, or discomfort, or feeling "off" about one's normal self after adjusting for baseline characteristics [Figure 2].

First-degree family history of atrial fibrillation

Of those with AF, 768 (13.7%) had at least one first degree family member with AF. Baseline characteristics of those with and without first-degree family history are reported in [Table 2]. Those with a first-degree family history of AF were more likely to be older, female, and from the US, but less likely to be of Hispanic ethnicity and have diabetes, coronary artery disease, and congenital heart disease [Table 2]. Though there was no significant differences in having paroxysmal AF or history of cardioversion, those with a first-degree family history of AF were more likely to have had an AF ablation. As with those with any family history of AF, those with a first degree family history were more likely to experience a variety of symptoms during their AF episodes [Table 2].

In a multivariable adjusted analysis including demographics, medical history and habits, older age, female sex, and being born in the US were each significantly associated with having a first-degree family history of AF [Figure 3]. When AF characteristics (including AF type, AF-related history, and AF-related symptoms) were also added to the multivariable model, having a first-degree family history of AF was significantly associated with reporting symptoms of chest pain, pressure, or discomfort and feeling generally "off" about oneself during AF episodes [Figure 3].

Discussion

Among a large, remote cohort of AF patients, a family history of AF was more commonly observed in women and those born in the US. Those with a family history of AF exhibited more symptomatic AF. Our study validates the results of a previous registry-based study that females and those with more symptoms during AF are more likely to report a family history of the disease [12], extending those findings to a worldwide cohort.

The reasons for the consistent relationship between female sex and a family history of AF are unclear. This would appear to run contrary to the consistent observation that women are at a lower risk for AF than men [7,16,17]. Of note, the mechanisms underlying that difference have not been fully elucidated, may be multifactorial, and may be related to differences in body (and left atrial) size and or hormonal influences [18-20]. It is important to acknowledge that women may simply be more likely to report a family history of AF (even in the absence of an actual greater prevalence of a family history) because they are more attune to their family members' health history [21]. This itself may yet be clinically relevant information when considering the reliability of the family history from men versus women. Assuming there is truly a relationship between female sex and a family history of AF, these findings may point to some sex-related mechanisms that affect the penetrance of AF-related genes. In light of the overall greater prevalence of AF among men, such a finding would also suggest that the sex-specific differences influencing AF risk would be potent enough to otherwise suppress the emergence of AF in the general population of women.

In our international cohort, we were able to demonstrate that US-born participants were more likely to report an AF family history. Again, it is difficult to know whether this has more to do with the awareness of health problems and AF among American families versus a "true" phenomenon. It is possible that there are some genetic differences that render certain populations more prone to AF among those more likely to migrate to the US. There may also be some gene-environment interactions that are disproportionally influenced by some particular exposure in the US.

It is well known that AF patients can experience a variety of sensations during their episodes, ranging from completely asymptomatic to suffering debilitating symptoms [22]. While some of

Supplementary Material

Table 1: Online questionnaires from the Health eHeart Study

Basic demographics	
1. What is your biological sex?	□ Male □ Female
2. Where were you born (country)?	□ U.S.A. □ Mexico □ China □ India □ Philippines □ Other country
3. What is your racial background? Check all that apply.	□ Black or African American □ White □ Asian (including South Asian and Asian Indian) □ Native Hawaiian or Pacific Islander □ American Indian or Alaska Native □ Some other race □ Don't know
4. Are you of Hispanic, Latino or Spanish origin or ancestry?	□ No □ Yes, Mexican, Mexican American or Chicano □ Yes, Puerto Rican □ Yes, Cuban □ Yes, Other or Mixed Hispanic, Latino or Spanish origin □ Don't know
Medical history	
Have you ever been told by a doctor or nurse that you have, or have been treated for, any of the following conditions (in the past or currently?)	
1. Hypertension	□ Yes □ No □ Don't know
2. Diabetes? Do not include pre-diabetes.	□ Yes □ No □ Don't know
3. Coronary artery disease (blockages in your heart vessels) or angina (chest pain)?	□ Yes □ No □ Don't know
4. A heart attack?	□ Yes □ No □ Don't know
5. Congestive Heart Failure (CHF, Heart Failure)?	□ Yes □ No □ Don't know
6. Stroke or TIA (Transient Ischemic Attack or Mini-Stroke)?	□ Yes □ No □ Don't know
7. Do you or have you ever had a congenital heart disease (a heart birth defect)?	□ Yes □ No □ Don't know
8. Sleep apnea (obstructive sleep apnea, OSA)?	□ Yes □ No □ Don't know
9.COPD (emphysema, chronic bronchitis, obstructive pulmonary disease)?	□ Yes □ No □ Don't know
10. Asthma, to the point that you use inhalers daily or have been to the hospital for your asthma	□ Yes □ No □ Don't know
11. A cardiac arrest?	□ Yes □ No □ Don't know
12. Do you have an implanted device for your heart? If you have one, you were given a card which has this information on it.	□ No □ Pacemaker (not an ICD) □ ICD (Implantable Cardioverter-Defibrillator) □ Implanted Loop Recorder or rhythm monitor (e.g., Reveal, Confirm) □ Other
Smoking history	
1. Have you ever smoked cigarettes regularly (at least 1 cigarette per day and a total of 100 cigarettes in your lifetime)?	□ Yes □ No
2. Do you smoke now?	□ Daily □ Some days □ No
Alcohol history	
1. Did you drink any alcoholic beverages in the past year?	□ No □ Yes □ Don't know □ I refuse to answer
2. Did you drink alcohol more than once or twice in the past?	□ No □ Yes □ Don't know □ I refuse to answer
3. How many drinks of wine do you usually have per week? A drink is a 5-ounce glass. Round down.	_____ drinks per week
4. How many drinks of beer do you usually have per week? One beer is a 12-ounce glass, can, or bottle. Round down.	_____ drinks per week
5. How many drinks per week do you usually have of hard liquor? Count each shot, which is 1 ½ ounces, as one drink. Round down	_____ drinks per week
6. During the past 24 hours, how many drinks have you had?	_____ drinks per week
7. Approximately how many years ago did you stop drinking? Round do the nearest year except round ½ down; e.g., record 1 ½ as 1).	_____ years
8. What was the usual number of drinks you consumed per week before you stopped? Write in 00 if less than one drink per week.	_____ drinks per week
Atrial fibrillation history	
1. Did you have any symptoms (such as palpitations, dizziness, shortness of breath, chest discomfort, difficulty exercising, or generalized 'feeling bad') when you were first diagnosed (or prior to)?	□ Yes □ No □ Don't know
2. Are you in atrial fibrillation all the time?	□ Yes □ No. It comes and goes on its own □ No. It has stopped because of a shock to your heart or because of a medication □ Don't know
3. Have you ever had a shock to your check or cardioversion?	□ Yes □ No □ Don't know
4. Have you ever had an ablation for your atrial fibrillation?	□ Yes □ No
5. What symptoms do you have when you have atrial fibrillation? It's OK if you only experience these symptoms sometimes. Check all that apply.	□ I never have symptoms □ Palpitations or irregular or "funny" heartbeats □ Shortness of breath of difficulty breathing □ Difficulty exercising or exerting □ Chest pain, pressure, or discomfort □ Dizziness □ Feeling generally tired □ Feeling generally "off" your normal self □ Other □ Don't know

Supplementary Material

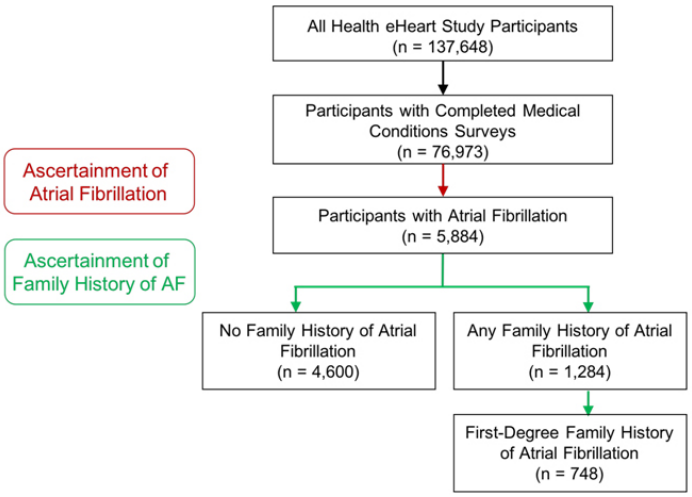

Figure 1 **Health eHeart Study enrollment of atrial fibrillation participants with and without a family history of atrial fibrillation.**

this variability is likely related to ventricular rates and differences in AV nodal conduction properties, the reasons some individuals are more or less symptomatic remain largely unknown. In addition to hemodynamic effects, there are likely neurologic and psychological components related to sensitivity to changes in heart rate and rhythm and reactions to stress [23]. The relationship between having a family history of AF and having more symptomatic AF was very consistent in our cohort, both before and after adjustment for potential confounders and mediators. Those with a family history more commonly described shortness of breath, chest pain pressver, or discomfort, and feeling "off" during their AF episodes. A possible explanation is that those who tend to be more symptomatic will seek out more family members with AF. Interestingly, it is also possible that having symptomatic AF itself is an inherited characteristic, which would certainly lend itself to becoming more apparent among family members. Inherited AF tends to be more dominant in otherwise healthier and younger individuals with the disease [9,12,24], who are more likely to have robust AV nodal conduction and thus more likely experience symptoms from rapid ventricular rates. While we demonstrated that older age was associated with having a first-degree family history, we were not able to determine the age of diagnosis with our database. Previous studies have reported that earlier diagnosis of AF in patients and their first-degree relatives is associated with higher risk of AF [5-7]. Finally, previous studies have suggested that women tend to experience more AF-related symptoms and worse quality-of-life than men [25-27]. As the relationship between female sex and a family history of AF as well as between symptoms and a family history of AF remained statistically significant after each was adjusted for the other, those previous studies may reveal a heritable AF subtype relevant to both relationships.

Our study has several potential limitations. As eluded to above, these data were based on self-report. However, as also mentioned, even if this explains the results observed, there may be clinically relevant lessons that can be gleaned from the data. We previously validated the accuracy of an AF diagnosis in the Health eHeart Study and found it to be very accurate among a small number of patients with available medical records.[15] In addition, for any misclassification of AF to be important, there would need to be a differential effect by predictor (such as family history of AF) for results to be affected. Although the mean age of our study cohort was 60 and more than 10% were of some race/ethnicity other than non-Hispanic white, Health eHeart Study participants are not completely representative of the general population (particularly as they require some ability to interact on the internet). However, this should limit generalizability of our findings rather than internal validity. We acknowledge that "any family history" is both broad and potentially vague, but our analyses restricted to just a first degree family history did not yield meaningfully different results. Finally, it is possible that we were not aware of or did not include other covariates that may have been important.

Conclusion

Among individuals with AF, a family history of the disease is more common in women, those born in the US, and those with symptomatic AF. These differences may help in understanding mechanisms underlying AF when a family history of the disease is present and may suggest that symptomatic AF reflects a particular biological subtype.

References

1. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le HY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: 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). Eur. Heart J. 2006;27 (16):1979–2030.
2. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. J. Am. Coll. Cardiol. 2001;37 (2):371–8.
3. Zulkifly H, Lip GYH, Lane DA. Epidemiology of atrial fibrillation. Int. J. Clin. Pract. 2018;72 (3);
4. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. Am. J. Cardiol. 2009;104 (11):1534–9.
5. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994;271 (11):840–4.
6. Benjamin EJ, Chen PS, Bild DE, Mascette AM, Albert CM, Alonso A, Calkins H, Connolly SJ, Curtis AB, Darbar D, Ellinor PT, Go AS, Goldschlager NF, Heckbert SR, Jalife J, Kerr CR, Levy D, Lloyd-Jones DM, Massie BM, Nattel S, Olgin JE, Packer DL, Po SS, Tsang TSM, Van Wagoner DR, Waldo AL, Wyse DG. Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. Circulation. 2009;119 (4):606–18.
7. Fox CS, Parise H, D'Agostino RB, Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA. 2004;291 (23):2851–5.
8. Lubitz SA, Yin X, Fontes JD, Magnani JW, Rienstra M, Pai M, Villalon ML, Vasan RS, Pencina MJ, Levy D, Larson MG, Ellinor PT, Benjamin EJ. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. JAMA.

2010;304 (20):2263–9.
9. Oyen N, Ranthe MF, Carstensen L, Boyd HA, Olesen MS, Olesen SP, Wohlfahrt J, Melbye M. Familial aggregation of lone atrial fibrillation in young persons. J. Am. Coll. Cardiol. 2012;60 (10):917–21.
10. Ellinor PT, Shin JT, Moore RK, Yoerger DM, Mac RCA. Locus for atrial fibrillation maps to chromosome 6q14-16. Circulation. 2003;107 (23):2880–3.
11. Christophersen IE, Ravn LS, Budtz-Joergensen E, Skytthe A, Haunsoe S, Svendsen JH, Christensen K. Familial aggregation of atrial fibrillation: a study in Danish twins. Circ Arrhythm Electrophysiol. 2009;2 (4):378–83.
12. Gudbjartsson DF, Arnar DO, Helgadottir A, Gretarsdottir S, Holm H, Sigurdsson A, Jonasdottir A, Baker A, Thorleifsson G, Kristjansson K, Palsson A, Blondal T, Sulem P, Backman VM, Hardarson GA, Palsdottir E, Helgason A, Sigurjonsdottir R, Sverrisson JT, Kostulas K, Ng Maggie CY, Baum L, So WY, Wong KS, Chan JCN, Furie KL, Greenberg SM, Sale M, Kelly P, Mac RCA, Smith EE, Rosand J, Hillert J, Ma RCW, Ellinor PT, Thorgeirsson G, Gulcher JR, Kong A, Thorsteinsdottir U, Stefansson K. Variants conferring risk of atrial fibrillation on chromosome 4q25. Nature. 2007;448 (7151):353–7.
13. Firouzi M, Ramanna H, Kok B, Jongsma HJ, Koeleman BPC, Doevendans PA, Groenewegen WA, Hauer RNW. Association of human connexin40 gene polymorphisms with atrial vulnerability as a risk factor for idiopathic atrial fibrillation. Circ. Res. 2004;95 (4):e29–33.
14. Gundlund A, Fosbøl EL, Kim S, Fonarow GC, Gersh BJ, Kowey PR, Hylek E, Mahaffey KW, Thomas L, Piccini JP, Peterson ED. Family history of atrial fibrillation is associated with earlier-onset and more symptomatic atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. Am. Heart J. 2016;175 ():28–35.
15. Dixit S, Pletcher MJ, Vittinghoff E, Imburgia K, Maguire C, Whitman IR, Glantz SA, Olgin JE, Marcus GM. Secondhand smoke and atrial fibrillation: Data from the Health eHeart Study. Heart Rhythm. 2016;13 (1):3–9.
16. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004;110 (9):1042–6.
17. Heeringa J, van der KuipDeirdre AM, Hofman A, Kors JA, van Herpen G, Stricker BH Ch, Stijnen T, Lip GYH, Witteman JCM. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur. Heart J. 2006;27 (8):949–53.
18. McManus DD, Yin X, Gladstone R, Vittinghoff E, Vasan RS, Larson MG, Benjamin EJ, Marcus GM. Alcohol Consumption, Left Atrial Diameter, and Atrial Fibrillation. J Am Heart Assoc. 2016;5 (9);
19. Marcus GM, Yang Y, Varosy PD, Ordovas K, Tseng ZH, Badhwar N, Lee BK, Lee RJ, Scheinman MM, Olgin JE. Regional left atrial voltage in patients with atrial fibrillation. Heart Rhythm. 2007;4 (2):138–44.
20. Seko Y, Kato T, Haruna T, Izumi T, Miyamoto S, Nakane E, Inoko M. Association between atrial fibrillation, atrial enlargement, and left ventricular geometric remodeling. Sci Rep. 2018;8 (1);
21. Sharma N, Chakrabarti S, Grover S. Gender differences in caregiving among family - caregivers of people with mental illnesses. World J Psychiatry. 2016;6 (1):7–17.
22. Rienstra M, Lubitz SA, Mahida S, Magnani JW, Fontes JD, Sinner MF, Van Gelder IC, Ellinor PT, Benjamin EJ. Symptoms and functional status of patients with atrial fibrillation: state of the art and future research opportunities. Circulation. 2012;125 (23):2933–43.
23. Sears SF, Serber ER, Alvarez LG, Schwartzman DS, Hoyt RH, Ujhelyi MR. Understanding atrial symptom reports: objective versus subjective predictors. Pacing Clin Electrophysiol. 2005;28 (8):801–7.
24. Kääb S, Darbar D, van Noord C, Dupuis J, Pfeufer A, Newton-Cheh C, Schnabel R, Makino S, Sinner MF, Kannankeril PJ, Beckmann BM, Choudry S, Donahue BS, Heeringa J, Perz S, Lunetta KL, Larson MG, Levy D, Mac RCA, Ruskin JN, Wacker A, Schömig A, Wichmann HE, Steinbeck G, Meitinger T, Uitterlinden AG, Witteman JCM, Roden DM, Benjamin EJ, Ellinor PT. Large scale replication and meta-analysis of variants on chromosome 4q25 associated with atrial fibrillation. Eur. Heart J. 2009;30 (7):813–9.
25. Zöller B, Ohlsson H, Sundquist J, Sundquist K. High familial risk of atrial fibrillation/atrial flutter in multiplex families: a nationwide family study in Sweden. J Am Heart Assoc. 2012;2 (1);
26. Ball J, Carrington MJ, Wood KA, Stewart S. Women versus men with chronic atrial fibrillation: insights from the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). PLoS ONE. 2013;8 (5);
27. Scheuermeyer FX, Mackay M, Christenson J, Grafstein E, Pourvali R, Heslop C, Mac PJ, Ward J, Heilbron B, McGrath L, Humphries K. There Are Sex Differences in the Demographics and Risk Profiles of Emergency Department (ED) Patients With Atrial Fibrillation and Flutter, but no Apparent Differences in ED Management or Outcomes. Acad Emerg Med. 2015;22 (9):1067–75.

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Cardiothoracic Surgery Residency Training in Surgical Ablation for Atrial Fibrillation

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Abstract

Background : As no standardized curriculum exists for training cardiothoracic surgery residents in surgical ablation for atrial fibrillation, there is potential for variation in operative technique, patient selection, and overall application. Thus we sought to assess the exposure of current residents in order to identify areas for improvement in their education.

Methods : A survey was emailed to residents inquiring about their training experience in surgical ablation for atrial fibrillation. Residents were asked about case volume, procedural variety, and guideline-based clinical scenarios where they felt ablation would be appropriate. Residents were also queried about their abilities to perform various lesion sets and overall satisfaction with training.

Results : The respondents performed a median of five cases during training with pulmonary vein isolation the most common lesion set. Seventy seven percent of residents are unable to independently perform a bi-atrial (Cox-Maze IV) lesion set. Residents are neutral regarding their satisfaction with training in surgical ablation for atrial fibrillation.

Conclusions : The findings of low case volume, incomplete lesion set use, and lack of training satisfaction suggests residents are being insufficiently exposed to surgical ablation of atrial fibrillation. These findings should inform educators on the importance of a more thorough experience during training given the increasing prevalence of atrial fibrillation and the need for appropriate and durable surgical intervention.

Introduction

Current guidelines support a broad use of concomitant and stand-alone surgical ablation for atrial fibrillation (AF).[1,2] Given the expected increase in AF prevalence and the burdens associated with its sequelae, it is conceivable that more surgeons will be tasked with performing ablations.[3,4] However, no standardized curricula exist regarding training in surgical ablation of AF. With likely substantial variation of lesion sets and the potential for indiscriminate application of surgical ablation, it remains unknown if current cardiothoracic (CT) surgical residents are receiving adequate instruction during training. The consequence of this may result in inadequate ablation techniques as well as missed opportunities for patient intervention.[5,6] Hence, we sought to better understand the current state of ablation education by evaluating current CT surgery residents' training experience in surgical AF ablation.

Key Words

Atrial Fibrillation, Ablation, Surgery, Training, Residency.

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Methods

The University of Utah Institutional Review Board determined this study exempt. An anonymous survey was emailed to current United States CT surgery residents in May 2018. Email addresses were obtained from the Thoracic Surgery Directors Association (TSDA) list. Senior-level residents (post graduate year six and greater) were included in the final analysis, as they were considered likely to have had significant or focused exposure to cardiac surgery and are nearing entering the workforce. The full survey with questions & response choices appears in the appendix. The total of possible respondents was based on the number of 2018 senior-level in-service examinees (n=248). Residents were excluded if their TSDA-supplied email addresses were non functional (n=36) as was the first author and other residents at the sponsoring institution (n=4). Participants were queried on training program characteristics, AF ablation/arrhythmia surgery case volume (non-pacemaker or pacemaker lead related), observed surgical approaches and lesion sets, and management strategy for the left atrial appendage. Residents were also asked about their opinion on the appropriate application of stand-alone and concomitant ablation in clinical scenarios based on recent society guidelines. Finally, residents rated their abilities to independently perform various lesion sets and their overall satisfaction with training in AF

ablation via five-point Likert scales ("unable/unsatisfied, somewhat unable/unsatisfied, neutral, somewhat able/satisfied, completely able/satisfied;" numeric values: 1-5, respectively). Program names and other identifying data, such as region of the country, were not collected in this study.

Results

Fifty-two senior residents responded yielding a response rate of 25% (52/208). Most are training at two- and three-year "traditional" residencies (n=45, 86.5%) rather than integrated programs and are pursuing a "cardiac-focused" path. Residents performed a median of five ablations (interquartile range [IQR]: 3-10) as the primary surgeon. Most trainees' programs do not perform stand-alone ablation surgery (n= 29, 55.8%). A median sternotomy (94.2%) is the most employed approach to performing ablations with a pulmonary vein isolation (PVI) being the predominant lesion set at trainees' programs (44.2%). A combination of cryothermy and radiofrequency are the most commonly employed energy sources for creating lesions (63.4%) and the left atrial appendage is primarily excluded via an external device ligation (57.7%). Responses to training environment characteristic questions appear in [Table 1]. The percentages of responders finding it appropriate to perform concomitant and stand-alone ablations in various guideline-based clinical scenarios appear in [Table 2].

Residents stated they are "somewhat able" (median: 4, IQR: 3-4) to independently perform PVI. The majority of residents (86.5%, n=45) stated they are unable to independently perform a bi-atrial Cox Maze (CM) III or IV (median: 1, IQR: 1-1.25; median: 2, IQR: 1-3, respectively). Finally, residents stated they are "neutral" (median: 3, IQR 2-4) with regard to their satisfaction in surgical AF ablation training. Procedural ability and training satisfaction results appear graphically in [Figure 1]

Table 1: Survey questions & responses of the 52 senior resident participants

Survey Question	Respondents (n=; %)
What is your current post-graduate year level (PGY) of training?	
PGY-6	24; 46.2
PGY-7	20; 38.4
PGY-8	8; 15.4
In which type of training program are you enrolled?	
Traditional 2-year	28; 53.8
Traditional 3-year	17; 32.7
Integrated or combined (I-6, 4+3)	7; 13.5
Which training track are you pursuing?	
Cardiac	35; 67.3
Thoracic	8; 15.4
None	9; 17.3
Does your program surgical ablation of AF as a stand-alone operation?	
No	29; 55.8
Yes	23; 44.2
Which approach does your program use to perform ablation? (select all that apply)	
Median sternotomy	49; 94.2
Thoracoscopic	14; 26.9
Right thoracotomy	8; 15.4
Bilateral thoracotomy	3; 5.8
What is the predominant lesion set used at your program?	
Pulmonary vein isolation	23; 44.2
Bi-atrial (full) maze	21; 40.4
Left atrial maze	8; 15.4
Which energy sources does your program use? (select all that apply)	
Combined radiofrequency &cryothermy	33; 63.4
Cryothermy alone	30; 57.7
Radiofrequency alone	20; 38.5
Cut and sew	4; 7.7
How does your program manage the left atrial appendage?	
External ligation/device	30; 57.7
Excision and oversewing	13; 25.0
Internal (intra-atrial) suture closure	7; 13.5
Stapling	2; 3.8

Discussion

Our survey of senior CT surgery residents aimed to examine the training environment of surgical ablation for AF by evaluating various components of the resident experience though operative volume, case diversity, and clinical scenarios based on current guidelines. With the current recommendations and increasing prevalence of AF alongside safe and durable surgical techniques, it is likely that cardiac surgeons will be tasked with performing more ablations.[1-3] Given that incomplete ablation procedures have been demonstrated to yield worse long-term outcomes as compared to bi-atrial lesion sets with regard to maintenance of sinus rhythm, it is imperative that graduating trainees are competent with both the indications for and performance of AF ablation surgery.[6]

Although this survey had a modest response rate, it is within expected response percentages for internet-based, non-incentivized, voluntary surveys with a single request for participation.[7] We acknowledge the potential for sampling error as the responders may not fully represent the entire cohort of senior CT surgery residents and may demonstrate bias toward dissatisfaction in training with ablation surgery. Indeed, those with more robust experiences may have elected not to respond. Nevertheless, while there may be training programs which have a much more robust experience in ablation surgery, those programs are likely outliers rather than the norm across residencies. Additionally, it is unknown whether or not the contact information available from the TSDA contains email addresses that were functional or accessed by their owners during the survey administration. Regardless, there are important concerns identified from our results including the array of often-incomplete lesion sets (PVI), low case volume during residency, and inappropriate scenarios (aortic dissection, arrhythmia prophylaxis) or missed opportunities to perform an ablation. These findings would suggest a not-irrelevant proportion of residents being inadequately exposed to surgical ablation of AF. Although this survey focused on surgical ablation of AF, there may be other components of CT surgery residency training where residents are dissatisfied (for example: coronary artery

Table 2: Scenarios in which survey respondents would perform surgical ablation of AF

Scenario	Percentage of respondents (n=52)
Concomitant operation	
Mitral valve repair/replacement	98 %
Coronary artery bypass & valve replacement	90.4 %
Tricuspid valve repair/replacement	88.5 %
Coronary artery bypass	84.6 %
Aortic valve replacement	77.5 %
For postoperative AF prophylaxis	19.2 %
Repair of aortic dissection	17.3 %
Stand-alone ablation	
Symptomatic from arrhythmia	98 %
Failed catheter ablation	86.5 %
Refractory to anti-arrhythmic drug(s)	86.5 %
Contraindication to/intolerant of anticoagulation	82.7 %
Combined with catheter ablation (hybrid approach)	48.1 %
Asymptomatic but with long-standing persistent AF	17.3 %

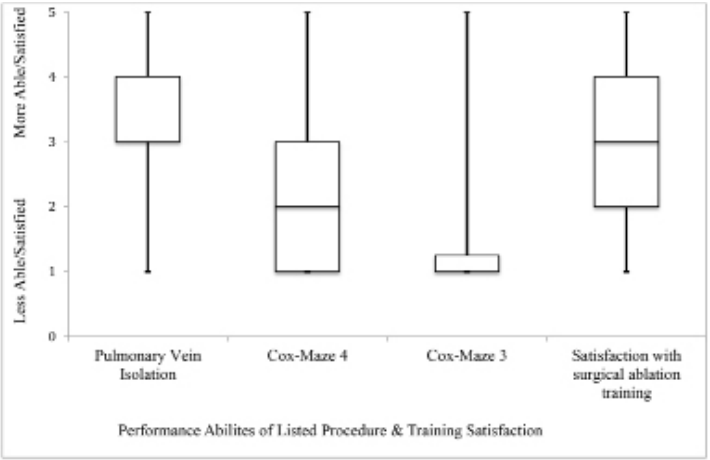

Figure 1: Box plot of the survey responders' self-rated abilities to perform specific ablation procedures & satisfaction with training in surgical ablation for AF (y-axis numeric Likert values 1-5 correlate with survey response choices appearing in the methods section).

bypass, aortic valve replacement). A comparison of perceptions of the training experience in various procedures may be of interest but is out of the scope of this work.

Current CT surgery residency graduation requirements mandate a minimum of 5 ablation surgeries of any type (PVI, bi-atrial, left atrial, etc.), which interestingly, matches our reported median case volume. With regard to training in other cardiac surgeries, minimum case volumes have been reported to demonstrate competency; however, these do not exist for surgical ablation. Yount and colleagues evaluated resident performance in coronary artery bypass surgery and identified 30 cases as a marker of proficiency in operative conduct. Significant improvement in operative conduct.[8] It is unknown whether or not the mandated 5 cases are sufficient; however, there is an appreciable range of skill required to perform a pulmonary vein isolation compared to a bi-atrial lesion set. Regardless, the likely inadequacy of the reported case volume is underscored by the respondents' overall self-perceived inability to independently perform standardized full lesion sets and neutral satisfaction in their training. Whether or not the survey participants overestimated or undervalued their skills is unknown as is their case logging habits. Resident case volume reporting is subject to variation as prior reports have suggested residents may consider themselves the primary surgeon if they are merely present at the operation.[9] Thus, there is a possibility that the actual number of ablation surgeries predominantly performed by a trainee is less than reported in our findings. Additionally, the survey may have captured residents with an additional 1-2 years of training remaining so those responders may graduate with a greater case volume.

Multiple opportunities exist for the improvement in training residents to perform surgical ablation for AF. While many leaders in the field of arrhythmia surgery provide seminars at professional meetings and industry-sponsored courses are available, formal and earlier exposure during residency has potential to strengthen a new/younger surgeon's repertoire. As exposure to complete ablations and familiarization with the anatomic boundaries may be accomplished during residency training in the way of simulation, tissue labs or higher-fidelity models would likely be necessary alongside a complete curriculum and proficient instructors. However, increasing case volume would likely provide a more robust grasp of the nuances and sequence of the operation. Regardless, increasing case number hinges on the adequacy of the instruction by teaching surgeons, as educators must employ complete lesion sets.

The lack of exposure to complete ablations is again suggested by our findings of PVI being the most commonly employed lesion set. While likely sufficient for paroxysmal AF, PVI has been demonstrated to be inferior to complete bi-atrial lesions regarding long-term maintenance of sinus rhythm for persistent or longstanding persistent AF.[6] The Society of Thoracic Surgeons (STS) guidelines offer Class I recommendations for performing surgical ablation for AF at the time of mitral valve, aortic valve, coronary artery bypass, and combined valvular and coronary bypass operations. Additionally, surgical ablation for AF for symptomatic patients refractory to antiarrhythmic medications or catheter-based therapy is recommended at the IIa level. Finally, a bi-atrial lesion set is recommended over a PVI.[1] Despite the majority (77-98%) of responders' adherence to the clinical scenarios in our survey based on the abovementioned guidelines, it is unknown if the residents would actually perform an ablation or complete lesion set in real time circumstances as well as if such recommendations are applied at their training program.

Possible barriers to adequate teaching by instructors include the perceptions that ablation may lead to increased morbidity and mortality, are time consuming, or yield no benefit to the patient. Despite data to the contrary, a persistently low percentage of surgeons perform ablations in appropriate settings.[5] Again, any improper training or technique of the supervising/instructing surgeon must be remedied so as to provide residents an appropriate exposure.

Conflicts/declarations of interest
None.

Conclusion

Overall, our findings of incomplete lesion sets, low case volume, and neutral satisfaction with training should inform educators of the need to intervene on these issues or perform further evaluation. The importance of more thorough clinical instruction in surgical ablation for AF during CT surgery residency as well as the development of standardized curricula may yield improved patient outcomes and greater application of surgical ablation.

References

1. Badhwar V, Rankin JS, Damiano RJ, Gillinov AM, Bakaeen FG, Edgerton JR, Philpott JM, Mc CPM, Bolling SF, Roberts HG, Thourani VH, Suri RM, Shemin RJ, Firestone S, Ad N. The Society of Thoracic Surgeons 2017 Clinical Practice Guidelines for the Surgical Treatment of Atrial Fibrillation. Ann. Thorac. Surg. 2017;103 (1):329–341.
2. Ad N, Damiano RJ, Badhwar V, Calkins H, La MM, Nitta T, Doll N, Holmes SD, Weinstein AA, Gillinov M. Expert consensus guidelines: Examining surgical ablation for atrial fibrillation. J. Thorac. Cardiovasc. Surg. 2017;153 (6):1330–1354.e1.
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. 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;285 (18):2370–5.
4. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. Circ Cardiovasc Qual Outcomes. 2011;4 (3):313–20.
5. Badhwar V, Rankin JS, Ad N, Grau-Sepulveda M, Damiano RJ, Gillinov AM, McCarthy PM, Thourani VH, Suri RM, Jacobs JP, Cox JL. Surgical Ablation of Atrial Fibrillation in the United States: Trends and Propensity Matched Outcomes. Ann. Thorac. Surg. 2017;104 (2):493–500.
6. Henn MC, Lancaster TS, Miller JR, Sinn LA, Schuessler RB, Moon MR, Melby SJ, Maniar HS, Damiano RJ. Late outcomes after the Cox maze IV procedure for atrial fibrillation. J. Thorac. Cardiovasc. Surg. 2015;150 (5):1168–76, 1178.e1-2.
7. Pedersen MJ, Nielsen CV. Improving Survey Response Rates in Online Panels: Effects of Low-Cost Incentives and Cost-Free Text Appeal Interventions. Soc Sci Comp Rev. 2016;0:229–243.
8. Yount KW, Yarboro LT, Narahari AK, Ghanta RK, Tribble CG, Kron IL, Kern JA, Ailawadi G. Outcomes of Trainees Performing Coronary Artery Bypass Grafting: Does Resident Experience Matter?. Ann. Thorac. Surg. 2017;103 (3):975–981.
9. Cadish LA, Fung V, Lane FL, Campbell EG. Surgical Case Logging Habits and Attitudes: A Multispecialty Survey of Residents. J Surg Educ. 2016;73 (3):474–81.

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Warfarin Use and Mortality, Stroke, and Bleeding Outcomes in a Cohort of Elderly Patients with non-Valvular Atrial Fibrillation

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Abstract

Aims : To determine exposure to warfarin and the associated outcomes in a population of older patients with non-valvular atrial fibrillation (NVAF).

Methods : Cohort study of patients aged 65-89 years admitted to hospital July 2003-December 2008 with newly-diagnosed or pre-existing AF. Outcomes at three years among one-year survivors post-index admission (landmark date) were all-cause mortality, stroke/systemic thromboembolism (stroke/TE) and bleeding. Multivariate Cox models were used to identify factors associated with each outcome.

Results : AF was the principal diagnosis for 27.5% of 17,336 index AF admissions. Of 14,634 (84.4%) patients alive at one-year 1,384 (9.5%) died in the following year. Vascular disease (42%) was the most frequent cause of death.
Warfarin use, prior to the index admission and/or the 1-year landmark, did not exceed 40%.
Compared to non-exposure or discontinuation at the index admission, initiation or persistence with warfarin prior to the landmark date was associated with reduced risk for all-cause mortality, a statistically non-significant reduction in risk for stroke/TE, and an increased risk for bleeding. Higher CHA2DS2-VASc scores were associated with increased risk for each outcome.

Conclusions : In a population-based cohort of hospitalised NVAF patients, the initiation and persistent use of warfarin was associated with lower all-cause mortality risk to three years, although reduction in risk for stroke/TE did not reach statistical significance. The apparent under-use of warfarin in this older, high-risk cohort reinforces the opportunity for further reduction in stroke/TE with the uptake of non-vitamin K oral anti-coagulants (NOACs) among those not prescribed, or not persistent with, warfarin.

Introduction

Atrial fibrillation (AF) is the most frequent arrhythmia among older adultswith a general population prevalence of less than 1% before the sixth decade but doubling with each subsequent decade [1]. It is associated with increased risk for thromboembolic stroke and increased mortality. In a meta-analysis of randomised trials, the use of an oral anticoagulant (warfarin) for high-risk patients, when compared to no antithrombotic treatment, was estimated to reduce the risk for thromboembolic stroke by 60% and mortality by 25%. Antiplatelet medication alone also reduced the risk for stroke, but risk was reduced by a further 40% by the use of adjusted-dose warfarin [2].

While the vitamin K antagonist warfarin has been the mainstay of stroke prevention for decades, its use is declining in favour of non-vitamin K oral anticoagulants (NOACs). A recent count of prescriptions filled under the Australian Pharmaceutical Benefits Scheme (PBS) for those eligible through the Department of Veteran's Affairs reported that NOACs were 67% of anticoagulants supplied for AF by mid-2017 [3]. Similar trends are reported from population studies in other countries [4-6]. Despite the increasing uptake of NOACs, warfarin is still a current first-line recommendation for stroke prevention [7,8], and switching from NOACs to warfarin occurs in certain situations[9].

While warfarin use continues, population outcomes for patients with non-valvular AF (NVAF) remain of current interest. They provide data for future risk/benefit comparisons as the use of NOACs accelerates, and are pertinent to prescribers and patients in aging populations.

The aim of this study was to examine the effect of exposure to warfarin on all-cause mortality, fatal and non-fatal stroke or thromboembolism (stroke/TE), and serious bleeding events in a population of older patients with AF.

Key Words

Atrial Fibrillation, Clinical Outcomes, Warfarin, Population Study, Linked Data, Landmark Analysis.

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Methods

Data sources and AF cohort

This analysis was a sub-study of the WAMACH study which used linked administrative data from the Hospital Morbidity Data Collection (in-patients) and Death Register from the Western Australian Data Linkage System, linked to Pharmaceutical Benefits Scheme (PBS) dispensing records.

The WAMACH study cohort has been described in detail previously and includes patients hospitalised in Western Australia for ischaemic heart disease (IHD), heart failure (HF) or atrial fibrillation [10]. The current study cohort was restricted to age 65 years or more as seniors gain concessional access to PBS listed drugs. The remaining cost after the lower co-payment is met by the Australian Government, giving rise to a dispensing record in the PBS data. This captures the majority of warfarin users as approximately 90% of Australians aged 65–75 years, and 95% of those aged 75 years and over had a concession card in 2004–2005 [11].

The NVAF study cohort comprised all people aged 65-89 years admitted to a public or private hospital in WA from 1 July 2003 to 31 Dec 2008, with a principal or secondary diagnosis of atrial fibrillation/atrial flutter identified by the International Classification of Diseases (ICD) 10th revision Australian Modification (ICD-10-AM) code I48. Patients with comorbid cardiac valve disease, or with a prosthetic valve, were excluded, as were those undergoing long-term renal dialysis. Cohort entry was the first admission in which AF was recorded during the study period (the index admission). NVAF patients with an additional clinical indication for short (weeks) or longer term (12 months) OAC, i.e. joint replacement or for venous thromboembolism, were not excluded as the major aim is to assess long-term persistence/adherence to OAC in patients with a strong clinical indication (AF and high CHA2DS2-VASc score) and no contraindication, or reason for discontinuation such as major bleeding.

Linked data available for the AF cohort were all hospital admissions from 1980 to end of 2013, deaths (and cause of death) to end of 2013, and PBS medication records for the period 1 July 2002 to 30 June 2011. There was a minimum 12 months of PBS records before and after the index admission.

As observational cohort studies of therapeutics are at risk of immortal person-time bias [12], we used a landmark analysis method on patients alive at one year post-index admission (1-year landmark date).

Measure of warfarin exposure

We used the standard dispensing (supply) of 50 tablets of any strength of warfarin, on at least one occasion in a one-year period, as indicating exposure to warfarin during that period. Warfarin use at the landmark time point was identified according to supply in both the year prior to the index admission, and in the year after hospital discharge to the 1-year landmark. Warfarin exposure was thereby categorised as 'persistent' for patients with supply in both one-year periods, 'discontinued' for those with supply prior to index but not in the one year after, 'initiated' for those with no supply before index but with supply in the one year after, and 'no warfarin' if no supply in either period.

Covariates

Age at the landmark date was grouped as 65-74, 75-79 and ≥80 years, approximating the cohort tertiles. AF at index admission was classified as either a 'principal' or a 'secondary diagnosis'.

Comorbidities (heart failure, diabetes mellitus, hypertension, stroke/transient ischaemic attack/thromboembolism and vascular disease) identified from administrative hospital records in the prior 10-years were used to calculate the CHA2DS2-VASc risk score [13] at the 1-year landmark. A history of major bleeding in the principal diagnosis was identified based on standardised bleeding definitions previously published [14,15], including intracranial haemorrhage (ICH) which incorporates intracerebral bleeding, subarachnoid haemorrhage, subdural and epidural bleeding, gastro-intestinal (GI) bleeding, and anaemia. Chronic kidney disease (CKD) was also identified.

Outcomes

Three outcomes were identified: time to death from any cause (censored at 3 years); time to a first stroke/TE (fatal or non-fatal) (censored at non-stroke death or 3 years); and time to a first serious bleeding episode requiring hospital admission, including fatal and non-fatal ICH (censored at death or 3 years). Outcome events based on hospital admissions were restricted to principal diagnosis only. The person-time incidence rate of stroke/TE and bleeding per 100 years (/100 PY) were calculated for each year from the landmark date.

The composite endpoint of stroke/TE was defined as ICD-10-AM codes I63 (ischaemic stroke), I64 (stroke, not specified as ischaemic or haemorrhagic) and I74 (arterial embolism and thrombosis) to identify fatal and non-fatal events. Combining I63 and I64 is recommended for identifying ischaemic stroke from electronic records for epidemiological studies [16], and is used in other population studies [17]. However, as nearly 90% of strokes as the 'cause of death' were coded as I64, a sensitivity analysis was done to determine the effect of excluding unspecified fatal and non-fatal stroke. All ICD codes are listed in Supplementary [Table 1].

Statistical analysis

Patient characteristics across warfarin exposure groups are described and compared using chi-square tests for categorical variables and ANOVA for quantitative variables. The annual sum, median, and interquartile range (IQR) of warfarin supplied (in milligrams, mg) were calculated.

Kaplan-Meier survival analysis was used to assess the associations between the outcomes and each categorical covariate, and the log-rank test used as a measure of their association with outcomes. Multivariable Cox regression models were used to compare outcomes across warfarin groups, adjusted for CHA2DS2-VASc score and other covariates (see [Table 1]).

A two-sided $p<0.05$ was considered statistically significant. Estimated hazard ratios with a 95% confidence interval that does not include the value 1.0 are significant at the 5% level. SPSS Statistics for Windows (IBM Version 22.0. Armonk, NY) was used for all analyses.

Ethics

The study was approved by the Human Research Ethics Committee (HREC) of the Department of Health (Western Australian 2014/11 and Federal Government) and the University of Western Australia (RA/4/1/8065), in addition to HREC approvals from all participating hospitals.

The datasets for this study, generated by the Data Linkage Branch of the Health Department of Western Australia, are held at the University of Western Australia. The data is not publicly available due to confidentiality agreements between the providers and the study investigators.

Results

There were 17,336 index NVAF admissions (27.5% as principal diagnosis). For patients with AF as a secondary diagnosis, the most frequent principal diagnoses were IHD (13.2%) and HF (6.6%); stroke/TE was 4.4%. Other frequent conditions such as , chronic obstructive lung disease and osteoarthritis of the knee and hip were each <5%. Patients with AF as the principal diagnosis were younger (76.2, SD 6.5 vs 78.5, SD 6.5 years, $p<0.001$) and had significantly less comorbid diabetes, HF, IHD, CKD, or prior stroke.

At one-year post-index admission, 14,634 patients (84.4%) were alive. Compared to survivors, those who died within the first year were older (80.5, SD 6.1 vs 77.4, SD 6.5 years, $p<0.001$) and had a higher mean CHA2DS2-VASc score (4.2 vs 3.6, $p<0.001$) at index admission. The most frequent cause of death was 'any vascular disease' (37.6%) including IHD (19.1%), ischaemic stroke (8.3%) and AF (2.8%); cancer was the next most frequent (32.4%).

Patient characteristics at index admission, at the one-year landmark, and by warfarin exposure at the landmark date are presented in [Table 1]. Warfarin use at the 1-year landmark was lower for women than men. Those with a history of CKD or bleeding prior to the index admission were less likely to use warfarinand more likely to discontinue it after admission [Table 1]. As expected, those admitted for bleeding at the index admission, or prior to the 1-year landmark, were less likely to initiate warfarin, and more likely to discontinue its use. Initiation was higher among those suffering stroke/TE at index or prior to the landmark.

Warfarin use

For those alive at the 1-year landmark, 40% were supplied with warfarin either prior to, or after, the index admission [Table 1]. Warfarin exposure exceeded 45% only for those with a CHA2DS2-VASc score ≥6, with those with a score of '2' at 38.6%.

The median total of warfarin dispensed in the 12 months pre-index was 700 mg (400-1150) for those who discontinued from the index admission and 900 mg (500-1450) for those persisting post-hospital discharge (data not shown). The totals in the year after discharge were 1150 mg (650-1650) for those initiating post-index, and 1150 mg (750-1650) for those persisting. Three patients supplied with fewer than 50 tablets (14-17 tablets) were excluded from comparisons.

Stroke/SE was the most frequent principal diagnosis at the index admission associated with a change in warfarin use. Among 30-day survivors of stroke (n=689), warfarin was initiated in 302 patients (43.8%). For all patients alive at the 1-year landmark, initiation was higher for those CHA2DS2-VASc scores ≥3, while persistent use was around 20% across the whole range of scores.

Mortality

Of the 14,634 alive at the one-year landmark, 1,384 (9.5%) died in the following year; crude all-cause mortality was 9.0%, and 8.7% in the subsequent years.

Among the 3,631 deaths at three years from the one-year landmark date, the cause was coded as 'vascular disease' for 1,519 patients (41.8%) which included IHD (29.4%), ischaemic stroke (6.2%), and ICH (1.5%). Cancer deaths were 25%.

Unadjusted survival was greater among patients persisting with, or initiating, warfarin prior to the landmark date compared with those not exposed to warfarin, and worse for those who had discontinued (Log Rank 83.35, df 3, $p<0.001$) [Figure 1]. Annualised survival overall and according to warfarin exposure is shown in [Table 2].

Multivariate associations with survival to three years from the one-year landmark

Warfarin exposure group, a CHA2DS2-VASc score ≥3, age, male sex, comorbidity and previous events were all independently associated with 3-year all-cause mortality in 1-year survivors of AF [Table 3].

Stroke/TE

Stroke/TE was the principal diagnosis at the index admission for 727 patients (4.2%). Among these patients, 38 (5.2%) died within 30-days. There were an additional 294 fatal and non-fatal strokes prior to the 1-year landmark.

There were 694 new stroke/TE events in the 3-year follow-up post-landmark date, of which 224 (32.3%) were ischaemic stroke

Table 1: Characteristics of the NVAF study cohort and one-year survivors, stratified by warfarin use at the 1-year landmark

At Index Admission		Alive at One-year Landmark Total and by warfarin use					
	All 17, 336 n (%)	Total 14 634 (84.4)	No warfarin 8 406 (57.4)	Discontinued 378 (2.6)	Initiated 3 009 (20.6)	Persistent 2 841 (19.4)	'p' value *
Women n (%)	8 290 (47.8)	7 077 (48.4)	4 255 (50.6)	179 (47.4)	1 457 (48.4)	1 186 (41.7)	<0.001
Age (years) - mean [SD]	77.9 [6.6]	78.4 [6.5]	78.6 [6.8]	79.2 [6.4]	78.1 [6.3]	78.0 [6.2]	<0.001
AF - principal diagnosis		4 452 (30.4)	2 075 (24.7)	99 (26.2)	1 110 (36.9)	1 168 (41.4)	<0.001
CHA2DS2-VASc score at index admission		Score at the 1-year landmark					
Mean [SD]	3.7 [1.5]	4.0 [1.6]	3.9 [1.7]	4.3 [1.8]	4.1 [1.7]	4.0 [1.7]	<0.001
1 n (%)	1 108 (6.4)	819 (5.6)	483 (5.7)	21 (5.6)	135 (4.5)	180 (6.3)	
2	2 837 (16.4)	2 181 (14.9)	1 340 (15.9)	44 (11.6)	378 (12.6)	419 (14.7)	
3	4 088 (23.6)	3 180 (21.7)	1 853 (22.0)	75 (19.8)	628 (20.9)	624 (22.0)	
4	3 962 (22.9)	3 138 (21.4)	1 813 (21.6)	63 (16.7)	661 (22.0)	601 (21.2)	
5	3 031 (17.5)	2 568 (17.5)	1 441 (17.1)	73 (19.3)	571 (19.0)	483 (17.0)	
6	1 641 (9.5)	1 603 (11.0)	849 (10.1)	50 (13.2)	397 (13.2)	307 (10.8)	
7-9	669 (3.9)	1 145 (7.8)	627 (7.5)	52 (13.8)	239 (7.9)	227 (8.0)	
Components of CHA2DS2-VASc score at the 1-year landmark							
Heart failure		3 948 (27.0)	2 095 (24.9)	125 (33.1)	893 (29.7)	835 (29.4)	<0.001
Hypertension		8 458 (57.8)	4 742 (56.4)	232 (61.3)	1 843 (61.3)	1 641 (57.8)	<0.001
Diabetes		3 107 (21.2)	1 742 (20.7)	116 (30.7)	596 (19.8)	653 (23.0)	<0.001
Vascular disease		6 415 (43.8)	3 731 (44.4)	172 (45.5)	1 288 (42.8)	1 224 (43.1)	NS
Stroke/TIA/TE		2 337 (16.0)	1 107 (13.2)	80 (21.2)	668 (22.2)	482 (17.0)	<0.001
Age 75 year or more		9 867 (67.4)	5 702 (67.9)	274 (72.5)	1 998 (66.4)	1 893 (66.6)	NS
History (10 years)							
Chronic kidney disease	1 226 (7.1)	1 109 (7.6)	692 (8.2)	46 (12.2)	187 (6.2)	184 (6.5)	<0.001
Bleeding	2 042 (11.8)	1 961 (13.4)	1 149 (13.7)	108 (28.6)	369 (12.3)	335 (11.8)	<0.001

SD=standard deviation, TIA=transient ischaemic attack, TE=thromboembolism* 'p' value for difference between the four warfarin use groups

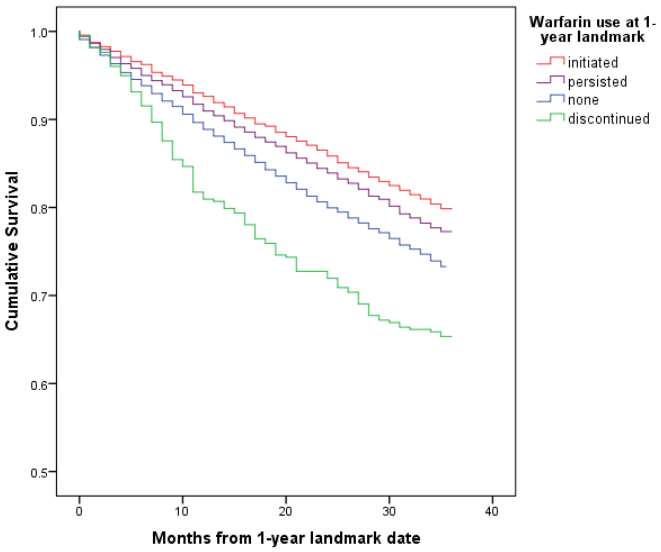

Figure 1: Kaplan-Meier survival to three years from the 1-year landmark after admission for AF (principal or secondary diagnosis) by warfarin use at the landmark date

deaths, and 199 (89%) coded as I64. The incidence rate of stroke/TE events by warfarin exposure is shown in [Table 2].

Univariate associations with stroke/TE

Survival to stroke/TE was worse for those who discontinued warfarin, compared with those not exposed, initiating or persisting, but the difference was not statistically significant (Log Rank 6.17, df 3, p=0.10) [Figure 2]. Women, those with higher CHA2DS2-VASc scores, aged ≥80 years, with a history of bleeding or CKD, and with AF as a secondary diagnosis were at higher risk for stroke/TE.

Multivariate associations with stroke/TE

CHA2DS2-VASc scores ≥5 were independently associated with the risk for stroke/TE, with the adjusted hazard more than doubling [Table 4]. In a sensitivity analysis, the associations with the outcome were unchanged by exclusion of 281 events coded as 'unspecified' strokes.

Major Bleeding

There were 2,042 patients (11.8%) with an admission for major

Table 2: Annual cumulative survival and incidence of stroke/systemic thromboembolism and serious bleeding events per 100 person–years from the 1-year landmark, overall and by warfarin use.

Year	Overall	No warfarin	Discontinued	Initiated	Persisted
	Number of patients surviving Kaplan-Meier probability of unadjusted cumulative survival to 3 years				
1	13 247 0.90	7 534 0.90	309 0.82	2 786 0.93	2 606 0.92
2	12 052 0.82	6 776 0.81	279 0.72	2 602 0.86	2 399 0.84
3	11 003 0.75	6 159 0.73	247 0.65	2 402 0.80	2 195 0.77
	Number of stroke/systemic thromboembolism events (person-years observed) Incidence rate per 100 person-years (95% CI)				
1	293 (13 937) 2.1 (1.8-2.4)	187 (7 956) 2.4	9 (349) 2.6	42 (2 905) 1.4	55 (2 723) 2.0
2	199 (12 340) 1.6 (1.3-1.9)	106 (7 148) 1.5	9 (290) 3.1	52 (2 698) 1.9	32 (2 500) 1.3
3	200 (11 525) 1.7 (1.4-2.1)	114 (6 472) 1.8	6 (257) 2.3	46 (2 497) 1.8	34 (2 295) 1.5
Total	692 (37 802) 1.8 (1.7-1.9)	407 (21 576) 1.9 (1.7-2.1)	24 (896) 2.7 (-1.7-7.1)	140 (8 100) 1.7 (1.2-2.2)	121 (7 518) 1.6 (1.1-2.1)
	Number of serious bleeding events (person-years observed) Incidence rate per 100 person-years (95% CI)				
1	234 (13 847) 1.7 (1.4-2.0)	110 (7 918) 1.4	4 (348) 1.1	63 (2 878) 2.2	57 (2 700) 2.1
2	200 (12 554) 1.6 (1.3-1.9)	105 (7 105) 1.5	7 (288) 2.4	45 (2 678) 1.7	43 (2 481) 1.7
3	174 (10 886) 1.5 (1.2-2.0)	80 (6 181) 1.2	3 (244) 1.2	46 (2 313) 1.8	45 (2 149) 2.0
Total	608 (37 287) 1.6 (1.5-1.7)	295 (21 204) 1.4 (1.2-1.6)	14 (880) 1.6 (-2.9-6.1)	154 (7 869) 2.0 (1.4-2.5)	145 (7 330) 2.0 (1.4-2.5)

Table 3: Independent predictors of 3-year all-cause mortality among 14, 631 survivors with NVAF at the 1-year landmark

Factor	Hazard ratio (95% CI)	P value
Warfarin use vs none		
Discontinued	1.22 (1.02-1.45)	0.03
Initiated	0.74 (0.68-0.82)	<0.001
Persisted	0.87 (0.80-0.95)	<0.01
CHA2DS2_vasc score vs 1		
2	1.14 (0.88-1.50)	NS
3	1.49 (1.15-1.94)	<0.01
4	1.73 (1.33-2.25)	<0.001
5	2.02 (1.55-2.63)	<0.001
6	2.48 (1.89-3.26)	<0.001
7-9	3.07 (2.32-4.04)	<0.001
AF- principal vs secondary diagnosis	0.69 (0.64-0.76)	<0.001
History bleeding	1.28 (1.18-1.40)	<0.001
History of CKD	1.39 (1.25-1.54)	<0.001
Sex (female)	0.69 (0.65-0.74)	<0.001
Age vs <75 years		
75 -79	1.48 (1.31-1.66)	<0.001
80 years or more	2.81 (1.25-3.12)	<0.001

CKD=chronic kidney disease

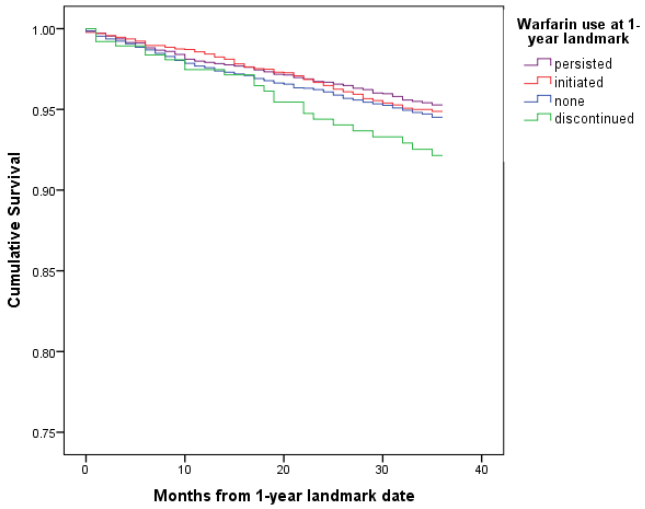

Figure 2: Kaplan-Meier time to a first fatal or non-fatal stroke/systemic thromboembolism in the 3-year follow-up from the landmark date by warfarin use at landmark

Table 4: Independent predictors of a first fatal or non-fatal stroke/systemic thromboembolism event in the 3-year follow-up for one-year survivors with NVAF

Factor	Hazard ratio (95% CI)	P value
Warfarin use vs none		
Discontinued	1.22 (0.81-1.85)	0.34
Initiated	0.89 (0.74-1.09)	0.26
Persisted	0.87 (0.71-1.07)	0.19
CHA2DS2_vasc score vs 1		
2	0.87 (0.48-1.58)	0.65
3	1.27 (0.71-2.25)	0.42
4	1.37 (0.77-2.45)	0.28
5	2.02 (1.13-3.62)	0.02
6	2.32 (1.28-4.23)	<0.01
7-9	3.96 (2.17-7.23)	<0.001
AF -principal vs secondary diagnosis	0.93 (0.78-1.12)	0.45
History bleeding	1.15 (0.94-1.24)	0.18
History of CKD	0.98 (0.75-1.28)	0.88
Sex	1.0 (0.85-1.17)	0.96
Age vs <75 years		
75-79	1.57 (1.21-2.03)	<0.01
80 or more years	2.22 (1.74-2.81)	<0.001

Table 5: Independent predictors of a first admission for major bleeding in the 3-year follow-up among 1-year survivors with NVAF

Factor	Hazard ratio (95% CI)	P value
Warfarin use vs none		
Discontinued	1.00 (0.458-1.72)	1.00
Initiated	1.39 (1.14-1.17)	<0.01
Persisted	1.42 (1.16-1.74)	<0.01
CHA2DS2_vasc score vs 1		
2	1.32 (0.79-2.20)	0.28
3	1.78 (1.09-2.92)	0.02
4	2.06 (1.25-3.39)	<0.01
5	2.27 (1.36-3.78)	<0.01
6	1.95 (1.12-3.38)	0.02
7-9	2.82 (1.61-4.94)	<0.01
AF-principal vs secondary diagnosis	1.02 (0.85-1.22)	0.83
History bleeding	1.65 (1.35-2.02)	<0.001
History of CKD	1.12 (0.84-1.50)	0.42
Sex (female)	0.72 (0.60-0.85)	<0.01
Age vs <75 years		
75-79	0.89 (0.70-1.13)	0.34
80 or more years	1.35 (1.10-1.66)	<0.01

* Diagnoses at discharge from index admission

bleeding in the 10 years prior to the index admission. Of the 249 patients with a principal diagnosis of bleeding at index admission, the majority were neurological events coded as ICH (n=74, 29.7%), 12 (4.8%) were sub-arachnoid and 33 (13.3%) epidural haemorrhages. A further 88 (35.3%) admissions were for gastro-intestinal bleeding, and 19 (7.6%) had respiratory tract bleeding.

There were 13 deaths (5.2%) within 30 days of admission, and an additional 48 deaths (20.3%) among 236 survivors of a serious bleed within the first year. There were 35 new bleeding events prior to the 1-year landmark.

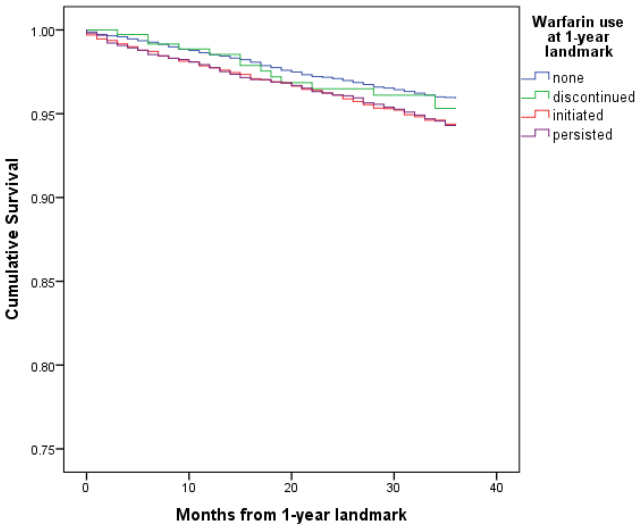

Figure 3: Kaplan-Meier time to admission for major bleeding within three years of the 1-year landmark date by warfarin use

Of those alive at the landmark date, 608 were hospitalised with a first or new major bleed within three years. The majority were gastrointestinal bleeds (n=410, 67.4%), with 124 ICH 124 (20.4%) and 61 coded as epidural haemorrhages (10%). Of the 22 deaths coded as intracerebral haemorrhages, 21 occurred in hospital. The incidence rate of bleeding events by warfarin exposure is shown in [Table 2].

Univariate associations with major bleeding

The risk for bleeding in the 3-year follow-up was significantly greater for men, those aged ≥80 years, with a prior bleeding event, and with a CHA2DS2-VASc score ≥4. Initiation of and persistence with warfarin were also associated with increased risk (Log Rank 18.01, df 3, p<0.001) [Figure 3].

Multivariate associations with major bleeding

After adjustment, the independent risk for a serious bleeding event was higher for males, those aged ≥80 years or with a history of bleeding, and for those both initiating and persisting with warfarin use [Table 5].

Discussion

This study has provided a real-world indication of outcomes from exposure to warfarin in an older population, with new or comorbid AF diagnosis identified in a hospital admission. Current warfarin use

one year after the index admission was independently associated with lower risk for all-cause mortality to three years, compared with non-exposure, and with increased risk for those discontinuing warfarin. The reduction in mortality for those exposed was not matched by a statistically significant reduction in the risk of stroke/TE. The hazard ratios, while lower than for non-users, were not statistically significant, and neither was the apparent increased hazard for those discontinuing warfarin. The initiation or ongoing exposure to warfarin was independently associated with increased risk for serious bleeding, compared with non-use.

Other factors may be responsible for the different risk for death and stroke for those exposed to warfarin. The selection for warfarin treatment of 'healthy users', with less life-limiting comorbidity such as renal failure, may have contributed to the mortality benefit. In addition, the rate of stroke/TE events was low in the unexposed and exposed groups (less than 2.0/100 PY, not including those discontinuing). The lack of statistical significance for stroke/TE risk may be due to insufficient power from the low number of stroke events. Other explanations include less than optimal management of warfarin leading to reduction in benefit, and inadequate measurement of exposure. Patients may have changed their status during follow-up, initiating or discontinuing warfarin during this time.

The low stroke/TE rate, although not age-standardised, was consistent with rates reported for Australia, Europe and other developed economies [18,19,20], but resulted in too few events for reliable estimates of rates within levels of the CHA2DS2-VASc risk score. For patients not exposed to warfarin, the overall incidence rate was lower than reported from a large study of patients in England (3.8/100 PY), with data from both primary and secondary care, while the rate for those exposed was the same (1.7/100 PY) [21]. In that population ,a net clinical benefit in stroke reduction from exposure to warfarin, defined using similar criteria as ours, was seen for CHA2DS2-VASc score ≥2 for men and ≥3 for women. The low stroke/TE rate among unexposed patients in our cohort may be related to the inclusion of both incident and prevalent cases. In addition, the use of antiplatelet medication in the unexposed group was not known, though nearly half had comorbid vascular disease. Major bleeding among those exposed to warfarin did not exceed the pooled estimate of 2.51/100 PY from the warfarin arms of 51 studies [22].

Current warfarin use never exceeded 40% overall in our cohort of older patients. Under 2012 European and US guidelines, none of our cohort patients were 'low risk'; all had CHA2DS2-VASc delete scores for which oral anti-coagulation would be considered or recommended (men ≥1, women ≥2), unless contraindicated [8,19] and this recommendation remains current [7]. While over 13% had a history of bleeding in the 10 years prior to the 1-year landmark date, use in others would be absolutely or relatively contraindicated. We did not have the clinical data to assess the proportion of patients for whom warfarin may have been contraindicated due to bleeding risk (as estimated by an algorithm such as the HAS-BLED score). We had insufficient clinical data to estimate bleeding risk. In addition, we could not identify those with cognitive impairment or frailty, groups of patients who are less likely to be prescribed OAC, despite being at higher predicted risk for stroke and death. [23]

While variation in the selection of patients for warfarin is widespread, with reported contraindications ranging from under 20% to over 50% [24], the low exposure to warfarin in our cohort of both prevalent and incident AF is consistent with other real-world studies. These have reported initial warfarin use below 60% overall, and below 70% among moderate/high risk patients [25,26]. Furthermore, there is considerable drop-off within a few years of starting, with rates in Australia and elsewhere falling below 30% [27,28].

Until/unless treatments to successfully control AF are developed, OAC, including warfarin, remain central to AF management. Ongoing research into early detection of AF, strategies to promote appropriate use of, and persistence with, OAC and the outcomes of these strategies is necessary [29].

Strengths and limitations

This use of linked state-wide morbidity and mortality data and the national pharmaceutical database allowed a large-scale population-level study with reliable and complete outcome data. Good ascertainment of stroke/TE and serious bleeding events is probable as most cases would require hospital admission. While clinical detail is reduced when using administrative data, it is sufficient for the calculation of the CHA2DS2-VASc score [30], an important predictor of stroke risk [15].

The externally coded cause of death uses coding conventions which may attribute death to underlying (antecedent or contributing) conditions or to the immediate 'cause'. The attribution of stroke as cause of death out of hospital to ICD-10-AM I64 (not specified as haemorrhage or infarction) is a worldwide limitation for studies of stroke [31,32,33].

As the cohort was identified from hospital admissions, the patients may not be representative of the wider population with AF. They are likely to have poorer health and suffer more comorbidity. The proportion of patients with comorbid cardiovascular disease exceeded 40%. We could not quantify the use of anti-platelets (including aspirin) in these patients, a factor in apparent 'under-use' of OAC [34]. Use of antiplatelet and OAC drugs among those not in the cohort (not hospitalised for any reason during the study period) may well have differed from those studied.

Exposure to warfarin is difficult to quantify with accuracy from pharmacy data alone, as dose may vary with age, sex and comorbidity [35]. Regimens such as different dosing on alternate days and varying strength of tablets make calculation of measures such as a 'defined daily dose' impractical. Without INR data, more reliable measures such as 'time within the therapeutic range' cannot be assessed [36].

Access to other clinical databases, such as laboratory results, will further strengthen large-scale cohort studies using linked data, with the potential to provide detailed information about the changing use of oral anticoagulants and the resulting outcomes in AF and other

thromboembolic conditions.

Conflicts of Interest

None declared.

Acknowledgement

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Conclusion

In this real-world cohort of older patients hospitalised with newly diagnosed or comorbid AF, the use of warfarin in a period predating the widespread availability of NOACs was lower than recommended in treatment guidelines. Initiation and persistent use of warfarin was associated with a lower mortality risk, with an apparent reduction in the risk of stroke/TE which did not reach statistical significance. The probable under-use of warfarin presents the opportunity for further reduction in stroke/TE, facilitated by the uptake of NOACs among those not prescribed, or not persistent with, warfarin.

References

1. Kannel WB, Benjamin EJ. Current perceptions of the epidemiology of atrial fibrillation. Cardiol Clin. 2009;27 (1):13–24, vii.
2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann. Intern. Med. 2007;146 (12):857–67.
3. Pol D, Curtis C, Ramkumar S, Bittinger L. NOACs Now Mainstream for the Use of Anticoagulation in Non-Valvular Atrial Fibrillation in Australia. Heart Lung Circ. 2019;28 (4):e40–e42.
4. Rodriguez-Bernal CL, Peiró S, Hurtado I, García-Sempere A, Sanfélix-Gimeno G. Primary Nonadherence to Oral Anticoagulants in Patients with Atrial Fibrillation: Real-World Data from a Population-Based Cohort. J Manag Care Spec Pharm. 2018;24 (5):440–448.
5. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National Trends in Ambulatory Oral Anticoagulant Use. Am. J. Med. 2015;128 (12):1300–5.e2.
6. Gadsbøll K, Staerk L, Fosbøl EL, Sindet-Pedersen C, Gundlund A, Lip GYH, Gislason GH, Olesen JB. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. Eur. Heart J. 2017;38 (12):899–906.
7. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J. Am. Coll. Cardiol. 2019;74 (1):104–132.
8. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron EG, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, Mc MJ, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016;50 (5):e1–e88.
9. Hellfritzsch M, Grove EL, Husted SE, Rasmussen L, Poulsen BK, Johnsen SP, Hallas J, Pottegård A. Clinical events preceding switching and discontinuation of oral anticoagulant treatment in patients with atrial fibrillation. Europace. 2017;19 (7):1091–1095.
10. Gunnell AS, Knuiman MW, Geelhoed E, Hobbs MST, Katzenellenbogen JM, Hung J, Rankin JM, Nedkoff L, Briffa TG, Ortiz M, Gillies M, Cordingley A, Messer M, Gardner C, Lopez D, Atkins E, Mai Q, Sanfilippo FM. Long-term use and cost-effectiveness of secondary prevention drugs for heart disease in Western Australian seniors (WAMACH): a study protocol. BMJ Open. 2014;4 (9);
11. Australian Bureau of Statistics. Household expenditure on health: a snapshot, 2004–05. Canberra: Australian Bureau of Statistics (ABS). http://www.abs.gov.au/ausstats/abs@.nsf/mf/4836.0.55.001 . 2008;
12. Mi X, Hammill BG, Curtis LH, Lai ECC, Setoguchi S. Use of the landmark method to address immortal person-time bias in comparative effectiveness research: a simulation study. Stat Med. 2016;35 (26):4824–4836.
13. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137 (2):263–72.
14. Lamberts M, Staerk L, Olesen JB, Fosbøl EL, Hansen ML, Harboe L, Lefevre C, Evans D, Gislason GH. Major Bleeding Complications and Persistence With Oral Anticoagulation in Non-Valvular Atrial Fibrillation: Contemporary Findings in Real-Life Danish Patients. J Am Heart Assoc. 2017;6 (2);
15. Larsen TB, Lip GYH, Skjøth F, Due KM, Overvad K, Hvilsted RL. Added predictive ability of the CHA2DS2VASc risk score for stroke and death in patients with atrial fibrillation: the prospective Danish Diet, Cancer, and Health cohort study. Circ Cardiovasc Qual Outcomes. 2012;5 (3):335–42.
16. Woodfield R, Grant I, Sudlow CLM. Accuracy of Electronic Health Record Data for Identifying Stroke Cases in Large-Scale Epidemiological Studies: A Systematic Review from the UK Biobank Stroke Outcomes Group. PLoS ONE. 2015;10 (10);
17. Nielsen PB, Larsen TB, Skjøth F, Gorst-Rasmussen A, Rasmussen LH, LipGregory YH. Restarting Anticoagulant Treatment After Intracranial Hemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality, and Bleeding: A Nationwide Cohort Study. Circulation. 2015;132 (6):517–25.
18. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, Commerford P, Jansky P, Avezum A, Sigamani A, Damasceno A, Reilly P, Grinvalds A, Nakamya J, Aje A, Almahmeed W, Moriarty A, Wallentin L, Yusuf S, Connolly SJ. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. Lancet. 2016;388 (10050):1161–9.
19. Nielsen PB, Larsen TB, Skjøth F, Overvad TF, Lip GYH. Stroke and thromboembolic event rates in atrial fibrillation according to different guideline treatment thresholds: A nationwide cohort study. Sci Rep. 2016;6 ();
20. Albertsen IE, Rasmussen LH, Overvad TF, Graungaard T, Larsen TB, Lip GYH. Risk of stroke or systemic embolism in atrial fibrillation patients treated with warfarin: a systematic review and meta-analysis. Stroke. 2013;44 (5):1329–36.
21. Allan V, Banerjee A, Shah AD, Patel R, Denaxas S, Casas JP, Hemingway H. Net clinical benefit of warfarin in individuals with atrial fibrillation across stroke risk and across primary and secondary care. Heart. 2017;103 (3):210–218.

22. Lopes LC, Spencer FA, Neumann I, Ventresca M, Ebrahim S, Zhou Q, Bhatnaga N, Schulman S, Eikelboom J, Guyatt G. Bleeding risk in atrial fibrillation patients taking vitamin K antagonists: systematic review and meta-analysis. Clin. Pharmacol. Ther. 2013;94 (3):367–75.
23. Madhavan M, Holmes DJN, Piccini JP, Ansell JE, Fonarow GC, Hylek EM, Kowey PR, Mahaffey KW, Thomas L, Peterson ED, Chan P, Allen LA, Gersh BJ. Association of frailty and cognitive impairment with benefits of oral anticoagulation in patients with atrial fibrillation. Am. Heart J. 2019;211 ():77–89.
24. Steinberg BA, Greiner MA, Hammill BG, Curtis LH, Benjamin EJ, Heckbert SR, Piccini JP. Contraindications to anticoagulation therapy and eligibility for novel anticoagulants in older patients with atrial fibrillation. Cardiovasc Ther. 2015;33 (4):177–83.
25. Molteni M, Cimminiello C. Warfarin and atrial fibrillation: from ideal to real the warfarin affaire. Thromb J. 2014;12 (1);
26. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GYH. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am. J. Med. 2010;123 (7):638–645.e4.
27. Simons LA, Ortiz M, Germanos P, Calcino G. Persistence on warfarin in patients with atrial fibrillation: experience in Australia 2006-2009. Aust Fam Physician. 2013;42 (9):659–61.
28. Mazzaglia G, Filippi A, Alacqua M, Cowell W, Shakespeare A, Mantovani LG, Bianchi C, Cricelli C. A national survey of the management of atrial fibrillation with antithrombotic drugs in Italian primary care. Thromb. Haemost. 2010;103 (5):968–75.
29. Kirchhof P. The future of atrial fibrillation management: integrated care and stratified therapy. Lancet. 2017;390 (10105):1873–1887.
30. Navar-Boggan AM, Rymer JA, Piccini JP, Shatila W, Ring L, Stafford JA, Al-Khatib SM, Peterson ED. Accuracy and validation of an automated electronic algorithm to identify patients with atrial fibrillation at risk for stroke. Am. Heart J. 2015;169 (1):39–44.e2.
31. Brown DL, Al-Senani F, Lisabeth LD, Farnie MA, Colletti LA, Langa KM, Fendrick AM, Garcia NM, Smith MA, Morgenstern LB. Defining cause of death in stroke patients: The Brain Attack Surveillance in Corpus Christi Project. Am. J. Epidemiol. 2007;165 (5):591–6.
32. Cheng TJ, Chang CY, Lin CY, Ke DS, Lu TH, Kawachi I. State differences in the reporting of 'unspecified stroke' on death certificates: implications for improvement. Stroke. 2012;43 (12):3336–42.
33. Subic A, Zupanic E, von Euler M, Norrving B, Cermakova P, Religa D, Winblad B, Kramberger MG, Eriksdotter M, Garcia-Ptacek S. Stroke as a Cause of Death in Death Certificates of Patients with Dementia: A Cohort Study from the Swedish Dementia Registry. Curr Alzheimer Res. 2018;15 (14):1322–1330.
34. Averlant L, Ficheur G, Ferret L, Boulé S, Puisieux F, Luyckx M, Soula J, Georges A, Beuscart R, Chazard E, Beuscart JB. Underuse of Oral Anticoagulants and Inappropriate Prescription of Antiplatelet Therapy in Older Inpatients with Atrial Fibrillation. Drugs Aging. 2017;34 (9):701–710.
35. Skeppholm M, Friberg L. Adherence to warfarin treatment among patients with atrial fibrillation. Clin Res Cardiol. 2014;103 (12):998–1005.
36. Abdou JK, Auyeung V, Patel JP, Arya R. Adherence to long-term anticoagulation treatment, what is known and what the future might hold. Br. J. Haematol. 2016;174 (1):30–42.

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Role of Prophylactic Magnesium Supplementation in Prevention of Postoperative Atrial Fibrillation in Patients Undergoing Coronary Artery Bypass Grafting: a Systematic Review and Meta-Analysis of 20 Randomized Controlled Trials.

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Abstract

Background : Several randomized trials have evaluated the efficacy of prophylactic magnesium (Mg) supplementation in prevention of post-operative atrial fibrillation (POAF) in patients undergoing cardiac artery bypass grafting (CABG). We aimed to determine the role of prophylactic Mg in 3 different settings (intraoperative, postoperative, intraoperative plus postoperative) in prevention of POAF.

Methods: A systemic literature search was performed (until January 19, 2019) using PubMed, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials to identify trials evaluating Mg supplementation post CABG. Primary outcome of our study was reduction in POAF post CABG.

Results: We included a total of 2,430 participants (1,196 in the Mg group and 1,234 in the placebo group) enrolled in 20 randomized controlled trials. Pooled analysis demonstrated no reduction in POAF between the two groups (RR 0.90; 95% CI, 0.79-1.03; p=0.13; I^2=42.9%). In subgroup analysis, significant reduction in POAF was observed with postoperative Mg supplementation (RR 0.76; 95% CI, 0.58-0.99; p=0.04; I^2=17.6%) but not with intraoperative or intraoperative plus postoperative Mg supplementation (RR 0.77; 95% CI, 0.49-1.22; p = 0.27; I^2=49% and RR 0.92; 95% CI, 0.68-1.24; p = 0.58; I^2=51.8%, respectively).

Conclusions: Magnesium supplementation, especially in the postoperative period, is an effective strategy in reducing POAF following CABG.

Introduction

Coronary artery bypass grafting (CABG) is the mainstay for the treatment of coronary artery disease in select patient population unless contraindicated [1]. During the cardiopulmonary bypass (CBP), cardioplegic perfusion is intermittently discontinued (15 minutes to up to 30 minutes, depending upon institutional practice) for distal anastomoses construction during which the myocardium is predisposed to ischemic injury [2-5], thereby resulting in ischemic-reperfusion injury [6] and/or reperfusion-induced atrial/ventricular arrhythmias [7,8]. New onset atrial fibrillation is the most common arrhythmia observed postoperatively with incidence ranging from 25% to 40%; typically peaking on post-operative day 2 [9-12]. Development of post-operative atrial fibrillation (POAF) also increases the risk of heart failure, stroke and deterioration in patient's hemodynamic status resulting in increased in-hospital mortality [13,14].

Multiple randomized clinical trials have evaluated the role of prophylactic magnesium (Mg) supplementation for prevention of POAF, with conflicting results [15-34]. With increasing evidence (and addition of new trials) we aimed to assess the role of prophylactic Mg supplementation in reduction of POAF. In addition, we also evaluated the role of prophylactic Mg in three different settings (intraoperative, postoperative, or in combination) in prevention of POAF..

Key Words

Magnesium, Atrial Fibrillation, Coronary artery bypass grafting, CABG.

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Methods

Search Strategy and Study Selection

We searched PubMed, The Cochrane Library, EMBASE, EBSCO, Web of Science and CINAHL databases from inception through January 19, 2019 to identify trials evaluating Mg supplementation in patients undergoing CABG surgery using the key words: magnesium, coronary artery bypass grafting, CABG and atrial fibrillation. The eligibility criteria for our systematic review and meta-analysis included: (1) randomized controlled study design; (2) human subjects undergoing CABG surgery only; (3) received Mg supplementation intraoperatively, postoperatively or in combination; (4) reported periprocedural incidence of atrial fibrillation; and (5) literature published in English. All studies without a comparator arm, undergoing concomitant valve repair, studies that did not report clinical outcomes, off-pump CABG surgery and observational studies/case reports were excluded from the analysis [Figure 1]. We used the longest available follow-up data from the individual studies for our analysis.

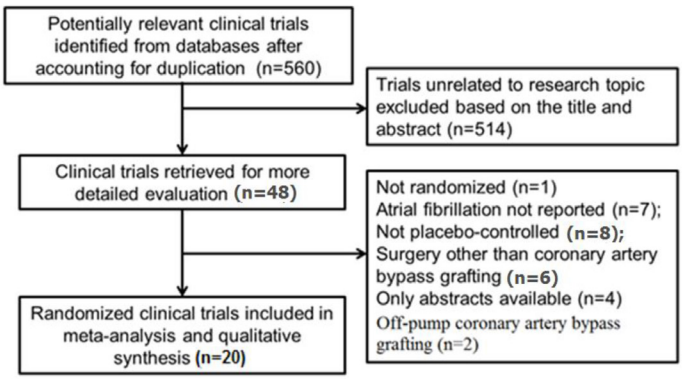


Figure 1: Process of study selection (PRISMA statement)

Data extraction and Quality appraisal

Clinical, interventional, and outcome data were extracted from individual studies by 2 independent abstractors (RC and JG) and entered into a data extraction form. This included information about study design, patient characteristics (age, gender, Mg supplementation, POAF, length of stay, aortic cross clamp time and follow up period). Jadad score was independently calculated by 2 investigators (RC and JG) [Table 1] [34]. Any disparities between the two investigators were discussed with a third investigator (MT) until consensus was reached. Final results were reviewed by senior investigators.

Outcome Variables

The primary outcome of our study was reduction in POAF burden. In order to assess possible differences in the timing of Mg administration, we further divided trials into three subdivisions (secondary outcomes): intraoperative, postoperative and a combination of intra-and postoperative Mg administration.

Statistical analysis

We conducted a meta-analysis of summary statistics from the individual trials because detailed, patient-level data were not available for all trials. Summary estimates and 95% confidence intervals (CI) were reported for continuous variables as difference in means. Mantel-Haenszel risk ratio (RR) fixed effects model was used to summarize data across treatment arms. We evaluated heterogeneity of effects using the Higgins I-squared (I^2) statistic [36]. In cases with heterogeneity (defined as I^2 >25%), random effects models of DerSimonian and Laird [37] were used. Publication bias was estimated visually by funnel plots [38,39]. If any bias was observed, further bias quantification was measured using the Begg-Mazumdar test [40], and Egger test [38]. All analyses were conducted using Comprehensive Meta-Analysis 2.0 software (Biostat, Inc., Englewood, NJ).

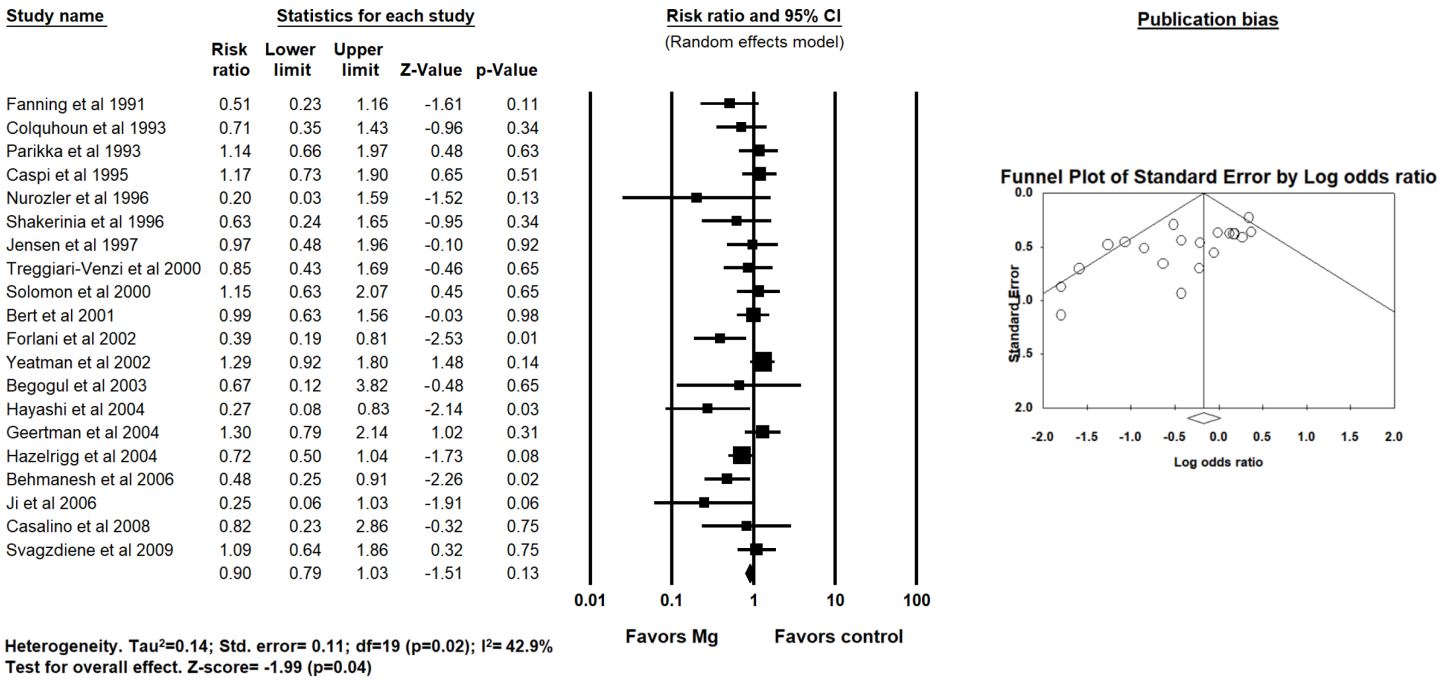


Figure 2: Forest plot demonstrating the effects of magnesium supplementation compared to placebo on post operative atrial fibrillation after CABG surgery (random effects model)

Table 1: Characteristics of participating studies (data presented as control group/study group)

Study name	No. of patients	Mean age (years)	Men (%)	Mean LVEF (%)	Previous MI (%)	Blinding	Infusion	Total amount (mmol)	Duration of aortic clamping (mean)	POAF (n)	Follow-up duration (hrs)	Jadad score
Intraoperative Magnesium supplementation												
Shakerinia et al 1996	25/25	65/67	68/64	65/67	72/80	NS	MgSO4	NA	NA	8/5	24	1
Yeatman et al 2002	200/200	63/64	78/83	NA	NA	DB	MgSO4	20	47/49	45/58	NA	3
Begogul et al 2003	50/50	61/64	88/86	40/40	14/18	DB	MgSO4	16	44/40	3/2	24	2
Hayashi et al 2004	35/35	NA	66/74	52/50	NA	NS	MgSO4	NA	62/47	11/3	NA	1
Ji et al 2006	20/20	56/59	60/70	47/49	12/11	NS	MgSO4	NA	59/61	8/2	NA	3
Casalino et al 2008	49/48	66/68	74/75	54/56	40/43	NS	MgSO4	32	38/37	5/4	120	2
Svagzdiene et al 2009	106/52	65/65	NA	44/46	NA	NS	MgSO4	NA	47/52	28/15	72	1
Postoperative Magnesium supplementation												
Fanning et al 1991	50/49	62/59	78/71	49/50	42/35	DB	MgSO4	84	66/66	14/7	96	4
Colquhoun et al 1993	64/66	59/57	80/83	NA	53/45	DB	MgCl	50	52/51	15/11	96	4
Parikka et al 1993	71/69	54/57	82/84	59/61	NA	NS	MgSO4	70	NA	18/20	48	2
Nurozler et al 1996	25/25	54/56	92/9%	66/67	28/32	DB	MgSO4	100	52/46	5/1	120	2
Jensen et al 1997	28/29	61/61	100/100	NA	NA	DB	MgSO4	110	NA	10/10	72	4
Treggiari-Venzi et al 2000	51/47	65/65	84/89	57/62	45/3%	DB	MgSO4	48	103/91	14/11	72	5
Behmanesh et al 2006	50/50	63/66	93/81	NA	50/36	NS	MgSO4	NA	44/44	21/10	168	3
Intra- + Postoperative magnesium supplementation												
Caspi et al 1995	48/50	62/60	83/89	49/48	NA	NS	MgSO4	48	45/50	18/22	36	4
Solomon et al 2000	82/85	61/62	73/80	54/53	NA	NS	MgSO4	150	63/60	16/19	24	4
Bert et al 2001	60/63	64/63	83/8%	49/48	NA	NS	MgSO4	49	60/55	23/24	96	4
Forlani et al 2002	50/54	64/64	88/85	55/52	66/65	NS	MgSO4	37	47/48	19/8	720	4
Geertman et al 2004	73/74	62/64	79/79	NA	NA	DB	MgSO4	50	48/50	19/25	36	4
Hazelrigg et al 2004	97/105	64/62	68/74	51/53	NA	DB	MgSO4	NA	55/61	41/32	120	4

Table 2: Baseline demographics of study population

Baseline Characteristic	Mg supplementation	Placebo	N	Studies (n)	RR or SMD (95% CI)	Heterogeneity		P for overall effect
						P value	I^2 (%)	
Age, yrs	62.3	61.6	2,008	15	0.21 (0.03 to 0.40)	0.02	75.58	<0.0001
Males, %	79.6	78.4	1,986	16	1.02 (0.98 to 1.06)	0.97	0	0.37
Hypertension, %	49.1	48.0	669	7	0.96 (0.86 to 1.09)	0.73	0	0.55
Diabetes mellitus, %	21.0	18.0	1,169	9	1.11 (0.73 to 1.67)	0.02	53.99	0.63
History of myocardial infarction, %	47.3	48.6	966	11	0.97 (0.86 to 1.10)	0.88	0	0.62
Preoperative use of beta-blockers, %	63.0	67.8	1,723	15	0.95 (0.87 to 1.03)	0.06	39.26	0.21
Need for vasopressors post-surgery, %	29.5	31.9	958	7	0.83 (0.62 to 1.12)	0.11	42.09	0.22

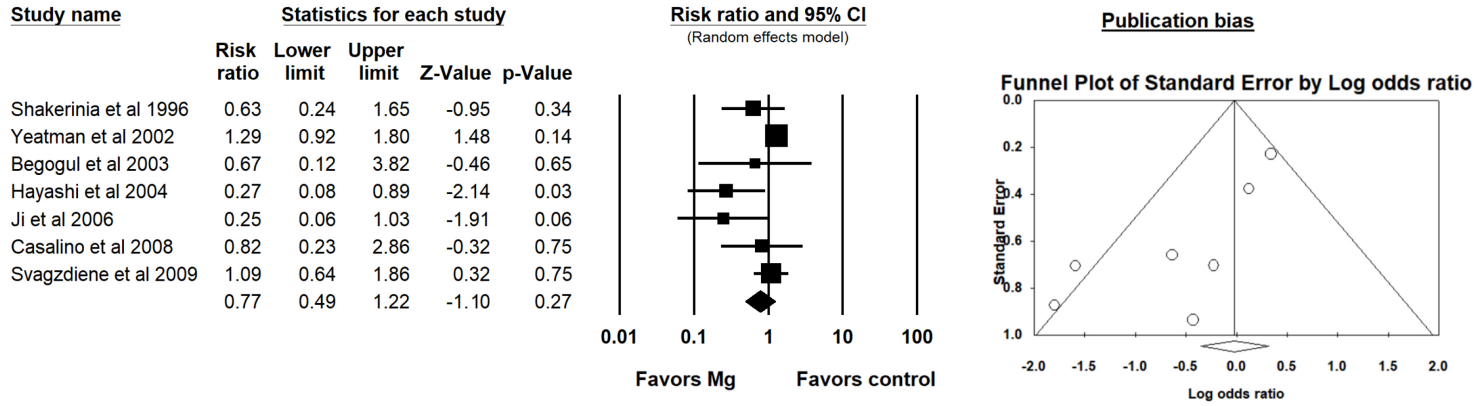
RR=Relative Risk; SMD=Standardized Mean Difference

Results

We included 20 randomized controlled trials [15-34] with a total of 2,430 patients - 1,196 patients in Mg supplementation group, while 1,234 patients in the placebo group. [Table 1] describes the baseline characteristics of included studies including patient demographics, Mg regimens, and incidence of POAF. [Table 2] describes the differences in baseline characteristics between Mg supplementation and placebo groups of included studies.

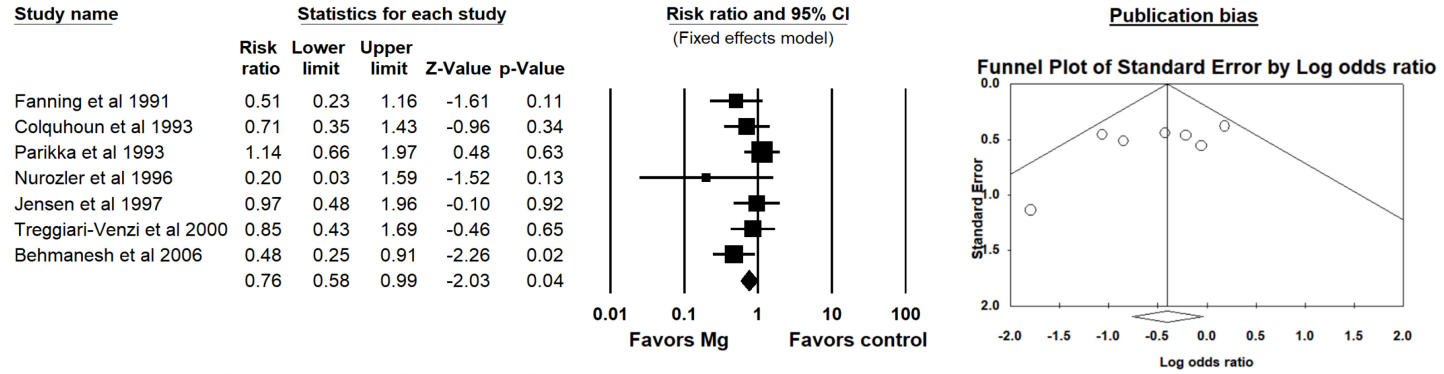
Four hundred and thirty patients received Mg intraoperatively, 335 patients received Mg postoperatively while 431 patients received Mg both intra- and post-operatively. By using random-effects model, pooled analysis for the primary outcome demonstrated no difference in POAF between the two groups (22% versus [vs.] 29% for Mg and placebo groups respectively, RR 0.90; 95% CI, 0.79-1.03; p = 0.13; I^2=42.9%) [Figure 2].

No significant difference was observed between the two groups for length of stay (6.75 days vs 6.77 days for Mg and placebo arm respectively, SMD 0; 95%CI -0.13 - 0.13, p=1.00; I^2=0%), perioperative myocardial infarction (MI) (2.7% vs. 2.2% for Mg and placebo groups respectively, RR 1.26, 95% CI, 0.67 - 2.38, p=0.47; I^2=0%), perioperative mortality (0.6% vs 0.6% for Mg and placebo groups respectively, RR 1.06, 95% CI, 0.43 - 2.62, p=0.90; I^2=0%), aortic cross-clamping time (53 minutes vs. 55 minutes for Mg and placebo groups respectively, SMD -0.12, 95% CI -0.55 - 0.32, p=0.60;I^2=95%) and duration of CPB (89 minutes vs. 88 minutes for Mg and placebo groups respectively, SMD 0.30, 95% CI -0.05 - 0.66, p=0.09; I^2=91%).



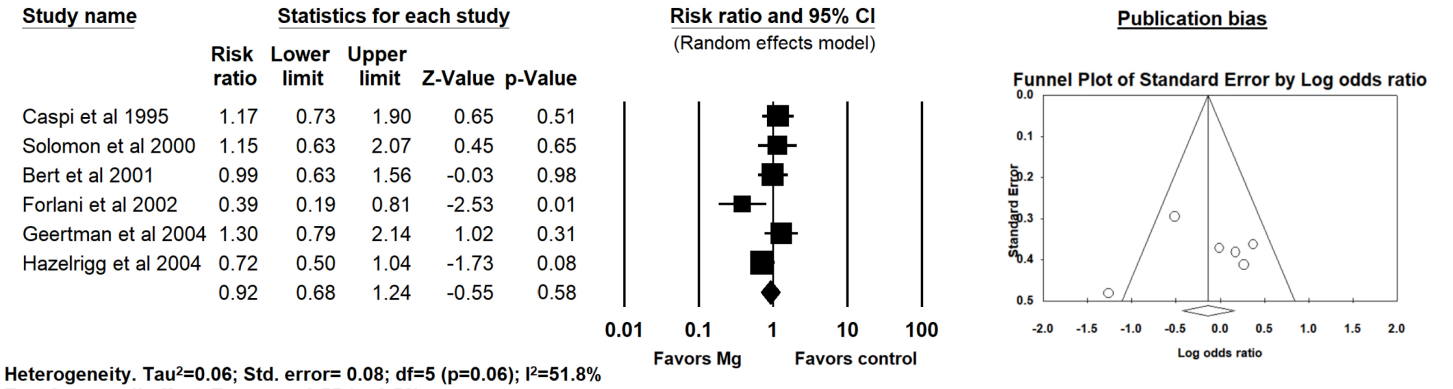
Heterogeneity. Tau²=0.15; Std. error= 0.20; df=6 (p=0.06); I²=48.9%
Test for overall effect. Z-score= -1.09 (p=0.27)

Figure 3: **Forest plot demonstrating the effects of intraoperative magnesium supplementation compared to placebo on post operative atrial fibrillation after CABG surgery (random effects model).**



Heterogeneity. Tau²=0.02; Std. error= 0.09; df=6 (p=0.29); I²=17.6%
Test for overall effect. Z-score= -2.02 (p=0.04)

Figure 4: **Forest plot demonstrating the effects of postoperative magnesium supplementation compared to placebo on post operative atrial fibrillation after CABG surgery (fixed effects model since I²<25%).**



Heterogeneity. Tau²=0.06; Std. error= 0.08; df=5 (p=0.06); I²=51.8%
Test for overall effect. Z-score= -0.55 (p=0.58)

Figure 5: **Forest plot demonstrating the effects of intraoperative+postoperative magnesium supplementation compared to placebo on post operative atrial fibrillation after CABG surgery (random effects model).**

Table 3: Summary of Egger's and Begg's test for publication bias

Outcomes	Egger's test p-value	Begg's test p-value
Overall POAF	0.002	0.008
POAF (Intraoperative Mg)	0.01	0.13
POAF (Postoperative Mg)	0.18	0.54
POAF (Intra- + Postoperative Mg)	0.84	1.00

p-value of <0.05 indicates publication bias

Intraoperative Magnesium supplementation subgroup

In 7 trials that evaluated prophylactic intraoperative Mg supplementation, 16% patients had POAF in the intraoperative Mg arm vs. 24% in the placebo arm with no reduction in POAF (RR 0.77; 95% CI: 0.49 - 1.22; p=0.27; I^2=48.9%) [Figure 3].

There were no significant differences observed between the two groups for perioperative MI (2.1% for Mg and placebo groups respectively, RR 1.00; 95% CI 0.29 - 3.40, p=1.00, I^2=0%), perioperative mortality (0.3% vs. 0.5% for Mg and placebo groups respectively, RR 1.44, 95% CI 0.23 - 9.04, p=0.70; I^2=18.16%), aortic cross-clamping time (SMD -0.10, 95% CI -1.46 - 1.28, p=0.89; I^2=98.33%) and duration of CPB (SMD 0.77, 95% CI -0.14 - 1.67, p=0.09; I^2=96.15%).

Postoperative Magnesium supplementation subgroup

Seven trials that evaluated postoperative Mg supplementation, there was a significant reduction in the incidence of POAF (20% vs 29% for Mg and placebo groups respectively, RR 0.76; 95% CI 0.58 - 0.99; p=0.04; I^2=17.6%) [Figure 4].

There were no significant differences observed between the two groups for perioperative MI (1.9% vs. 2.0% for Mg and placebo groups respectively, RR 0.98; 95% CI 0.25 - 3.77, p=0.97; I^2=0%), perioperative mortality (0.5% vs. 0.9% for Mg and placebo groups respectively, RR 0.79, 95% CI 0.17 - 3.66, p=0.77; I^2=0%), aortic cross-clamping time (SMD -0.32, 95% CI -0.74 - 0.10, p=0.14; I^2=75.28%) and duration of CPB (SMD -0.08, 95% CI -0.38 - 0.21, p=0.57; I^2=51%).

Intraoperative plus Postoperative Magnesium supplementation subgroup

In six trials evaluating a combined intra and postoperative magnesium supplementation strategy, no reduction in POAF (31% vs 34% for Mg and placebo groups respectively, RR 0.92; 95% CI 0.68 - 1.24; p=0.58; I^2=51.8%) [Figure 5], perioperative MI (RR 1.60; 95% CI 0.66 - 3.90, p=0.30; I^2=0%), perioperative death (RR 1.14; 95% CI 0.28 - 4.65, p=0.86; I^2=0%) and aortic cross-clamp time (SMD 0.03, 95% CI -0.15 - 0.22, p=0.73; I^2=40%) was observed. However, CPB time was significantly more in Mg group compared to placebo (90 minutes vs. 85 minutes, respectively, SMD 0.19, 95% CI 0.003 - 0.37, p=0.04; I^2=0%).

Publication bias and Quality appraisal

A significant publication bias was identified overall for POAF [Table 3]. Upon further stratification based on timing of Mg administration, publication bias was significant for intra-operative strategy only. No publication bias was observed for perioperative MI, mortality, aortic cross-clamping time and duration of CPB. The publication bias observed did not change even after adjustments using Duval and Tweedie's trim and fill and addition of imputed studies.

Discussion

The current meta-analysis analyzed 2,430 patients and demonstrated a significant reduction in POAF among patients undergoing on-pump CABG surgery who received prophylactic Mg supplementation in the postoperative period only. No significant differences were observed in perioperative MI, mortality, aortic cross-clamp time or duration of CPB between the two groups. To the best of our knowledge, this is the first meta-analysis demonstrating the role of prophylactic Mg supplementation (and different administration strategies) in patients undergoing on-pump CABG surgery in preventing POAF [41-46].

The precise mechanism by which prophylactic Mg supplementation reduces POAF remains unclear. Hypomagnesaemia has been shown to be proarrhythmic with studies demonstrating an increased risk of atrial and ventricular arrhythmias [47,48]. In addition, studies have shown that serum Mg levels do not correlate with myocardial tissue magnesium levels [49], with low extracellular Mg associated with abnormalities of depolarization, repolarization and automaticity [50]. Mg supplementation therefore significantly increases atrial refractoriness by prolonging the action potential duration and atrial effective refractory period [51-53]. A possible explanation to the efficacy of postoperative Mg supplementation in reducing POAF, as observed in our study, likely stems from the myocardial Mg depletion in immediate postoperative period (circulating volume dilution from extracorporeal support, use of diuretics which promotes Mg excretion and/or norepinephrine induced redistribution of Mg from intracellular to extracellular compartment). Myocardial Mg depletion would not be reflected on serum Mg levels; and therefore could be responsible for provoking atrial arrhythmias despite normal serum Mg levels. Magnesium supplementation in the postoperative period possibly offsets this process. In addition, POAF predominantly occurs between postoperative day 1 and day 4 with the peak incidence at day 2, which is often associated with hypomagnesemia. This time course also correlates with increased sympathetic activation (from surgical stress and exaggerated by ß-blockers withdrawal) and has been associated with POAF. Therefore, prophylactic Mg supplementation postoperatively may attenuate adrenergic medicated automaticity and reduce the incidence of POAF as observed in this study. Interestingly, there was no reduction in POAF in patients with intraoperative or intraoperative plus post-operative magnesium supplementation. The exact explanation remains uncertain. Theoretically, the duration of aortic cross-clamp time and CPB might be responsible for POAF reduction, nonetheless no significant differences were observed between the two groups.

Development of POAF after CABG adds a potentially preventable significant burden to healthcare and is associated with increased length of hospital stay. In a study by Aranki et al, length of stay increased from 9.3 ± 19.6 days to 15.3 ± 28.6 days (p=0.001), which was estimated to an additional charge of $10,055 for in-patient hospital charges per patient [54]. Multiple agents have been explored

to reduce the incidence of POAF after CABG including beta-blockers, anti-arrhythmic agents (sotalol and amiodarone) and Mg supplementation. Amongst these agents, Mg is the least likelihood of drug interactions and side effects, is readily available, well tolerated by patients and inexpensive [55].

Due to multiple randomized clinical trials exploring the role and utility of Mg prophylaxis, several meta-analyses have been conducted in the past. The results of our study contrasts from the previously reported meta-analyses by Gu et al and De Oliveira et al, both of which demonstrated an overall reduction in POAF with magnesium supplementation (RR=0.64; 0.50-0.83 and OR=0.69; CI 0.53-0.90, respectively) [43,44]. In a sub-analysis by De Oliveira et al comparing POAF between high-quality and low-quality studies, no reduction of POAF was found with magnesium supplementation in higher quality studies but a significant reduction was seen with low-quality studies. However, no such differences were found in our sub-analysis without any significant reduction in POAF when stratified by high or low-quality studies (data not shown).

There are several limitations in this study. First, the studies included in this study span a time of 25 years during which there has been tremendous evolution in the surgical techniques. Second, majority of trials included in our analysis did not specify concomitant use of beta-blockers, which might have overestimated the effectiveness of Mg in the postoperative sub-group. Finally, a publication bias was observed in the overall results of the study and the included trials had diverse dosing regimens, mode of supplementation and follow-up time period. However, no significant heterogeneity was observed for POAF reduction in the postoperative Mg supplementation group.

Acknowledgement

None.

Conclusions

Magnesium supplementation, especially in the postoperative period, is an effective strategy in reducing POAF following on-pump CABG surgery. Further large randomized controlled trials are needed to validate our results and whether this reduced incidence of POAF would translate into reducing length of stay and healthcare cost.

References

1. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Di SVJ, Hiratzka LF, Hutter AM, Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD, Jacobs AK, Anderson JL, Albert N, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Ohman EM, Stevenson W, Yancy CW. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J. Thorac. Cardiovasc. Surg. 2012;143 (1):4–34.
2. Calafiore AM, Teodori G, Mezzetti A, Bosco G, Verna AM, Di Giammarco G, Lapenna D. Intermittent antegrade warm blood cardioplegia. Ann. Thorac. Surg. 1995;59 (2):398–402.
3. Ali IM. Interrupted warm blood cardioplegia. Eur J Cardiothorac Surg. 1996;10 (6).
4. Minatoya K, Okabayashi H, Shimada I, Tanabe A, Nishina T, Nandate K, Kunihiro M. Intermittent antegrade warm blood cardioplegia for CABG: extended interval of cardioplegia. Ann. Thorac. Surg. 2000;69 (1):74–6.
5. Randomised trial of normothermic versus hypothermic coronary bypass surgery. The Warm Heart Investigators. Lancet. 1994;343 (8897):559–63.
6. Tünerir B, Colak O, Alataş O, Beşoğul Y, Kural T, Aslan R. Measurement of troponin T to detect cardioprotective effect of trimetazidine during coronary artery bypass grafting. Ann. Thorac. Surg. 1999;68 (6):2173–6.
7. Komori S, LiB, Matsumura K, Takusagawa M, Sano S, Kohno I, Osada M, Sawanobori T, Ishihara T, Umetani K, Ijiri H, Tamura K. Antiarrhythmic effect of magnesium sulfate against occlusion-induced arrhythmias and reperfusion-induced arrhythmias in anesthetized rats. Mol. Cell. Biochem. 1999;199 (1-2):201–8.
8. Caputo M, Bryan AJ, Calafiore AM, Suleiman MS, Angelini GD. Intermittent antegrade hyperkalaemic warm blood cardioplegia supplemented with magnesium prevents myocardial substrate derangement in patients undergoing coronary artery bypass surgery. Eur J Cardiothorac Surg. 1998;14 (6):596–601. [PubMed]
9. Lauer M S, EagleK A, BuckleyM J, DeSanctisR W. Atrial fibrillation following coronary artery bypass surgery. Prog Cardiovasc Dis. 1989;31 (5):367–78.
10. Cox JL. A perspective of postoperative atrial fibrillation in cardiac operations. Ann. Thorac. Surg. 1993;56 (3):405–9.
11. Vecht RJ, Nicolaides EP, Ikweuke JK, Liassides C, Cleary J, Cooper WB. Incidence and prevention of supraventricular tachyarrhythmias after coronary bypass surgery. Int. J. Cardiol. 1986;13 (2):125–34.
12. Gerges C, Gerges M, Skoro-Sajer N, Zhou Y, Zhang L, Sadushi-Kolici R, Jakowitsch J, Lang MB, Lang IM. Hemodynamic Thresholds for Precapillary Pulmonary Hypertension. Chest. 2016;149 (4):1061–73.
13. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van PB, Vardas P. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur. Heart J. 2016;37 (38):2893–2962.
14. Mostafa A, El-Haddad MA, Shenoy M, Tuliani T. Atrial fibrillation post cardiac bypass surgery. Avicenna J Med. 2012;2 (3):65–70.
15. Fanning WJ, Thomas CS, Roach A, Tomichek R, Alford WC, Stoney WS. Prophylaxis of atrial fibrillation with magnesium sulfate after coronary artery bypass grafting. Ann. Thorac. Surg. 1991;52 (3):529–33.
16. Colquhoun IW, Berg GA, el-Fiky M, Hurle A, Fell GS, Wheatley DJ. Arrhythmia prophylaxis after coronary artery surgery. A randomised controlled trial of intravenous magnesium chloride. Eur J Cardiothorac Surg. 1993;7 (10):520–3.
17. Parikka H, Toivonen L, Pellinen T, Verkkala K, Järvinen A, Nieminen MS. The influence of intravenous magnesium sulphate on the occurrence of atrial fibrillation after coronary artery by-pass operation. Eur. Heart J. 1993;14 (2):251–8.
18. Caspi J, Rudis E, Bar I, Safadi T, Saute M. Effects of magnesium on myocardial function after coronary artery bypass grafting. Ann. Thorac. Surg. 1995;59 (4):942–7.
19. Nurözler F, Tokgözoglu L, Pasaoglu I, Böke E, Ersoy U, Bozer AY. Atrial fibrillation after coronary artery bypass surgery: predictors and the role of MgSO4 replacement. J Card Surg. 1996;11 (6):421–7.
20. Shakerinia T, Ali IM, Sullivan JA. Magnesium in cardioplegia: is it necessary?. Can J Surg. 1996;39 (5):397–400.
21. Jensen BM, Alstrup P, Klitgård NA. Magnesium substitution and postoperative arrhythmias in patients undergoing coronary artery bypass grafting. Scand. Cardiovasc. J. 1997;31 (5):265–9.
22. Treggiari-Venzi MM, Waeber JL, Perneger TV, Suter PM, Adamec R, Romand JA. Intravenous amiodarone or magnesium sulphate is not cost-beneficial prophylaxis for atrial fibrillation after coronary artery bypass surgery. Br J Anaesth. 2000;85 (5):690–5.

23. Solomon AJ, Berger AK, Trivedi KK, Hannan RL, Katz NM. The combination of propranolol and magnesium does not prevent postoperative atrial fibrillation. Ann. Thorac. Surg. 2000;69 (1):126–9.
24. Bert AA, Reinert SE, Singh AK. A beta-blocker, not magnesium, is effective prophylaxis for atrial tachyarrhythmias after coronary artery bypass graft surgery. J. Cardiothorac. Vasc. Anesth. 2001;15 (2):204–9.
25. Forlani S, De Paulis R, de Notaris S, Nardi P, Tomai F, Proietti I, Ghini AS, Chiariello L. Combination of sotalol and magnesium prevents atrial fibrillation after coronary artery bypass grafting. Ann. Thorac. Surg. 2002;74 (3):720–5.
26. Yeatman M, Caputo M, Narayan P, Lotto AA, Ascione R, Bryan AJ, Angelini GD. Magnesium-supplemented warm blood cardioplegia in patients undergoing coronary artery revascularization. Ann. Thorac. Surg. 2002;73 (1):112–8.
27. Beşoğul Y, Tünerir B, Ozdemir C, Aslan R. Magnesium-flush infusion into the aortic root just before reperfusion reduces the requirement for internal defibrillation and early post-perfusion arrhythmias. J. Int. Med. Res. 2003;31 (3):202–9.
28. Hayashi Y, Ohtani M, Sawa Y, Hiraishi T, Akedo H, Kobayashi Y, Matsuda H. Minimally-diluted blood cardioplegia supplemented with potassium and magnesium for combination of 'initial, continuous and intermittent bolus' administration. Circ. J. 2004;68 (5):467–72.
29. Geertman H, van der SJA, Sie HT, Beukema WP, van Rooyen-Butijn M. Magnesium in addition to sotalol does not influence the incidence of postoperative atrial tachyarrhythmias after coronary artery bypass surgery. J. Cardiothorac. Vasc. Anesth. 2004;18 (3):309–12.
30. Hazelrigg SR, Boley TM, Cetindag IB, Moulton KP, Trammell GL, Polancic JE, Shawgo TS, Quin JA, VerhulstStephen. The efficacy of supplemental magnesium in reducing atrial fibrillation after coronary artery bypass grafting. Ann. Thorac. Surg. 2004;77 (3):824–30.
31. Behmanesh S, Tossios P, Homedan H, Hekmat K, Hellmich M, Müller-Ehmsen J, Schwinger RHG, Mehlhorn U. Effect of prophylactic bisoprolol plus magnesium on the incidence of atrial fibrillation after coronary bypass surgery: results of a randomized controlled trial. Curr Med Res Opin. 2006;22 (8):1443–50.
32. Ji B, Liu J, Liu M, Feng Z, Wang G, Lu F, Long C. Effect of cold blood cardioplegia enriched with potassium-magnesium aspartate during coronary artery bypass grafting. J Cardiovasc Surg (Torino). 2006;47 (6):671–5.
33. Casalino S, Tesler UF, Novelli E, Stelian E, Renzi L, Alessi C, Lanzillo G, Cerin G, Diena M. The efficacy and safety of extending the ischemic time with a modified cardioplegic technique for coronary artery surgery. J Card Surg. 2008;23 (5):444–9.
34. Svagzdiene M, Sirvinskas E, Benetis R, Raliene L, Simatoniene V. Atrial fibrillation and changes in serum and urinary electrolyte levels after coronary artery bypass grafting surgery. Medicina (Kaunas). 2009;45 (12):960–70.
35. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. Control Clin Trials. 1996;17 (1):1–12.
36. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018;391 (10128):1357–1366.
37. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7 (3):177–88.
38. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315 (7109):629–34.
39. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, Carpenter J, Rücker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JPT. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343 ().
40. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50 (4):1088–101.
41. Shiga T, Wajima Z, Inoue T, Ogawa R. Magnesium prophylaxis for arrhythmias after cardiac surgery: a meta-analysis of randomized controlled trials. Am. J. Med. 2004;117 (5):325–33.
42. Miller S, Crystal E, Garfinkle M, Lau C, Lashevsky I, Connolly SJ. Effects of magnesium on atrial fibrillation after cardiac surgery: a meta-analysis. Heart. 2005;91 (5):618–23.
43. Gu WJ, Wu ZJ, Wang PF, Aung LHH, Yin RX. Intravenous magnesium prevents atrial fibrillation after coronary artery bypass grafting: a meta-analysis of 7 double-blind, placebo-controlled, randomized clinical trials. Trials. 2012;13 ().
44. De OGS, Knautz JS, Sherwani S, Mc CRJ. Systemic magnesium to reduce postoperative arrhythmias after coronary artery bypass graft surgery: a meta-analysis of randomized controlled trials. J. Cardiothorac. Vasc. Anesth. 2012;26 (4):643–50.
45. Burgess DC, Kilborn MJ, Keech AC. Interventions for prevention of post-operative atrial fibrillation and its complications after cardiac surgery: a meta-analysis. Eur. Heart J. 2006;27 (23):2846–57.
46. Alghamdi AA, Al-Radi OO, Latter DA. Intravenous magnesium for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and meta-analysis. J Card Surg. 2005;20 (3):293–9.
47. Klevay LM, Milne DB. Low dietary magnesium increases supraventricular ectopy. Am. J. Clin. Nutr. 2002;75 (3):550–4.
48. Guideri G, Lehr D, Horowitz S. Enhanced incidence of isoproterenol-induced ventricular fibrillation in the magnesium-deficient rat. J Am Coll Nutr. 1985;4 (2):139–55.
49. Millane TA, Jennison SH, Mann JM, Holt DW, McKenna WJ, Camm AJ. Myocardial magnesium depletion associated with prolonged hypomagnesemia: a longitudinal study in heart transplant recipients. J. Am. Coll. Cardiol. 1992;20 (4):806–12.
50. Roden DM, Iansmith DH. Effects of low potassium or magnesium concentrations on isolated cardiac tissue. Am. J. Med. 1987;82 (3A):18–23.
51. Rasmussen HS, Thomsen PE. The electrophysiological effects of intravenous magnesium on human sinus node, atrioventricular node, atrium, and ventricle. Clin Cardiol. 1989;12 (2):85–90.
52. Christiansen EH, Frost L, Andreasen F, Mortensen P, Thomsen PE, Pedersen AK. Dose-related cardiac electrophysiological effects of intravenous magnesium. A double-blind placebo-controlled dose-response study in patients with paroxysmal supraventricular tachycardia. Europace. 2000;2 (4):320–6.
53. Redwood SR, Taggart PI, Sutton PM, Bygrave A, Bashir Y, Purkayastha DD, Camm AJ, Treasure T. Effect of magnesium on the monophasic action potential during early ischemia in the in vivo human heart. J. Am. Coll. Cardiol. 1996;28 (7):1765–9.
54. Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, Vander VM, Collins JJ, Cohn LH, Burstin HR. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation. 1996;94 (3):390–7.
55. Trappe HJ, Brandts B, Weismueller P. Arrhythmias in the intensive care patient. Curr Opin Crit Care. 2003;9 (5):345–55.

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The Safety and Feasibility of Same-Day Discharge After Implantation of MICRA Transcatheter Leadless Pacemaker System

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Abstract

Background : Data suggests that same day discharge after implantation of trans-venous pacemakers is safe and feasible. We sought to determine whether same day discharge was feasible and safe following implantation of Medtronic MICRA leadless pacemakers.

Methods : We retrospectively identified all patients undergoing MICRA placement at our institution between April 2014 to August 2018 (n=167). Patients were stratified into two groups: those discharged on the same day as their procedure (SD, n=25), and those observed for at least one night in the hospital (HD, n=142). The primary endpoint included a composite of major complications including: access site complications, new pericardial effusion, device dislodgement, and need for device revision up to approximately 45 days of follow up.

Results : SD and HD had similar age (75±13 vs. 75±13 years, p=0.923), prevalence of male sex (49 vs. 44%, p=0.669), and frequency of high-grade heart block as an indication for pacing (38 vs. 32%, p=0.596). There were more Caucasians in the SD group (72 vs. 66%, p=0.038). The rate of the composite endpoint was statistically non-significantly higher in the HD group (3.5% vs. 0.0%, p=1.00). The rates of each individual components comprising the composite endpoint were similar between groups.

Conclusions : Our data suggest that in appropriately selected patients, same day discharge can occur safely following Micra leadless pacemaker implantation.

Introduction

Currently over one million cardiac pacemakers are implanted each year, with 200,000 of those placed in the United States[1,2]. A relatively novel development in pacemaker technology is the advent of leadless pacemakers, designed to avoid long-term complications associated with traditional transvenous systems[3,4]. The Medtronic MIRCA transcatheter pacing system (TPS) is a single chamber ventricular pacemaker with functionality similar to traditional transvenous pacing systems[5-7]. It is, however, 93% smaller than traditional transvenous systems[7]. The device is implanted directly into the right ventricle via percutaneous femoral venous access and is affixed to the myocardium with 4 nitinol tines[5]. The MICRA TPS[6] has enjoyed a high rate of procedural success[5,7]. However, consensus on optimal strategies for post-implantation management for the MICRA system are yet to be established.

Same-day discharge after cardiac implantable electronic device procedures is often considered routine[8,9]. While the transvenous access required for placement of the MICRA system is large (27 French outer diameter sheath)[6], the procedural stress of implantation of leadless pacemaker devices is, in principle, similar to other transcatheter cardiovascular procedures. Longer hospital stay is typically associated with higher cost to the patient and health care system[8] and can expose patients to hospital acquired complications. Thus, elucidating the shortest time required to safely monitor patients after MICRA TPS is desirable. We sought to investigate the safety and feasibility of same-day discharge after MICRA TPS implantation.

Key Words

MICRA, Pacemaker, Discharge.

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Methods

Patient Selection

We retrospectively evaluated all patients who underwent placement of the Medtronic MICRA leadless pacemaker system from April of 2014 to May of 2018 at three hospitals within our institution (Emory University Hospital, Emory University Hospital Midtown and Emory Saint Joseph's Hospital). This study was approved by our institutional review board.

Data collection and Endpoints

We evaluated all routine medical history and pre-procedure medication information and procedural characteristics including time to discharge. We also evaluated metrics relevant to the procedure including indications for pacing, continuation of active anticoagulation during the periprocedural period, mode of sedation, fluoroscopy time (as a surrogate for difficulty of device placement), whether hemostasis was achieved in the lab or in the recovery area, as well as use of a superficial soft tissue "figure of eight" hemostatic suture[11], as each of these could potentially influence the need for further inpatient observation. We also included information regarding the status and performance of the leadless pacemaker and procedure-related complications following the procedure and during routine post-procedural follow up (typically 4-6 weeks after implantation).

Device performance at implant/discharge and up to routine first post-implant follow up were characterized. Device malfunction was defined according to the criteria used in the MICRA investigational device exemption (IDE) study[6]. Complications were grouped into 1) procedure-related major complications (death, permanent loss of device function, need for system revision or replacement with a transvenous pacing system), and 2) groin access site related complications (hematoma, retroperitoneal bleeding, pseudoaneurysm, arteriovenous fistula, infection) which were characterized as "major" for any complication that required direct intervention including medical therapy or percutaneous or operative intervention) and "minor" if they were only observed and did not require direct clinical intervention. The primary endpoint of the study was a composite of all major groin access and procedure related complications. Each individual endpoint was secondarily evaluated individually.

Statistical Analysis

Patients were categorized into two groups for analysis: those discharged on the same day as their procedure (same day discharge) and those observed at least overnight (or longer) in the hospital (hospital admission group). Among the hospital admission (HD) group, a subgroup analysis was done by stratifying the group between those admitted after placement of the MICRA TPS (n=73) and those that were admitted for other primary indications and underwent MICRA TPS during the course of their hospital stay (n=69). Among those for whom quantitative metrics from follow up device interrogations were not available, there was a subset (n=24) for whom qualitative results (i.e. "normal function" vs. "device malfunction") were available and were included in the final analysis for device malfunction. Normality of distribution of continuous variables was tested using the Kolmogorov–Smirnov test. Comparisons of continuous baseline variables across groups were performed using the Student's t-, and Mann-Whitney U tests, for normally and non-normally distributed data, respectively. The mean differences between initial and final values included those pertaining to the function of the pacemaker device: impedance (in Ohms), pacing capture threshold (in Volts), and sensing amplitude (in millivolts) were evaluated using the paired-t test for normally distributed variables, or Wilcoxon signed rank test for variables found to have non-normal distributions. Comparison of categorical variables was performed using Chi-squared and Fisher's Exact tests for binary categorical variables where appropriate, and Mann-Whitney U test for ranked ordinal level variables. All analyses was performed using IBM SPSS ver. 25 (2017; IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp).

Results

Baseline and Procedure Related Characteristics

We identified 167 patients that underwent MICRA TPS implantation during the study period. Patients in the same-day discharge (SD) group (n=25) were more often white and Hispanic compared to the HD group. The HD group had a statistically non-significant higher burden of comorbidities [Table 1] including coronary artery disease (42.2% vs. 28%), congestive heart failure (44.4% vs. 24.0%), peripheral vascular disease (20.4% vs. 8.0%), end stage renal disease (17/6% vs. 4.0%), bacteremia (8.5% vs. 0.0%), and endocarditis (5.6% vs. 0.0%).

Table 1: Baseline Clinical Characteristics

	HD (n=142)	SD (n=25)	P-level
Age (years)	75 (±13)	75 (±13)	0.923
Sex (Male)	49.3%	44.0%	0.669
Race			0.038
White	66.2%	72.0%	
African American	33.1%	20.0%	
Hispanic	0.7%	8.0%	
Other	0.0%	0.0%	
Hypertension	81.7%	80.0%	1.000
Diabetes	33.8%	36.0%	1.000
Hyperlipidemia	62.0%	64.0%	1.000
Coronary Artery Disease	42.3%	28.0%	0.194
Congestive Heart Failure			0.204
Systolic	9.9%	4.0%	
Diastolic	34.5%	20.0%	
Stroke	12.0%	12.0%	1.000
Peripheral Vascular Disease	20.4%	8.0%	0.172
Tobacco Abuse	20.4%	20.0%	1.000
COPD	16.9%	16.0%	1.000
CKD			0.238
Stage I	4.4%	16.0%	
Stage II	3.7%	0.0%	
Stage III	11.8%	8.0%	
Stage IV	5.9%	0.0%	
Stage V	4.4%	0.0%	
End Stage Renal Disease	17.6%	4.0%	0.131
Type of Renal Replacement			0.365
Hemodialysis	16.2%	4.0%	
Peritoneal Dialysis	1.4%	0.0%	
Other	0.7%	0.0%	
History of Bacteremia	8.5%	0.0%	0.217
History of Endocarditis	5.6%	0.0%	0.283
History of Syncope	26.1%	24.0%	1.000
EKG Metrics			
PR interval (ms)	199 (±82)	200 (±200)	0.620

QRSd (ms)	115 (±42)	111 (±111)	0.846
Bundle Branch Block Type			0.472
Right Bundle	19.3%	20.8%	
Left Bundle	9.3%	12.5%	
IVCD	7.1%	4.2%	
QTc (ms)	458 (±50)	456 (±41)	0.242
INR	1.61 (±0.65)	1.85 (±0.57)	0.674
Aspirin Therapy	43.3%	32.0%	0.380
Other Antiplatelet Agents	12.1%	0.0%	0.059
Statin Therapy	49.3%	56.0%	0.665
Beta Blocker	44.0%	44.0%	1.000
Calcium Channel Blocker	33.3%	36.0%	0.821
ACE/ARB Therapy	35.5%	36.0%	1.000
Aldactone	2.8%	12.0%	0.070
Antiarrhythmic Therapy	9.4%	8.0%	1.000
Warfarin	35.2%	48.0%	0.264
DOAC	26.1%	24.0%	1.000

Baseline Characteristics at the time of MICRA TPS implantation. ACE =Angiotensinogen Converting Enzyme Inhibitor; ARB=Angiotensin Receptor Blocker; CKD=Chronic Kidney Disease; COPD=Chronic Obstructive Pulmonary Disease; ; DOAC=Direct Oral Anticoagulant; EKG=Electrocardiogram; ms=milliseconds; INR=International Normalize Ratio; IVCD=(nonspecific) Interventricular Conduction Delay; QTc=Corrected QT interval.

Both groups otherwise had similar baseline characteristics including ECG characteristics and active medications [Table 1]. There was a similar distribution of indications for pacing between groups [Table 2].

There were no significant differences in procedural characteristics between groups [Table 2]. The procedure was primarily performed under moderate sedation in both groups (96.0% vs. 97.7%, p=1.00). The length of fluoroscopy time was similar between the SD and HD groups (4.1 vs. 5.3 minutes, p=0.206), as was utilization of a "figure of eight" hemostatic suture (80.0% vs. 70.4%, p=0.47). Similarly, there was no significant difference in the proportion of patients in SD and HD that underwent the procedure while on therapeutic anticoagulation (18.0% vs. 12.1%, p=1.00).

All patients had follow-up sufficient to assess groin and procedure related complications. Follow up device interrogations were available in 74% (125/167) of patients. In total, 33 patients did not have quantitative follow up interrogation data (two in the SD group and thirty-one in the HD group). These patients were either lost to follow up to the device clinic (n=26), had their device revised (n=1), or died (n=6) prior to their follow up interrogations. Interrogation data from both the time of implantation and at follow up was available in 76% (19/25) of patients in the same day discharge group and 69% (97/142) of patients in the HD group. However, after including patients for whom qualitative results were available (see Methods), follow up device function was available in 89% (149/167) of patients.

Procedural Outcomes

Baseline and follow up metrics of device function were similar between groups [Table 3].

Table 2: Procedure Related Characteristics

	HD (n=142)	SD (n=25)	P-level
Anticoagulation Interrupted	78.9%	72.0%	1.000
Indication for Pacing			0.792
Sinus Node Dysfunction	32.4%	32.0%	
AV Block	40.1%	40.0%	
His Ablation	22.5%	20.0%	
Symptomatic Bradycardia	1.4%	1.4%	
Other Indication NOS	3.5%	4.0%	
Fluoroscopy Time (minutes)	5.34 (±4.69)	4.09 (±2.89)	0.206
Anesthesia type			1.000
Moderate Sedation	97.7%	96.0%	
General Anesthesia	1.5%	4.0%	
Figure of Eight Suture Used	70.4%	80.0%	0.470
Length of Stay, Median (IQR)	0 (0)	1 (1)	N/A

Procedure related characteristics among SD and HD groups. AV=Atrioventricular; IQR=Interquartile Range; NOS=Not Otherwise Specified.

Table 3: Device Performance Metrics at Implantation and Follow up

	HD	SD	P-level
At Implantation	(N=132)	(N=22)	
Final Pacing Impedance (Ohms)	699 (±196)	768 (±177)	0.127
Final Pacing Capture Threshold (Volts)	0.631 (±0.469)	0.685 (±0.434)	0.620
Pulse Width (milliseconds)	0.329 (±0.216)	0.317 (±0.109)	0.816
Final Sensing Amplitude (in mV)	10.753 (±5.408)	10.996 (±5.554)	0.846
Lower Rate (BPM)	62 (±12)	60 (±12)	0.515
At Follow Up	(N=103)	(N=22)	
Follow up Pacing Impedance (Ohms)	614 (±123)	624 (±107)	0.729
Follow up Pacing Capture Threshold (Volts)	0.633 (±0.601)	0.768 (±0.495)	0.328
Pulse Width (milliseconds)	0.31 (±0.09)	0.3 (±0.08)	0.699
Follow up sensing amplitude (mV)	12.625 (±5.778)	13.532 (±7.12)	0.598
Follow Up Lower Rate	62 (±11)	60 (±10)	0.462
Changes from Implantation to Follow Up	(N=98)	(N=19)	
Change in Impedance (Ohms)	-98 (±171)	-155 (±100)	0.166
Change in Capture Threshold (Volts)	0.014 (±0.570)	0.016 (±0.227)	0.992
Change in Pulse Width (milliseconds)	-0.018 (±0.263)	-0.015 (±0.127)	0.965
Change in Sensing Amplitude (mV)	2.28 (±4.88)	2.59 (±4.68)	0.802
Change in Impedance (%)	-16.88 (±29.25)	-23.63(±15.06)	0.331
Change in Capture Threshold (%)	-17.78 (±73.69)	-4.98 (±35.93)	0.255
Change in Pulse Width (%)	-15.65 (±105.48)	-10.49 (±44.98)	0.844
Change in Sensing Amplitude (%)	4.59 (±89.11)	2.56 (±69.07)	0.928

Device Performance metrics from interrogations from those in whom quantitative interrogations were available. BPM=beats per minute; mV=millivolts.

Table 4: Procedure Related Complications

	HD (n=142)	SD (n=25)	P-level
Major Groin Complication	1.4% (2/142)	0% (0/25)	1.000
Hematoma	0% (0/2)	0%	
Pseudoaneurysm	50% (1/2)	0%	
Retroperitoneal Bleed	0% (0/2)	0%	
Other (including infection)	50 (1/2)%	0%	
Minor Groin Complication	2.8% (4/142)	8.0% (2/25)	0.223
Hematoma	75% (3/4)	50% (1/2)	
Pseudoaneurysm	0% (0/4)	0% (0/2)	
Retroperitoneal Bleed	0% (0/4)	0% (0/2)	
Other (including infection)	25% (1/4)	50% (1/2)	
Procedural Complications			
Pericardial Effusion	0.7% (1/142)	0% (0/25)	1.000
Any Dislodgment*	2.4% (3/125)	0%	0.226
Need for Revision of System	1.4% (2/142)	0%	1.000
Transvenous Pacemaker after MICRA	1.4% (2/142)	0%	1.000

Procedure Related Complications over total follow up time. *Among those that had follow up interrogations with quantitative or qualitative data available.

The rate of the composite endpoint was statistically non-significantly higher in the HD group (3.5% vs. 0.0%, p=1.00). There was a similar rate of major and minor groin complications between groups [Table 4].

Similarly, there was no significant difference in the rate of procedure-related compilations between either group [Table 4]. The mean length of stay for the HD group was 2.5 ± 3.5 days. The mean length of stay for those admitted after MICRA TPS was 1.4 ± 1.4 days, whereas it was 3.8 ± 4.5 days among those admitted for other reasons that underwent MICRA TPS during the course of their hospitalization (p<0.001).

Mean time to initial follow up after MICRA TPS was shorter for the SD compared to HD groups (58 ± 52 vs. 119 ± 172 days, p=0.003). However, total follow up time for the study was similar between the SD and HD groups (477 ± 429 vs. 507 ± 450 days, p=0.760).

Major Procedure Related Complications

In the HD group, two (2/140) patients developed major groin complications. One patient developed a small pseudoaneurysm and associated hematoma which resolved with observation alone and a superficial groin site infection (considered minor) treated conservatively with oral antibiotics with good result. The second developed an acute right iliac and femoral vein DVT on post-procedure day 2, in the setting of having oral anticoagulation held. Oral anticoagulation was resumed without further incident. There were no major groin complications in the same day discharge group (0/25).

Two patients in the HD group had procedure related complications. The first patient had a micro-dislodgement with significant rise in capture thresholds and required upgrade to a transvenous system approximately 6 weeks after implantation. The second had a difficult implantation with subsequent pericardial effusion and tamponade requiring drainage. The patient did eventually require upgrade to a transvenous system, but this was approximately 10 months after the procedure. There were no major procedure related complications in the same day discharge group.

Discussion

Optimal strategies for post-procedural management of MICRA TPS placement have not been described. In this small single center study, same-day discharge after MICRA TPS placement appears to be safe and feasible. We did not identify any difference in major complications, including problems with device function, procedural and access complications, between those discharged on the day of procedure compared to HD.

The goal of this study was primarily to demonstrate feasibility of early discharge among patients undergoing MICRA TPS. The goal of early discharge is this setting is to facilitate early mobility and decrease unnecessary utilization of medical resources. A wide range of lengths of stays have been previously reported for leadless pacemaker systems[13,14]. However, to the best of our knowledge, no report to date has described same day discharge among patients undergoing MICRA TPS, nor outcomes after early compared to late discharge. Ritter et al. reported that time to discharge varied widely geographically among those undergoing MICRA TPS[13]. Of those not discharged on the day of procedure, the length of stay in our study was similar to previously reported data[13].

Importantly, there were notable differences between the SD and HD groups. Patients in the HD group had a higher, albeit statistically non-significant incidence of end-stage renal disease, bacteremia and endocarditis compared to those in the SD group. The HD group was also, in part, comprised of patients admitted for other acute or decompensated illness who received a MICRA TPS as part of their overall care. Given this, the SD group represents a cohort of patients who were likely less sick and had fewer co-morbidities than the HD group. Taken together, our data suggest that same day discharge, while not appropriate for all patients, is indeed safe and feasible among properly selected patients at the discretion of the treatment team.

Our study has several limitations. Same day versus overnight observation after MICRA implantation was not randomly allocated and it's likely that selection bias played a role in identifying those felt most suitable for same day discharge. As such, it is likely that the patients that were discharged on the same day were those of lowest clinical risk.In addition, the practice of same day discharge was embraced after the investigators acquired ample experience with this procedure. However, this would still argue that, in properly selected patients and in the hands of experienced operators,s same-day discharge is feasible in patients after TPS. Moreover, baseline and pre-procedural characteristics, as well as indications for pacing, were similar between groups. Second, our sample size, especially the same day discharge group, was small. As such, our ability to detect differences in rare complications was limited. Our study also suffered

from a high rate of loss to follow up in terms of quantitative device interrogations (15.6%). Furthermore, the rate of loss to follow up in this regard was higher in the hospital admission group compared to the SD group (17% vs. 8%). However, our complication rates were consistent with prior studies[5]. Likewise, the metrics of device function at implantation and on follow up that were available were consistent with prior reports[6].

Conclusion

Our data suggest that in appropriately selected individuals, same discharge after MICRA TPS is feasible and safe.

References

1. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, Pavri BB, Kurtz SM. Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures. J. Am. Coll. Cardiol. 2012;60 (16):1540–5.
2. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009--a World Society of Arrhythmia's project. Pacing Clin Electrophysiol. 2011;34 (8):1013–27.
3. Bhatia N, El-Chami M. Leadless pacemakers: a contemporary review. J Geriatr Cardiol. 2018;15 (4):249–253.
4. Sperzel J, Burri H, Gras D, Tjong FVY, Knops RE, Hindricks G, Steinwender C, Defaye P. State of the art of leadless pacing. Europace. 2015;17 (10):1508–13.
5. El-Chami MF, Al-Samadi F, Clementy N, Garweg C, Martinez-Sande JL, Piccini JP, Iacopino S, Lloyd M, Viñolas PX, Jacobsen MD, Ritter P, Johansen JB, Tondo C, Liu F, Fagan DH, Eakley AK, Roberts PR. Updated performance of the Micra transcatheter pacemaker in the real-world setting: A comparison to the investigational study and a transvenous historical control. Heart Rhythm. 2018;15 (12):1800–1807.
6. Reynolds D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S, Narasimhan C, Steinwender C, Brugada J, Lloyd M, Roberts PR, Sagi V, Hummel J, Bongiorni MG, Knops RE, Ellis CR, Gornick CC, Bernabei MA, Laager V, Stromberg K, Williams ER, Hudnall JH, Ritter P. A Leadless Intracardiac Transcatheter Pacing System. N. Engl. J. Med. 2016;374 (6):533–41.
7. El-Chami MF, Al-Samadi F, Clementy N, Garweg C, Martinez-Sande JL, Piccini JP, Iacopino S, Lloyd M, Viñolas PX, Jacobsen MD, Ritter P, Johansen JB, Tondo C, Liu F, Fagan DH, Eakley AK, Roberts PR. Updated performance of the Micra transcatheter pacemaker in the real-world setting: A comparison to the investigational study and a transvenous historical control. Heart Rhythm. 2018;15 (12):1800–1807.
8. Osman F, Krishnamoorthy S, Nadir A, Mullin P, Morley-Davies A, Creamer J. Safety and cost-effectiveness of same day permanent pacemaker implantation. Am. J. Cardiol. 2010;106 (3):383–5.
9. Darda S, Khouri Y, Gorges R, Al Samara M, Jain SKA, Daccarett M, Machado C. Feasibility and safety of same-day discharge after implantable cardioverter defibrillator placement for primary prevention. Pacing Clin Electrophysiol. 2013;36 (7):885–91.
10. Shroff A, Kupfer J, Gilchrist IC, Caputo R, Speiser B, Bertrand OF, Pancholy SB, Rao SV. Same-Day Discharge After Percutaneous Coronary Intervention: Current Perspectives and Strategies for Implementation. JAMA Cardiol. 2016;1 (2):216–23.
11. Aytemir K, Canpolat U, Yorgun H, Evranos B, Kaya EB, Şahiner ML, Özer N. Usefulness of 'figure-of-eight' suture to achieve haemostasis after removal of 15-French calibre femoral venous sheath in patients undergoing cryoablation. Europace. 2016;18 (10):1545–1550.
12. Gammage MD, Lieberman RA, Yee R, Manolis AS, Compton SJ, Khazen C, Schaaf K, Oleson KA, Crossley GH. Multi-center clinical experience with a lumenless, catheter-delivered, bipolar, permanent pacemaker lead: implant safety and electrical performance. Pacing Clin Electrophysiol. 2006;29 (8):858–65.
13. Ritter P, Duray GZ, Steinwender C, Soejima K, Omar R, Mont L, Boersma LVA, Knops RE, Chinitz L, Zhang S, Narasimhan C, Hummel J, Lloyd M, Simmers TA, Voigt A, Laager V, Stromberg K, Bonner MD, Sheldon TJ, Reynolds D. Early performance of a miniaturized leadless cardiac pacemaker: the Micra Transcatheter Pacing Study. Eur. Heart J. 2015;36 (37):2510–9.
14. Reddy VY, Exner DV, Cantillon DJ, Doshi R, Bunch TJ, Tomassoni GF, Friedman PA, Estes NAM, Ip J, Niazi I, Plunkitt K, Banker R, Porterfield J, Ip JE, Dukkipati SR. Percutaneous Implantation of an Entirely Intracardiac Leadless Pacemaker. N. Engl. J. Med. 2015;373 (12):1125–35.

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Risk Factors for Symptomatic Atrial Fibrillation-Analysis of an Outpatient Database

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Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in practice and is the leading cause of debilitating strokes with significant economic burden. It is currently not known whether asymptomatic undiagnosed AF should be treated if detected by various screening methods. Currently United States guidelines have no recommendations to identify patients with asymptomatic undiagnosed AF due to lack of evidence. The American Heart Association Center for Health Technology & Innovation undertook a plan to identify tools in 3 phases that may be useful in improving outcomes in patients with undiagnosed AF. In phase I we sought to identify AF risk factors that can be used to develop a risk score to identify high-risk patients using a large commercial insurance dataset. The principal findings of this study show that individuals at high risk for AF are those of advance age, the presence of heart failure, coronary artery disease, hypertension, metabolic disorders, and hyperlipidemia. Our analysis also found that chronic respiratory failure was a significant risk factor for those over 65 years of age and chronic kidney disease for those less than 65 years of age.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in practice and is the leading cause of debilitating strokes[1], leading to significant economic burden[2]. While AF presently affects 2.7-6.1 million, it is expected to increase to 12.1 million by 2030.[1] AF may be asymptomatic and underdiagnosed with the first presentation being a stroke.[3] Studies estimate that 13% to 40% of patients with AF are undiagnosed.[4,5] Strokes associated with AF have worse outcomes resulting in larger cerebral infarct size, more hemorrhagic transformation, subsequent disabilities, and death.[6] Increasing awareness of AF by clinicians and patients may lead to an earlier diagnosis and treatment, resulting in fewer adverse health outcomes. However, the United States Preventive Task Force has stated there is insufficient evidence to endorse electrocardiographic (ECG) screening for AF.[7]

The American Heart Association's Center for Health Technology & Innovation undertook a plan to identify tools that may be useful in improving outcomes in patients with undiagnosed AF. The work plan consists of 3 phases. Phase I is to develop a predictive screening tool, using multivariate logistic regression to calculate the risk of developing AF. Phase II is to create and evaluate the use of the screening tool developed in Phase I to prospectively identify individuals at high risk for the onset of AF, as compared to usual care. Phase III will ask patients with newly diagnosed with AF to enroll in a study that would compare compliance with AF treatment in patients using a digital tracking device to usual care. The results of our analysis reported here are from phase I of the study. The aim of this analysis was to address the problem of undiagnosed AF in the US population by gaining a better understanding of the factors associated with AF.

We hypothesized that using a large population database could potentially identify clinically important risk factors associated with AF. The primary objective of this phase of the study was to identify patients at high risk for undiagnosed AF.

Methods

We performed a retrospective cohort study using a commercial dataset to identify risk factors that are associated with AF ICD diagnosis codes of 427.31.

Key Words

Atrial fibrillation, Left atrial appendage, Stroke.

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Data source

A commercial dataset representing over 50 health plans and self-insured employers, representing all 50 states and containing 535,499 records, including 4862 cases of AF from 2010-17 was used in this analysis. The dataset was cross-sectional, and all records were de-identified. The dataset included demographic data, including age and gender, frequency of 40 chronic conditions as identified by ICD codes, biometric measures, including height, weight, and blood pressure, and cost data, including pharmacy and total paid claims.

Calculations

To assess the risk of stroke in this patient population the $CHADS_2$ and CHA_2DS_2-VASc scores were calculated,[8] as well as the number of chronic conditions.

Statistical analysis

Statistical analysis was performed with SPSS version 25. Chi Square, binary logistic regression and hierarchical logistic regression were conducted to test the hypothesis that AF could be predicted from demographic, biometric, and claims data. Chronic conditions, including AF were coded as binary variables, Yes=1 and No=0. Frequencies, prevalence of AF and odds ratios were calculated from the binary variables. Frequencies of AF were calculated by $CHADS_2$ and CHA_2DS_2-VASc scores. Independent sample t-tests were calculated for height, weight, body mass index, systolic blood pressure, diastolic blood pressure, number of chronic conditions, age, total pharmacy cost, and lifetime paid claims, comparing cases with AF and cases without AF. Binary and hierarchical logistic regression was performed with AF as the dependent variable.

Results

Descriptive statistics

[Table 1] provides a breakdown of cases with and without AF by gender and age. The total number and rate of AF was higher in males than in females. The rate of AF increased with age. [Figure 1] shows the age distribution of the patient population in the database. [Table 2] shows the distribution of the presence of AF with respect to sex and age.

There was a slight majority of male participants (n = 286,710; 53.4%) to female participants (n = 248,101; 46.2%). For the male participants, (n = 3,255; 1.14%) were coded YES for AF and (n = 283,455; 98.86%) were coded NO for AF. For the female participants, (n = 1,603; 0.65%) were coded YES for AF and (n = 246,496; 99.35%) were coded NO for AF. Overall for both genders, (n = 4,858; 0.91%) were coded YES for AF and (n = 529,963; 99.09%) were coded NO for AF.

Table 1: Frequency of AF by age and gender

Group	+ AF	-AF	Rate /1000
Male	3255	283455	.011
Female	1603	246498	.003
Age: 18-64	2488	466468	.005
Age: 65-74	1302	31724	.039
Age: ≥75	1403	11092	.112

Most participants were under the age of 65 years (n = 490,566; 91.6%). A clear minority of participants were age 65 years or older (n = 44,883; 8.4%). For the under age 65-year participants, (n = 2,353; 0.48%) were coded YES for AF and (n = 488,213; 99.5%) were coded NO for AF. For the age 65 years or older, (n = 2,509; 5.59%) were coded YES for AF and (n = 42,374; 94.41%) were coded NO for AF. Overall for both age groups, (n = 4,862; 0.91%) were coded YES for AF and (n = 530,587; 99.09%) were coded NO for AF.

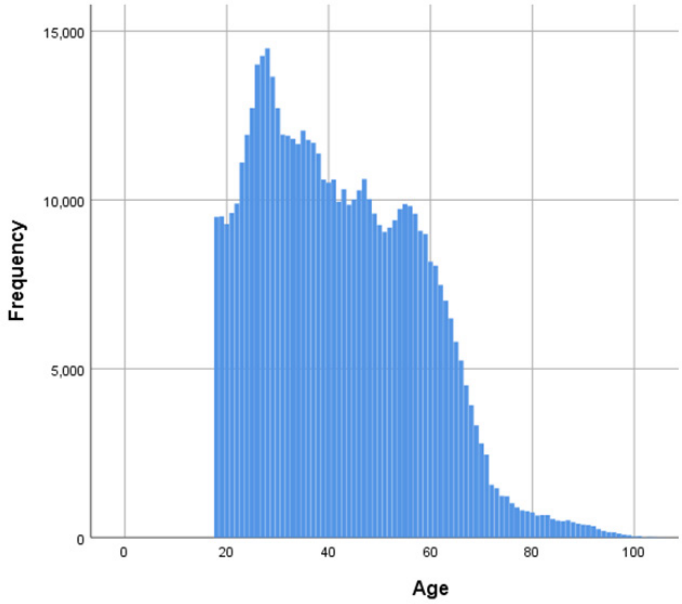

Figure 1: Age distribution of the patient population in the database.

Table 2: Distribution of age and sex in patients with AF.

	<65 years	≥65 years
Males	0.66%	7.03%
Females	0.28%	4.75%

Associated chronic conditions

The dataset included a total of 40 of the most common chronic conditions to look for possible trends. Metabolic disorders included unspecified metabolic conditions not including metabolic syndrome or diabetes. [Table 3] is a breakdown of each condition, including a 2X2 table of the presence or absence of AF and each chronic condition. From the table the rate of AF and each factor can be calculated, as well as the odds ratio. A Chi Square analysis was performed for each chronic condition to determine of there was a statistically significant relationship between AF and each chronic condition. The top 10 chronic conditions were used in the logistic regression model. Since age of a robust predictor of AF, and since this commercial dataset is heavily weighted to younger individuals, the rates, odds ratio and Chi Square were conducted for cases under age 65 and over age 65.

$CHADS_2$ and CHA_2DS_2-VASc and AF. The $CHADS_2$ and CHA_2DS_2-VASc scores were calculated from the data. [Table 4] is a summary of the rate of AF by $CHADS_2$ scores, and [Table 5] is the summary of the rate of AF by CHA_2DS_2-VASc scores. In both scores the rate of AF increases with each level.

Table 3: Calculation of odds ratio and Chi Square for common chronic conditions for the total group.

Factor	+AF, + Factor	+AF, -Factor	-AF, + Factor	-AF, -Factor	Odds Ratio	Chi Square	P value
ADHD	26	4837	7148	524546	.394	23.9	<.05
Affective psychosis	33	4830	3073	528621	1.2	.848	NS
Alzheimer's	62	4801	236	531458	29.1	1314	<.05
Asthma	343	4520	14726	516968	2.6	323	<.05
Autism	0	4863	228	531466	.99	2.086	NS
Blood disorders	1428	3435	21495	510199	9.8	7555	<.05
Bronchopulm. dysplasia	0	4863	3	531691	.99	.027	NS
CAD	1652	3211	9675	522019	27.7	24105	<.05
CKD	638	4225	4064	537630	19.6	8468	<.05
COPD	690	4173	4547	527147	19.1	8864	<.05
Cancer	997	3866	16434	515260	8.0	4647	<.05
Cerebral palsy	1	4862	139	531555	.787	.058	NS
Chromosomal abnorm.	4	4859	161	531533	2.7	4.3	<.05
Chronic pain	317	4546	7089	524605	5.1	951	<.05
Chronic resp fail	227	4636	638	531056	40.7	6192	<.05
Heart failure	1354	3509	2902	528792	70.3	45630	<.05
Demyelinating diseases	16	4847	953	530741	1.8	5.9	<.05
Depression	257	4606	14358	517336	2.0	121	<.05
Developmental disorders	5	4858	308	531386	1.7	1.6	NS
Diabetes	1370	3493	28755	502939	6.8	4712	<.05
ESRD	154	4709	682	531012	25.4	2859	<.05
Eating disorders	39	4824	745	530949	5.7	144	<.05
HIV/AIDS	8	4855	341	531353	2.5	7.4	<.05
Hyperlipidemia	2717	2146	61692	470002	9.6	8939	<.05
Hypertension	3628	1235	70102	461592	19.3	15336	<.05
Immune disorders	48	4815	1006	530668	5.2	156	<.05
Inflammatory bowel dis	54	4809	2171	529523	2.7	57	<.05
Intellectual disabilities	2	4861	77	531617	2.8	2.3	NS
Liver diseases	289	4574	6625	525069	5.0	835	<.05
Lower back pain	825	4038	37016	494678	2.7	735	<.05
Metabolic disorders	3305	1558	76023	455671	12.7	11015	<.05
Metabolic syndrome	49	4814	1586	530108	3.4	79.8	<.05
Morbid obesity	420	4443	8780	522914	5.6	1395	<.05
Osteoarthritis	1072	3791	18686	513008	7.7	4664	<.05
Paralysis	82	4781	690	531004	13.1	812	<.05
Peripheral vascular dis	341	4522	2183	529511	18.2	4485	<.05
Rheumatoid Arthritis	98	4765	2480	529214	4.3	241.7	<.05
Sickle cell disease	1	4862	88	531606	1.2	.047	NS
Sleep apnea	1389	3474	23540	508154	8.6	6336	<.05
Stroke	1303	3850	9511	499791	17.8	13595	<.05

+AF indicates number of positive cases of atrial fibrillation, -AF indicates number of negative cases of atrial fibrillation, +Factor means the number of positive cases of condition listed on the left, - Factor means the number of negative cases of the condition listed on the left. ADHD = attention deficit and hyperactive disorder, CAD=coronary artery disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, ESRD=end stage renal disease.

Comparison of means

The dataset included a subset of continuous variables including body composition, blood pressure, number of chronic conditions and cost variables. [Table 6] shows the results of independent samples t-test comparing cases with AF to those without AF. While there was no difference in height or blood pressure, there were statistically significant differences in weight and body mass index. Individuals with AF were significantly older, had more chronic conditions and had higher medical and pharmacy costs than those without AF.

Logistic Regression

Since the chronic conditions are binary factors (yes or no) simple binary logistic regression was used to determine the relationship between AF and each chronic condition [Table 7]. The highest Nagelkerke r squared is for the number of chronic conditions. Age, hypertension (HTN), coronary artery disease (CAD), congestive heart failure (CHF) and metabolic disorders had the highest Nagelkerke scores. Binary logistic regression was also performed on the under age 65 and over age 65 cohorts.

Table 4: CHADS2 score distribution of the patient population

$CHADS_2$	Total	%	AF	%	Rate/1000
0	415,583	80.8	874	0%	2.10
1	66,589	12.9	1,362	2%	20.45
2	22,089	4.3	1,078	5%	48.80
3	5,671	1.1	751	13%	132.43
4	3,136	.6	544	17%	173.47
5	1,110	.2	398	36%	358.56
6	268	.1	146	54%	544.78

CHADS2=CHADS2 score, Total: Number of cases in CHADS2 score, %: percentage of cases in CHADS2 score, AF=number of cases of atrial fibrillation, %=percentage of atrial fibrillation cases.

Table 5: CHA2DS2-VASc score distribution of the patient population

$CHA2DS_2$-VASc Score	Total	%	AF	%	Rate/1000
0	193,811	37.7	490	0%	2.53
1	241,617	47.0	964	0%	3.99
2	48,182	9.4	965	2%	20.03
3	19,012	3.7	838	4%	44.08
4	6,461	1.3	613	9%	94.88
5	2,902	.6	524	18%	180.57
6	1,511	.3	370	24%	244.87
7	663	.1	259	39%	390.65
8	237	.0	101	43%	426.16
9	39	.0	27	69%	692.31

Total: Number of cases in CHA2DS2VASc score, %: percentage of cases in CHA2DS2VASc score, AF=number of cases of atrial fibrillation, %=percentage of atrial fibrillation cases

A hierarchical logistic regression model was performed for the whole group [Table 8] and separately for the under 65 and over 65 cohorts. Variables selected for the logistic regression model were based on the variables with the top 10 odds ratios. Since age resulted in a higher Nagelkerke score than any of the chronic conditions it was added to the model.

CAD, HTN, CHF, chronic respiratory failure and age were common to all 3 models. Only CKD in the under 65 cohort and COPD in the over 65 cohort were added. Since age is in the model and the highest ROC and Nagelkerke r squared was achieved in the total group there appears to be no reason to have a separate predictive model for each age group.

Discussion

Our principal findings show that individuals at high risk for AF are those of advance age, the presence of CHF, CAD, HTN, metabolic disorders, and hyperlipidemia. Our analysis also found that chronic respiratory failure was a significant risk factor for those over 65 years of age and chronic kidney disease for those less than 65 years of age.

Risk scores for predicting AF have been developed by the Framingham Heart Study and Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)-AF consortium. The risk score was validated in different ethnic groups including whites, Hispanics and African Americans.[9] In a community-based cohort, the CHARGE-AF risk score was compared to the CHA_2DS2-VASc risk score and found to perform better at predicting AF.[10] In another AF risk score study COPD was found to be a significant risk factor in a Chinese population study. [11]

Table 6: Comparison of means for continuous variables

Factor	AF	N	Mean	SD	P value
Height	Yes	526	65.53	15.8	.105
	No	47285	64.48	14.9	
Weight	Yes	526	211.07	75.1	.000
	No	47285	182.37	62.0	
Body mass index	Yes	526	25.4	15.3	.000
	No	47285	22.0	13.8	
Systolic blood pressure	Yes	526	124.6	17.8	.896
	No	47285	122.1	34.1	
Diastolic blood pressure	Yes	526	77.4	11.3	.051
	No	47285	76.2	13.1	
# of chronic conditions	Yes	4863	5.64	2.9	.000
	No	531694	.8	1.5	
Age	Yes	4862	66.1	14.6	.000
	No	530587	42.0	15.4	
Total Rx cost	Yes	4852	9800.9	32100	.000
	No	417586	2578.9	15861	
Lifetime paid claims	Yes	4852	163592	70031	.000
	No	417586	46933	12007	

Awareness of this high-risk group can be a signal to primary care physicians to pay more attention to the possibility that these patients are at greater risk for AF and, in turn, for stroke. This predictive tool has the potential, following further validation, to assess large amounts of patient claims and electronic medical record data to identify patients in need for AF detection devices. An additional possible use of this data would be in risk stratifying corporate employees for proactive encouragement to establish a relationship, and to stay engaged with a primary care physician.

Several studies are underway to determine if opportunistic AF detection leads to decreased strokes, heart failure and mortality. [12] Screening tools such as pulse palpation followed by ECG, sphygmomanometer with rhythm determinations and rhythm monitoring devices are being studied to identify patients with asymptomatic AF.[12] However, it has yet to be determined whether asymptomatic AF detected through opportunistic means such as implanted devices or screening studies should prompt the same treatment for symptomatic AF.[12] The AF Screen International Collaboration acknowledged that health resources vary widely between countries and health systems and thus AF screening should be both country- and health system-specific. Large randomized outcomes studies are needed to strengthen the evidence base of the value of detecting asymptomatic AF. Guidelines vary in their recommendations for opportunistic screening for AF. The European Society of Cardiology AF guidelines has a level IB recommendation for opportunistic screening for AF by pulse taking or ECG rhythm strip in patients >65 years of age as well as routine detections of atrial high rate episodes in patients with implanted devices. Further evaluation for treatment of AF is then recommended.[13] The American guidelines make no recommendations for opportunistic AF screening but consider it a priority for stroke prevention. Efforts are underway to provide randomized controlled trials to determine the value of opportunistic AF screening.

Table 7: Binary Logistic Regression for total group and common chronic conditions

Factor	Wald	Nagelkerke	OR	LL	UL	P value
ADHD	.22.298	.001	.394	.268	.580	.000
Affective psychosis	.846	.000	1.175	.833	1.658	.846
Alzheimer's	551.969	.005	29.082	21.954	38.527	.000
Asthma	299.409	.004	2.644	2.384	2.977	.000
Blood disorders	5036.616	.066	9.867	9.263	10.511	.000
CAD	10807.959	.130	27.759	26.073	29.544	.000
CKD	4315.374	.046	19.605	17.940	21.425	.000
COPD	4564.768	.049	19.169	17.595	20.884	.000
Cancer	3298.310	.042	8.086	7.529	8.683	.000
Chromosomal abnorm.	3.898	.000	2.718	1.007	7.332	.048
Chronic pain	765.563	.010	5.160	4.594	5.796	.000
Chronic respiratory failure	2220.662	.022	40.757	34.933	47.552	.000
Heart failure	13202.329	.148	70.311	65.391	75.601	.000
Demyelinating diseases	5.815	.000	1.838	1.121	3.016	.016
Depression	116.379	.002	2.010	1.771	20282	.000
Developmental disorders	1.621	.000	1.176	.734	4.298	.203
Diabetes	3521.769	.048	6.860	6.437	7.310	.000
ESRD	1282.070	.013	25.463	21.328	30.400	.000
Eating disorders	112.783	.001	5.762	4.171	7.960	.000
HIV/AIDS	6.939	.000	2.568	1.273	5.179	.008
Hyperlipidemia	6026.756	.103	9.646	9.109	10.214	.000
Hypertension	7964.790	.177	19.343	18.125	20.643	.000
Immune disorders	125.030	.002	5.259	3.931	7.035	.000
Inflammatory bowel disorder	52.901	.001	2.739	1.572	3.593	.000
Intellectual disabilities	2.124	.000	2.841	.698	11.566	.145
Liver diseases	677.300	.009	5.008	4.435	5.654	.000
Lower back pain	677.651	.010	2.730	2.531	2.945	.000
Metabolic disorders	6736.697	.135	12.715	11.966	13.511	.000
Metabolic syndrome	70.554	.001	3.402	2.557	4.527	.000
Morbid obesity	1097.189	.014	5.630	5.083	6.236	.000
Osteoarthritis	3354.483	.043	7.763	7.243	8.321	.000
Paralysis	480.473	.005	13.199	10.480	16.624	.000
Peripheral vascular disease	2337.602	.024	18.291	16.258	20.579	.000
Rheumatoid Arthritis	202.197	.003	4.389	3.579	5.381	.000
Sleep apnea	4414.928	.059	8.0631	8.099	9.198	.000
Gender	352.507	.007	.565	.532	.600	.000
Age	9395.060	.192	1.091	1.089	1.093	.000
Age group	7409.449	.118	12.285	11.603	13.007	.000
Chronic conditions	16330.588	.319	1.856	1.839	1.874	.000
$CHADS_2$	15633.265	.234	3.301	2.959	3.063	.000
$CHA2DS_2$-VASc	13933.352	.211	2.358	2.325	2.392	.000

OR=Odds ratio, LL=lower limit of the odds ratio, UL=upper limit of the odds ratio, ADHD = attention deficit and hyperactive disorder, CAD=coronary artery disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, ESRD=end stage renal disease.

For the next phase of our study, we plan to develop and use the predictive screening tool using the high-risk conditions to see if this would predict the presence of asymptomatic AF in patients in different populations and other databases. In addition, we will need to evaluate the risk of stroke and thromboembolism in patients with asymptomatic subclinical AF since this is not yet known. The threshold amount of AF that should be treated with anticoagulation in these patients is not yet universally established.

Limitations

There are several limitations in our study. The commercial dataset is derived from specific codes of the diseases entered by healthcare providers and errors from incorrect coding from misclassification of diseases may be possible. Another limitation was that the accuracy of the diagnosis of AF was not verified by cardiologists. We assume the patients in the dataset were symptomatic, as asymptomatic diagnosis is unlikely with the exception of occasional incidental diagnosis in a routine visit with an observation such as an irregular pulse. Our study

Table 8: Hierarchical logistic regression total group

Factor	Wald	Nagelkerke	Odds Ratio	95% CI	ROC
Heart failure	13202.329	0.148	70.31	65.40-75.60	0.636
CAD	10807.959	0.13	27.76	26.07-29.54	0.661
Hypertension	7964.79	0.177	19.34	18.13-20.64	0.807
Metabolic disorders	6736.697	0.135	12.72	11.97-13.51	0.768
Hyperlipidemia	6026.756	0.103	9.65	9.109-10.21	0.721
Age	9395.06	0.192	1.10	1.089-1.093	0.798

strength is the large cohort of a diverse population in terms of sex and age. Because the database consists only of patients known to have been diagnosed with AF, the findings of AF markers in this report may or may not hold for undiagnosed AF. Other considerations such as treatment for hypertension or slower ventricular rate that may reduce symptoms must be taken into account, and thus further validation is needed.

Disclosures

Dr. Waldo has received consulting fees/honoraria from Biosense Webster, AtriCure, Milestone Pharmaceuticals, Cardiac Insight, Correvio Pharms, Pfizer, Bristol-Myers Squibb; Dr. Naccarelli has received consulting fees/honoraria from Acesion, Glaxo-Smith-Kline, Janssen, Milestone, Omecos, and Sanofi; Dr. Albert has received funding from the NIH (R01 HL116690; Dr. Turkhia has received grants from Janssen, AstraZeneca, Veterans Health Administration, Boehringer Ingelheim, Cardiva Medical, Bristol Myers-Squibb, and the American Heart Association, and consulting fees/honoraria from Medtronic, AliveCor, Abbott, Precision Health Economics, Zipline Medical, IBeat, and iRrythm. The remaining authors have no disclosures.

Conclusions

This analysis demonstrates that individuals at risk for AF can be identified from the general population with the use of a predictive algorithm. Increasing age and the presence of heart failure, coronary artery disease, hypertension, metabolic disorders, and hyperlipidemia represent this high-risk group. Respiratory failure and chronic kidney disease may also identify certain age groups at risk for AF. Awareness of this high-risk group can be a signal to primary care physicians to pay more attention to the possibility that these patients are at greater risk for AF, and, in turn, for stroke. With further validation, this predictive tool can be used to determine the need for AF detection devices, clinical decision-support tools and appropriate treatment plans.

References

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018;137 (12):e67–e492.
2. Turakhia MP, Shafrin J, Bognar K, Goldman DP, Mendys PM, Abdulsattar Y, Wiederkehr D, Trocio J. Economic Burden of Undiagnosed Nonvalvular Atrial Fibrillation in the United States. Am. J. Cardiol. 2015;116 (5):733–9.
3. Bisson A, Clementy N, Bodin A, Angoulvant D, Babuty D, Lip GYH, Fauchier L. Relationship of Preexisting Cardiovascular Comorbidities to Newly Diagnosed Atrial Fibrillation After Ischemic Stroke. Stroke. 2017;48 (10):2878–2880.
4. Turakhia MP, Shafrin J, Bognar K, Trocio J, Abdulsattar Y, Wiederkehr D, Goldman DP. Estimated prevalence of undiagnosed atrial fibrillation in the United States. PLoS ONE. 2018;13 (4).
5. Reiffel JA, Verma A, Kowey PR, Halperin JL, Gersh BJ, Wachter R, Pouliot E, Ziegler PD. Incidence of Previously Undiagnosed Atrial Fibrillation Using Insertable Cardiac Monitors in a High-Risk Population: The REVEAL AF Study. JAMA Cardiol. 2017;2 (10):1120–1127.
6. Tu Hans TH, Campbell BCV, Christensen S, Collins M, De Silva DA, Butcher KS, Parsons MW, Desmond PM, Barber PA, Levi CR, Bladin CF, Donnan GA, Davis SM. Pathophysiological determinants of worse stroke outcome in atrial fibrillation. Cerebrovasc. Dis. 2010;30 (4):389–95.
7. Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, Doubeni CA, Epling JW, Kemper AR, Kubik M, Landefeld CS, Mangione CM, Silverstein M, Simon MA, Tseng CW, Wong JB. Screening for Atrial Fibrillation With Electrocardiography: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;320 (5):478–484.
8. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline 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 Heart Rhythm Society. J. Am. Coll. Cardiol. 2014;64 (21):e1–76.
9. Shulman E, Kargoli F, Aagaard P, Hoch E, Di BL, Fisher J, Gross J, Kim S, Krumerman A, Ferrick KJ. Validation of the Framingham Heart Study and CHARGE-AF Risk Scores for Atrial Fibrillation in Hispanics, African-Americans, and Non-Hispanic Whites. Am. J. Cardiol. 2016;117 (1):76–83.
10. Christophersen IE, Yin X, Larson MG, Lubitz SA, Magnani JW, Mc MDD, Ellinor PT, Benjamin EJ. A comparison of the CHARGE-AF and the CHA_2DS_2-VASc risk scores for prediction of atrial fibrillation in the Framingham Heart Study. Am. Heart J. 2016;178 ():45–54.
11. Li YG, Pastori D, Farcomeni A, Yang PS, Jang E, Joung B, Wang YT, GuoYT, Lip GYH. A Simple Clinical Risk Score (C_2HEST) for Predicting Incident Atrial Fibrillation in Asian Subjects: Derivation in 471,446 Chinese Subjects, With Internal Validation and External Application in 451,199 Korean Subjects. Chest. 2019;155 (3):510–518.
12. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, Albert CM, Anderson CS, Antoniou S, Benjamin EJ, Boriani G, Brachmann J, Brandes A, Chao TF, Conen D, Engdahl J, Fauchier L, Fitzmaurice DA, Friberg L, Gersh BJ, Gladstone DJ, Glotzer TV, Gwynne K, Hankey GJ, Harbison J, Hillis GS, Hills MT, Kamel H, Kirchhof P, Kowey PR, Krieger D, Lee Vivian WY, Levin LÅ, LipGregory YH, Lobban T, Lowres N, Mairesse GH, Martinez C, Neubeck L, Orchard J, Piccini JP, Poppe K, Potpara TS, Puererfellner H, Rienstra M, Sandhu RK, Schnabel RB, Siu CW, Steinhubl S, Svendsen JH, Svennberg E, Themistoclakis S, Tieleman RG, Turakhia MP, Tveit A, Uittenbogaart SB, Van Gelder IC, Verma A, Wachter R, Yan BP. Screening for Atrial Fibrillation: A Report of the AF-SCREEN International Collaboration. Circulation. 2017;135 (19):1851–1867.

13. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur. Heart J. 2016;37 (38):2893–2962.

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A Rare Case of Bronchopericardial Fistula Following Atrial Fibrillation Ablation

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Abstract

Radiofrequency ablation (RFA) for atrial fibrillation (AF) has emerged as an effective and reliable treatment modality. Since its introduction in the 1990s, major and minor complications have been identified. Major complications include periprocedural death, atrioesophageal (AE) fistula, stroke, cardiac perforation and tamponade, pulmonary venous stenosis, phrenic nerve injury, retroperitoneal hematoma, and arrhythmias. Minor complications include pseudoaneurysms and arteriovenous fistulas . We report an extremely rare and life-threatening complication of bronchopericardial fistula following AF ablation resulting in respiratory complications.

Background

Radiofrequency ablation (RFA) for atrial fibrillation (AF) has emerged as an effective and reliable treatment modality. Since its introduction in the 1990s, major and minor complications have been identified. Major complications include periprocedural death, atrioesophageal (AE) fistula, stroke, cardiac perforation and tamponade, pulmonary venous stenosis, phrenic nerve injury, retroperitoneal hematoma, and arrhythmias. Minor complications include pseudoaneurysms and arteriovenous fistulas [1-3]. We report an extremely rare and life-threatening complication of bronchopericardial fistula following AF ablation resulting in respiratory complications.

Case Report

A 51-year-old male with a past medical history of symptomatic paroxysmal atrial fibrillation (PAF), hypertension, hyperlipidemia, obesity, depression, and obstructive sleep apnea presented with complaints of fatigue and palpitations. Holter monitor documented a 50% AF burden. Transthoracic echocardiogram revealed normal left ventricular function and LA diameter of 4.5cm. Patient was started on flecainide and referred to an electrophysiologist for continued fatigue and PAF. Ablation was recommended but patient preferred medical therapy. He was admitted for dofetilide. After the 4th dose, QT became prolonged. He was started on amiodarone and underwent RFA. 2 weeks after the ablation, patient endorsed non-productive cough without fever and chills. Chest x-ray was obtained and showed pneumopericardium [Figure 1]. Suspicion for AE fistula was high and patient was started on broad spectrum antibiotics. Patient required intubation for chest CT due to hypoxia upon lying supine. CT chest showed pneumopericardium [Figure 2]. CT surgery was consulted and pericardial window was performed to evacuate the pneumopericardium. EGD revealed no evidence of esophageal injury or fistulous connection. Subsequent bronchoscopy revealed distal left mainstem bronchus ulceration which presumably led to a bronchopericardial fistula. Patient had a prolonged course in the ICU with supportive care and serial bronchoscopies. Tracheostomy was performed and patient was eventually extubated after 10 days. Patient returned to baseline with rehab over the next 3 months and amiodarone was eventually stopped.

Key Words

Radiofrequency ablation (RFA), Atrial fibrillation (AF), Atrioesophageal (AE).

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Discussion

RFA procedures involve a 3-dimensional mapping system to reconstruct the left atrium and pulmonary veins. A catheter delivers radiofrequency energy in a circumferential fashion 1 to 2 cm from the left- and right-sided pulmonary veins [4]. Though regarded as a safe procedure, complications may arise. Our patient suffered a very rare complication: bronchopericardial fistula and pneumopericardium.

Bronchopericardial fistulas involve a communication between the tracheobronchial tree and the pericardial sac. Air enters the pericardium, resulting in a pneumopericardium and this may lead to cardiovascular collapse secondary to cardiac air tamponade [5]. A small pneumopericardium may present as cough, whereas a larger pneumopericardium may present with shortness of breath and chest pain. These fistulas have been identified as complications from bronchogenic carcinoma, necrotizing pulmonary infections such as tuberculosis and invasive pulmonary aspergillosis, penetrating chest trauma, and iatrogenic causes such as coronary artery bypass grafts and transbronchial biopsies [6]. It is rarely seen as a complication from RFA and has been reported in fewer than 5 cases. Given its low incidence, the pathophysiology is not fully understood.

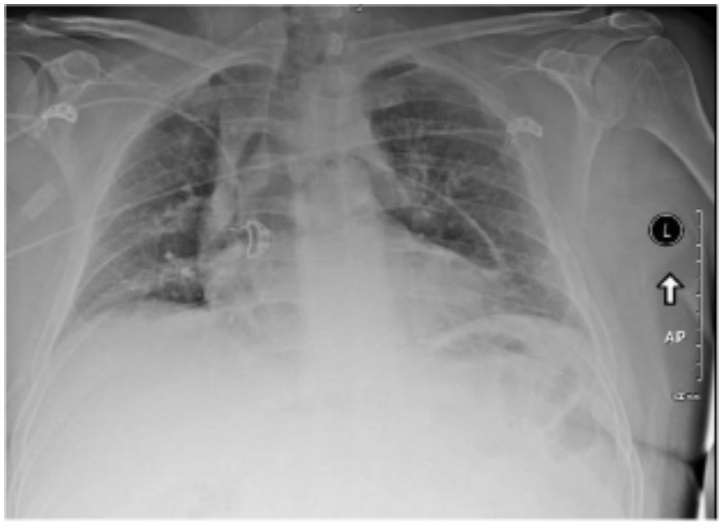

Figure 1: Chest x-ray revealing pneumopericardium most evident surrounding the left heart structures.

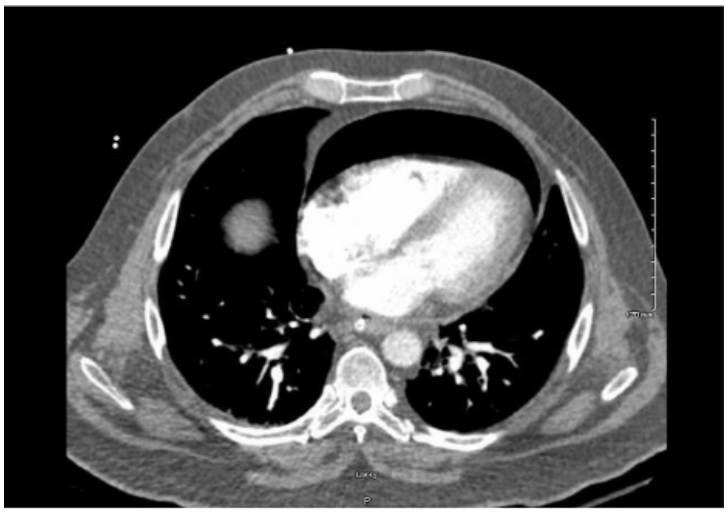

Figure 2: CT chest with large pneumopericardium noted in the anterior chest.

However, the pathophysiology can be derived from an understanding of AE fistulas, which are well-documented as a major complication of RFA with high mortality. The pathophysiology of AE fistulas arise from direct thermal injury to the esophagus, excessive catheter tip contact force, and extended RFA energy duration in the setting of a thin left atrial wall. Oftentimes, thermal injury occurs where ablation lines overlap. The injury creates a fistulous communication between the esophagus and left atrium, which are directly adjacent anatomically [7].

Similarly, the left atrium and pulmonary veins lie in close proximity to neighboring anatomic structures such as the aorta, left main bronchus, and phrenic nerves [Figure 3] and [Figure 4]. In our patient, RFA likely produced indirect thermal injury and ischemic necrosis to the left main bronchus and left atrium. The added risk factors of likely thin and dilated left atrial wall secondary to high AF burden and dilated pulmonary vasculature secondary to obstructive sleep apnea and obesity may have also contributed.

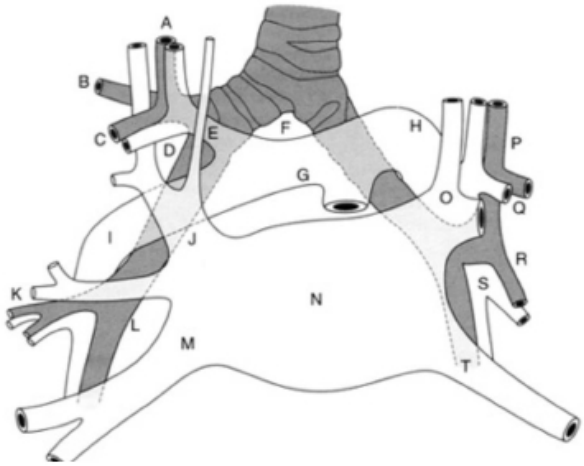

Figure 3: Anatomic depiction of the close proximity between the bronchial tree and pulmonary venous structures.

Though respiratory symptoms can be encountered after cryoballoon ablation (CBA) for AF, these symptoms are not commonly seen following RFA [8] . A study by Verma et al in which 10 patients underwent CBA with real-time bronchoscopy showed that ice formation in the left mainstem bronchus was seen in 70% of patients and in 59% of lesions. No ice formation was seen on the right side [9]. This can explain the cough and hemoptysis in some patients after CBA.

Perhaps early intervention via bronchoscopy needs to be considered in patients who present with respiratory symptoms after AF ablation. In the event of pneumopericardium, early intervention and evacuation of the pericardial space are paramount. Whether obstructive sleep apnea and/or pulmonary hypertension are risk factors for RFA fistulous complications is unknown.

Conclusion

The left mainstem bronchus is in close proximity to the left superior pulmonary vein and evaluation of bronchial injury or pneumopericardium should be considered in patients presenting with cough and/or hemoptysis post AF RFA.

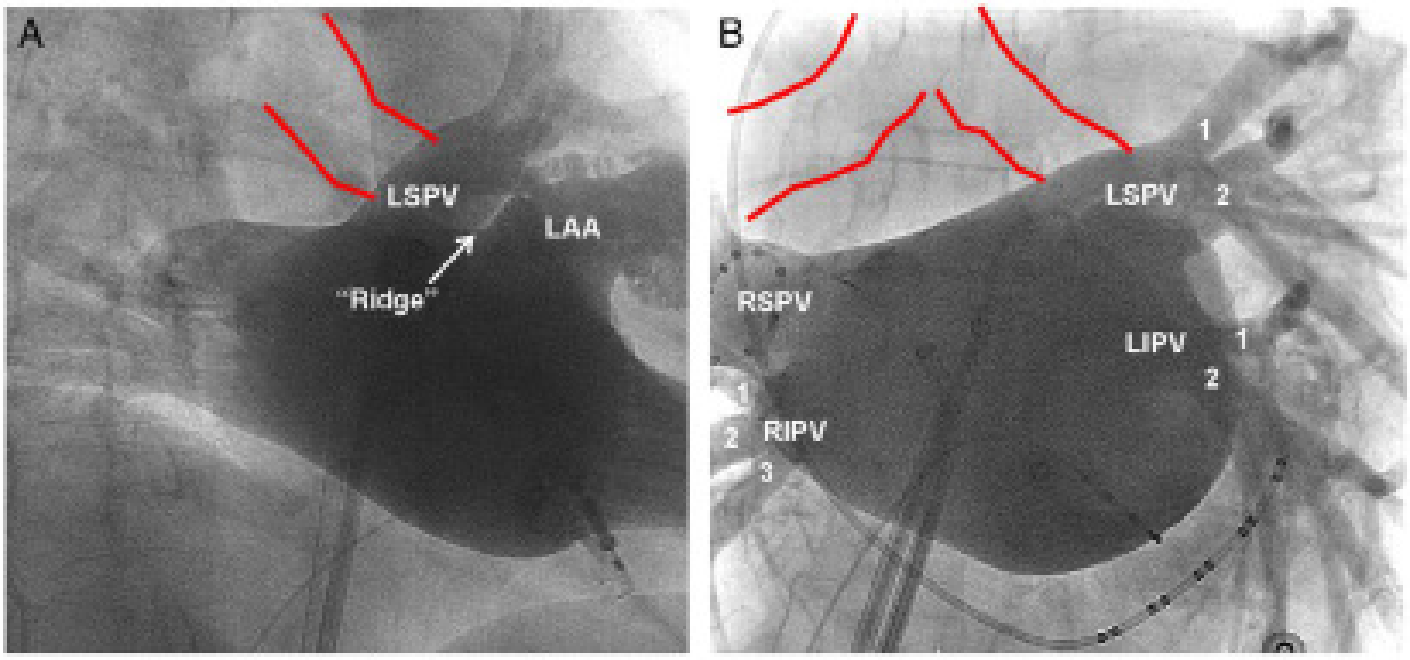

Figure 4: **A) Angiographic depiction of the proximity between the left main bronchus (red lines) and the left superior pulmonary vein, which is the focus of radiofrequency ablation. B) Angiographic depiction of the right and left main stem bronchi in relation to the pulmonary veins.**

References

1. Sparks A, Kozinn J, Wimmer A, Stewart JR. Distal Left Main Bronchial Injury after Catheter Ablation for Atrial Fibrillation: Report of Two Cases. . Clin Surg. 2017;
2. Gupta A, PereraT, Ganesan A, Sullivan T, Lau DH, Roberts-Thomson KC, Brooks AG, SandersPrashanthan. Complications of catheter ablation of atrial fibrillation: a systematic review. Circ Arrhythm Electrophysiol. 2013;6 (6):1082–8.
3. Wongcharoen W, Lo LW, Chen SA. Collateral Damage from Catheter Ablation of Atrial Fibrillation Lessons Learnt in the Past Decade. J Atr Fibrillation. 2013;5 (6);
4. Safaei N, Montazerghaem H, Azarfarin R, Alizadehasl A, Alikhah H. Radiofrequency ablation for treatment of atrial fibrillation. Bioimpacts. 2011;1 (3):171–7.
5. Shelke A. Broncho-Pericardial Fistula with Air Tamponade – A Rare but Lethal Condition. . EC Pulmonology and Respiratory Medicine. 2018;0:173–177.
6. Dagres N, Kottkamp H, Piorkowski C, Doll N, Mohr F, Horlitz M, Kremastinos DT, Hindricks G. Rapid detection and successful treatment of esophageal perforation after radiofrequency ablation of atrial fibrillation: lessons from five cases. J. Cardiovasc. Electrophysiol. 2006;17 (11):1213–5.
7. Pappone C, Vicedomini G, Santinelli V. Atrio-Esophageal Fistula After AF Ablation: Pathophysiology, Prevention &Treatment. J Atr Fibrillation. 2013;6 (3);
8. Desai AK, Osahan DS, Undavia MB, Nair GB. Bronchial injury post-cryoablation for atrial fibrillation. Ann Am Thorac Soc. 2015;12 (7):1103–4.
9. Verma N, Gillespie CT, Argento AC, Tomson T, Dandamudi S, Piña P, Ringwala S, Lin AC, Chicos AB, Kim S, Arora R, Passman RS, Knight BP. Bronchial effects of cryoballoon ablation for atrial fibrillation. Heart Rhythm. 2017;14 (1):12–16.

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Bronchial Injury – Yet Another Collateral Damage of Cryoablation

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Abstract

With the aging population, the burden of atrial fibrillation is increasing. Cryoablation is a novel technique for pulmonary vein isolation and is considered equally effective as radiofrequency ablation. Some of the known complications of cryoablation include phrenic nerve damage, esophageal injury, pulmonary vein stenosis, new onset atrial flutter, pericardial effusion, and stroke. We present a case of bronchial injury immediately after cryoablation for symptomatic paroxysmal atrial fibrillation. A 67-year-old woman underwent successful pulmonary vein isolation using cryoablation. Her post-operative period was complicated with cough and hemoptysis. During the procedure, she had an extra 3 minutes of freezing of the left inferior pulmonary vein. Her bronchoscopy examination showed blood and erythema in the left main bronchus. She was managed conservatively with cough suppressants and anticoagulation was stopped. Possible etiology of bronchial injury is likely cryoenergy transfer between the pulmonary veins and the bronchus due to their close anatomic proximity. With the increasing use of cryoablation for atrial fibrillation, more cases of bronchial injury will likely be reported in the future. Physicians including electrophysiologist and pulmonologists should be aware of this complication.

Introduction

In 1998 Haissaguerre et al. observed that foci of ectopic beats originating from pulmonary veins are capable of triggering atrial fibrillation (AF), which led to the basis of Pulmonary Vein Isolation (PVI) technique. [1] PVI is associated with improvement in morbidity, and quality of life when compared with medical therapy in patients with AF. In the recently published Catheter Ablation vs ANtiarrhythmic Drug Therapy in Atrial Fibrillation (CABANA) trial investigators reported that compared to drug therapy, ablation leads to significant improvement in the quality of life at 12 months. [2] PVI can be achieved by balloon cryoablation or radiofrequency ablation. The "Fire and Ice" trial showed cryoablation was non-inferior to radiofrequency ablation. [3] Routine complications like stroke, pericardial effusion and new onset atrial flutter can arise from any type of ablation procedure but cryoablation is unique to cause possible injury to nearby structures like esophagus, phrenic nerve and bronchial injury. In the "STOP AF" trial, 163 patients were followed after cryoablation for AF and cough was reported in 17% of patients with no reports of bronchial injury or hemoptysis. [4] In the "Fire and Ice" trial, out of 374 patients in the cryoablation group, cough was reported in 3 (0.8%) and hemoptysis was reported in 1 (0.3%) patients. [3] We report a case of bronchial injury which presented as hemoptysis within 2 hours of cryoablation. In addition, we also reviewed the available literature regarding bronchial injury after cryoablation and its management.

Key Words

Atrial Fibrillation, Bronchial Injury, Cryoablation, Cryoballoon Catheter Ablation, Hemoptysis.

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Case

A 67-year-old woman was referred to electrophysiology clinic for symptomatic paroxysmal AF. She was switched from diltiazem to sotalol a few months ago; However, she continued to have breakthrough episodes. Her past medical history was significant for hypertension, diabetes mellitus, tobacco use, coronary artery disease, Takotsubo cardiomyopathy, transient ischemic attack, and renal vein thrombosis. Given failed medical management a decision was made for PVI using cryoablation technique. She was taking apixaban for anticoagulation which was stopped two days before the procedure. Her echocardiogram showed a normal left ventricle function and a normal size left atrium. Physical examination was benign and laboratory studies pre-procedure were within normal limits. EKG showed normal sinus rhythm on the day of the procedure. The patient underwent successful PVI using a 28 mm cryobaloon catheter (Arctic FrontTM Cardiac Cryoballoon, Medtronic, Inc., Minneapolis, Minnesota) and NavX™ cardiac mapping system (Abbott, Chicago, IL, USA). Peri-procedural heparin was used to maintain activated clotting time (ACT) between 350-400. All four pulmonary veins (PV) showed pulmonary vein potential. Cryoablation was performed using the freeze-thaw-freeze technique, 3 + 3 minutes, for each PV. Contrast was used to verify complete occlusion of pulmonary veins with the cryoballoon before each isolation. Left inferior PV (LIPV) had an extra 3 minutes of cryoablation for complete isolation. Complete isolation was achieved only after the third freeze. The

lowest temperatures noted in the left superior PV (LSPV) were -50 °C and -51°C in two freezes and in the LIPV temperatures were -38 °C, -31 °C, and -37 °C in three freezes. All four PVs were ablated, and successful exit block was documented. The procedure was completed without any complication and heparin was reversed using protamine. The patient was extubated and transferred to the recovery room where she started complaining of a sore throat and cough. Two hours post procedure she had multiple episodes of hemoptysis. A chest CT showed left lower lobe infiltrate without any evidence of pulmonary embolism, aortic dissection or thrombosis [Figure 1]. The patient continued to have a small amount of hemoptysis. Apixaban was not restarted and aspirin was stopped. A diagnostic bronchoscopy showed a moderate amount of dark maroon blood in the left mainstem bronchus, which was completely occluding it. After the blood was suctioned away, an area of redness approximately 1 cm was seen just proximal to the origin of the left upper lobe bronchus, and no active bleeding was noted [Figure 2]. A small amount of maroon

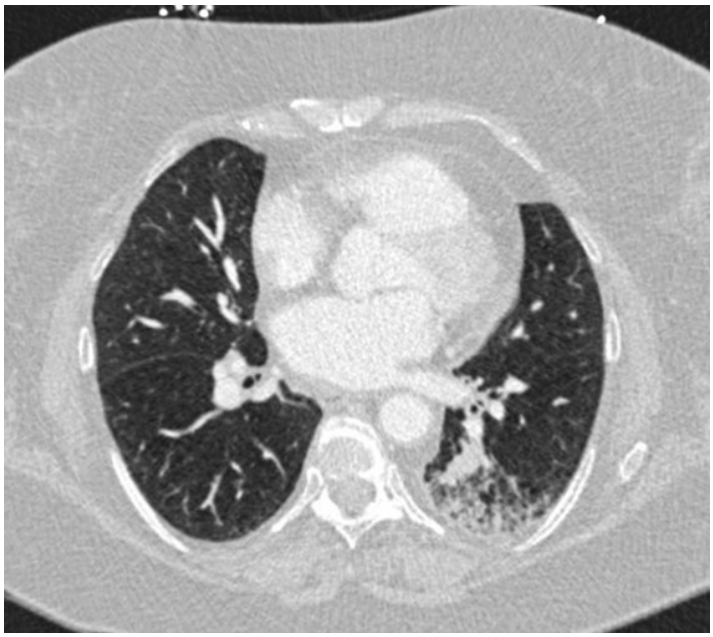

Figure 1: Illustration showing left lower lobe consolidation in Computed Topography of the chest with contrast.

colored secretion was present more distally as well as in the left lower lobe. The patient was hemodynamically stable and was managed with cough suppressants. Hemoptysis completely resolved two weeks after the initial procedure. Repeat chest CT after four weeks showed complete resolution of left lower lobe infiltrate. Aspirin was resumed once the hemoptysis stopped and anticoagulation was resumed after 4 weeks. At six months follow up the patient was asymptomatic and in sinus rhythm.

Discussion

Hemoptysis after cryoablation is a rare but can be a life-threatening complication, and so far very few cases have been reported [Table 1]. [6,11] The overall incidence is around 1.7 - 2.1% based on retrospective studies. [11,12] Reported cases of hemoptysis vary in their presentation from mild, self-limiting to massive life-threatening, causing respiratory compromise and requiring intubation. Even the time of

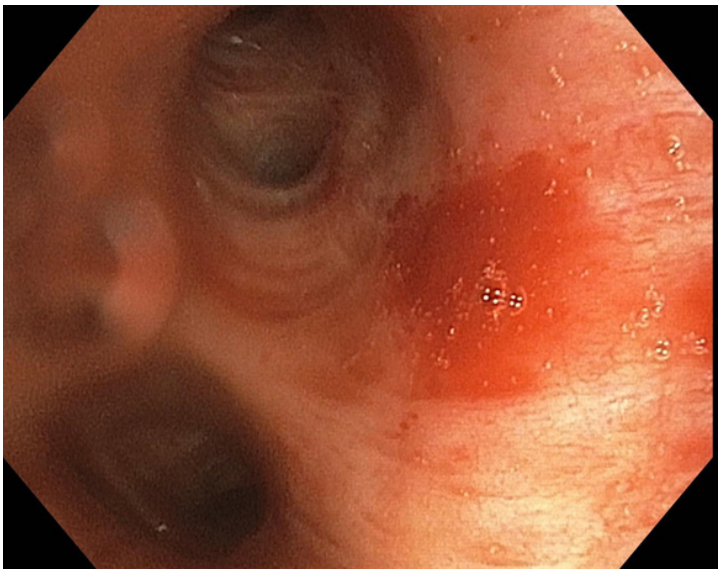

Figure 2: Bronchoscopic imaging showing erythema proximal to the origin of the left upper lobar bronchus.

onset of presentation ranges from hours to days to even months after cryoablation. Case reports of hemoptysis after radiofrequency (RF) ablation are also found in the literature. [13,14] Etiology of hemoptysis after RF ablation seems likely secondary to PV stenosis, but serious complications like atrio-bronchial fistula and communication between bronchus and pericardium have also been reported. [13,14] Overall incidence of PV stenosis after ablation is around 0.5-1.5 % and associated cases of hemoptysis are even less. [15,16] In a single center, prospective, observational study of 124 patients with PV stenosis mainly after RF ablation, the incidence of hemoptysis was reported in 27 % of patients.[17]

Previous studies have discussed the possible etiologies of hemoptysis following cryoablation, though the exact cause is still not very clear. [11] Animal studies done by Aryana et al. and review of previous studies give us some insight . Animal models suggest collateral injury and prolonged duration with low temperature as the possible culprit. [18] Initial case reports suggested PV stenosis and pulmonary infarction might be the cause but this had been refuted by CT imaging and histopathologic studies. The left and right mainstem bronchus are in close proximity with PVs making them vulnerable for injury from cryoablation. [19] Kumar et al. reviewed retrospective data of 283 patients and noted hemoptysis in 6 patients. In their study, lower temperature and deeper positioning of cryoballoon during cryoablation are possible risk factors for bronchial injury. [12] In another human study, frequent ice formation was noted in left mainstem bronchus in patients undergoing cryoablation. [20] Verma et al. performed simultaneous bronchoscopy in 10 patients undergoing cryoablation and found ice formation in 7 out of 10 patients in the left main bronchus only during LSPV isolation. They found no significant differences in minimum balloon temperature in freezes with or without ice formation. In a recent study, patients undergoing ablation with second-generation cryoballoon were followed by post-procedure bronchoscopy next day. [21] Out of 11 patients only 1 patient showed bronchial injury. In that study, they measured the distance between LSPV and LMB and the mean distance was 6.4 ±

Table 1: Individual case reports of bronchial injury after cryoablation for atrial fibrillation.

Case	Author, Year	Patient Age (y), Sex	Presentation	Time after Procedure	Site of Injury	Temperature (°C)	Duration of Cryo	Special Note
1 (6)	Van Opstal, 2011	65, M	Hemoptysis	4 Days	Division of left upper & lower bronchus	LIPV: -64	NA	Deep application in LIPV during procedure
2 (7)	Marti- Almor, 2014	55, M	Cough & Hemoptysis	24 Hours	Lingular bronchus bifurcation	LSPV: -70 LIPV: -73 RSPV: -56 RIPV: -48	2 x 300s	NA
3 (8)	Desai, 2015	29, M	Hemoptysis	Post Procedure	Left Mainstem Bronchus	Left PV: -60	150s	Rapid & sustained drop in temperature
4 (9)	Aksu, 2015	55, M	Hemoptysis	Intra-operatively	NA	LSPV: -50	NA	Imaging suggestive of Pulmonary Hemorrhage
5 (11)	Jayaschandran, 2017	59, M	Epistaxis, hemoptysis, Dyspnea & chest pressure	1 Month	Left Mainstem Bronchus	NA	NA	Life threatening hemoptysis requiring intubation
6	Rout, 2019	67, W	Cough & Hemoptysis	2 Hours	Proximal to left upper lobar bronchus	LSPV: -50 & -51 LIPV: -38, -31 & -37	LSPV: 2x 180s LIPV: 180s, 50s &180s	Three freezes to LIPV

2.7 mm. Interestingly, the distance was 2.1 mm in the patient with the bronchial injury. They also reported intraoperative coughing during the thawing phase and proposed it as a predictor of bronchial injury. [21] In our patient, symptoms started within 2 hours of procedure. The possible contributing factor for bronchial injury may have been the extra 3 minutes of cryoablation to the LIPV, though the temperatures recorded were not very low especially when compared to the temperatures in LSPV isolation.

Currently, no specific guidelines exist for prevention of bronchial injury. Review of literature provides some information, though they are mainly based on single-center experience. [19] Duration of cryotherapy and temperature play a significant role in the extent of the bronchial injury. We suggest limiting these factors as much as possible. In recent years, the concept of "less is better" has been advocated for cryoablation to reduce collateral damage in the adjacent esophagus, phrenic nerve, and bronchus. With the advent of 3rd generation cryoballoon catheter, it is possible to decrease the duration of freeze without compromising the efficacy of the procedure as shown by Pott et al. [22] Future trials need to validate whether decrease in duration will lead to improvement in safety outcomes. While we have means of avoiding phrenic nerve injury by constant pacing to monitor diaphragmatic stimulation and we also have esophageal probe to monitor intraoperative temperatures, currently no such similar techniques or tools are available to avoid bronchial injury. Physicians need to be extra vigilant in cases where longer duration or extreme temperature are seen during the procedure. A low threshold should be maintained for bronchoscopy and CT imaging with the initial onset of symptoms and this will prevent misdiagnosis and facilitate early initiation of higher level of care if required. will help prevent misdiagnosis and early initiation of intensive level of care if required. Once diagnosed, management mainly consists of cough suppressants, airway monitoring and holding anticoagulation. Repeat bronchoscopy may be warranted if symptoms fail to improve or depending on the extent of the initial injury requiring follow up.

Conflicts of Interest

The authors have no conflicts to disclose.

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Acknowledgement

None.

Conclusion

As cryoablation is getting more popular for AF ablation, it is likely that the number of cases of bronchial injury will increase. Given the close proximity of the left and right bronchus to the pulmonary veins, the bronchus is always at risk for injury. The mechanism of injury seems to be a direct collateral injury from the cryoablation. High level of suspicion for bronchial injury should be maintained in symptomatic patients. Diagnosis can be made by early imaging and bronchoscopy. is mostly conservative and close monitoring is advised.

References

1. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N. Engl. J. Med. 1998;339 (10):659–66.
2. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, Daniels MR, Bahnson TD, Poole JE, Rosenberg Y, Lee KL, Packer DL. Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. JAMA. 2019;321 (13):1275–1285.
3. Kuck KH, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KR Julian, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. N. Engl. J. Med.

2016;374 (23):2235–45.
4. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, Ruskin JN. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. J. Am. Coll. Cardiol. 2013;61 (16):1713–23.
5. van Opstal JM, Timmermans C, Blaauw Y, Pison L. Bronchial erosion and hemoptysis after pulmonary vein isolation by cryoballoon ablation. Heart Rhythm. 2011;8 (9).
6. Martí-Almor J, Jauregui-Abularach ME, Benito B, Vallès E, Bazan V, Sánchez-Font A, Vollmer I, Altaba C, Guijo MA, Hervas M, Bruguera-Cortada J. Pulmonary hemorrhage after cryoballoon ablation for pulmonary vein isolation in the treatment of atrial fibrillation. Chest. 2014;145 (1):156–157.
7. Desai AK, Osahan DS, Undavia MB, Nair GB. Bronchial injury post-cryoablation for atrial fibrillation. Ann Am Thorac Soc. 2015;12 (7):1103–4.
8. Aksu T, Ebru G, Yalin K. Haemoptysis and pulmonary haemorrhage associated with cryoballoon ablation. Europace. 2015;17 (8).
9. Kasper Ł, Gross-Sondej I, Machalica B, Soja J, Pawlik W, Sładek K. Hemoptysis and lung disease as a manifestation of pulmonary vein stenosis after cryoballoon catheter ablation for atrial fibrillation. Pol. Arch. Med. Wewn. 2016;126 (1-2):94–6.
10. Jayaschandran V, Mertens AN, Patel VK, Dalal B. Life-Threatening Massive Hemoptysis After Cryoablation for Atrial Fibrillation. J Bronchology Interv Pulmonol. 2018;25 (1):67–69.
11. Bhagwandien Rohit, Van BY, de Groot N, Jordaens L. Hemoptysis after pulmonary vein isolation with a cryoballoon: an analysis of the potential etiology. J. Cardiovasc. Electrophysiol. 2011;22 (9):1067–9.
12. Kumar N, Timmermans C, Das M, Dassen W, Philippens S, Maessen J, Crijns HJ. Hemoptysis after cryoablation for atrial fibrillation: truth or just a myth?. Chest. 2014;146 (5):e173–e175.
13. Doshi RN, Kaushal R, Cesario DA, Shivkumar K. Atriobronchial fistula formation as a devastating complication of left atrial catheter ablation for atrial fibrillation. Heart Rhythm. 2006;
14. A Sparks, JR Stewart, J Kozinn. Wimmer A Distal left main bronchial injury after catheter ablation for atrial fibrillation: Report of two cases. Cardiovasc Disord Med. . https://www.oatext.com/distal-left-main-bronchial-injury-after-catheter-ablation-for-atrial-fibrillation-report-of-two-cases.php. 2018;3.
15. Gupta A, PereraT, Ganesan A, Sullivan T, Lau DH, Roberts-Thomson KC, Brooks AG, Sanders P. Complications of catheter ablation of atrial fibrillation: a systematic review. Circ Arrhythm Electrophysiol. 2013;6 (6):1082–8.
16. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3 (1):32–8.
17. Fender EA, Widmer RJ, Hodge DO, Cooper GM, Monahan KH, Peterson LA, Holmes DR, Packer DL. Severe Pulmonary Vein Stenosis Resulting From Ablation for Atrial Fibrillation: Presentation, Management, and Clinical Outcomes. Circulation. 2016;134 (23):1812–1821.
18. Aryana A, Bowers MR, Hayatdavoudi SM, Zhang Y, Afify A, D'Avila A, O'Neill PG. Impact of Pulmonary Vein Cryoballoon Ablation on Bronchial Injury. J. Cardiovasc. Electrophysiol. 2016;27 (7):861–7.
19. Kulkarni N, Su W, Wu R. How to Prevent, Detect and Manage Complications Caused by Cryoballoon Ablation of Atrial Fibrillation. Arrhythm Electrophysiol Rev. 2018;7 (1):18–23.
20. Verma N, Gillespie CT, Argento AC, Tomson T, Dandamudi S, Piña P, Ringwala S, Lin AC, Chicos AB, Kim S, Arora R, Passman RS, Knight BP. Bronchial effects of cryoballoon ablation for atrial fibrillation. Heart Rhythm. 2017;14 (1):12–16.
21. Bellmann B, Hübner RH, Lin T, Paland M, Steiner F, Krause P, Tscholl V, Nagel P, Roser M, Suttorp N, Landmesser U, Rillig A. Bronchial Injury After Atrial Fibrillation Ablation Using the Second-Generation Cryoballoon. Circ Arrhythm Electrophysiol. 2018;11 (3).
22. Pott A, Kraft C, Stephan T, Petscher K, Rottbauer W, Dahme T. Time-to-isolation guided titration of freeze duration in 3rd generation short-tip cryoballoon pulmonary vein isolation - Comparable clinical outcome and shorter procedure duration. Int. J. Cardiol. 2018;255 ():80–84.

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Safe Delivery of Endoscopic Brachytherapy in a Patient with a Dual Chamber Pacemaker

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Abstract

In patients with advanced esophageal cancer, management of dysphagia is a challenge with significant implications on patient quality of life. Brachytherapy has been shown to be an effective and safe treatment option for symptoms related to dysphagia. The effect of endoscopic brachytherapy on patients with a cardiac implantable electronic device has not previously been described in literature.

We present an 89-year-old female with a dual chamber permanent pacemaker who elected to undergo palliative brachytherapy delivered via endoscopy for treatment of dysphagia secondary to locally advanced esophageal adenocarcinoma.

Introduction

Esophageal cancer is the seventh most common cancer worldwide [1], more than half of diagnosed patients are not surgical candidates either due to significant comorbidities or advanced cancer staging [2]. In these patients, dysphagia is a common presenting symptom associated with malnutrition, dehydration, renal failure, and increased risk of infection [3]. Intra-luminal brachytherapy is emerging as an increasingly popular treatment option due to its low complication rate, positive impact on health-related quality of life, and sustained effect on dysphagia palliation [4,5].

The effects of radiation delivered by brachytherapy on cardiac implantable electronic devices (CIEDs) are unknown. We describe a patient with a dual chamber pacemaker who received intra-luminal brachytherapy.

Case Report

An 89-year-old female with a dual chamber permanent pacemaker (St. Jude Medical 2272 Assurity, St. Jude Medical 2088TC Tendril STS leads programmed in bipolar configuration) implanted due to symptomatic tachycardia-bradycardia syndrome presented with progressive dysphagia and weight loss. On endoscopy, she was found to have a circumferential distal esophageal adenocarcinoma spanning 6 cm in length. Staging CT scan showed mild adjacent lymphadenopathy with no evidence of metastatic disease. Given her advanced age and multiple comorbidities including atrial flutter/fibrillation and diastolic heart failure, she was deemed not to be a candidate for curative surgical resection. She did not wish to have chemotherapy, and opted for palliative brachytherapy for her significant dysphagia. She was non-dependent on her pacemaker. Device programming parameters are outlined in [Table 1].

She underwent brachytherapy delivered via endoscopy over the course of two weeks, for a total of 1800 cGy over three treatment fractions with iridium-192. The distance from the first dwell position to the device was estimated to be 14 cm. On day 1 of treatment, metal oxide semiconductor field effect transistors (MOSFET) were applied to the area of the pacemaker and measured a daily dose of 6.1 cGy at the center of the device, and 7.5 cGy at the device edge closest to brachytherapy (Figure 1). The estimated total cumulative dose was 18.27 cGy at the center of the device and 22.5 cGy at the nearest device edge, or 1.0% of the treatment dose. Device interrogation was performed before the first treatment and after the last treatment, which demonstrated no evidence of device malfunction. Pacing/sensing thresholds, lead impedance and battery life expectancy before and after brachytherapy are outlined in [Table 2]. No over-sensed events were found, and the patient remained asymptomatic throughout treatment with no signs of syncope, presyncope, palpitations or chest pain. The patient had excellent response at the one-month follow-up post-treatment, with complete resolution of her dysphagia.

Discussion

We have described the safe usage of palliative intra-luminal brachytherapy for the treatment of dysphagia in a patient with a dual chamber permanent pacemaker, with no evidence of device malfunction. We estimate that the patient's device received a total cumulative dose of less than 25 cGy. In those who are pacing independent, a total cumulative radiation dose of less than 2 Gy is low risk for pacemaker dysfunction [6].

Key Words

Brachytherapy, Cardiac Implantable Electronic Devices (CIED), Pacemaker (PM).

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Table 1: Dual chamber pacemaker programmed parameters.

Mode	**DDDR**
Lower Rate	**60 bpm**
Higher Rate	**130 bpm**
Sensed AV delay	**225 ms**
Paced AV delay	**250 ms**
Capture duration	
Atrial	**0.4 ms**
Ventricular	**0.4 ms**
Percent pacing	
Right atrial	**14 %**
Ventricular	**5.3 %**

Abbreviations: bpm = beats per minute, ms = milliseconds

Table 2: Device interrogation parameters before and after brachytherapy.

	Before Brachytherapy	After Brachytherapy
Sensing amplitude		
Atrial	**1.3 mV**	**2.7 mV**
Ventricular	**6.8 mV**	**10.3 mV**
Pacing Threshold		
Atrial	**0.75 V**	**0.5 V**
Ventricular	**1.0 V**	**0.75 V**
Lead impedance		
Atrial	**362 Ω**	**350 Ω**
Ventricular	**487 Ω**	**362 Ω**
Remaining longevity	**9.2-10.3 years**	**8.5-9.3 years**

Abbreviations: V = volts, mV = millivolts, Ω = ohms

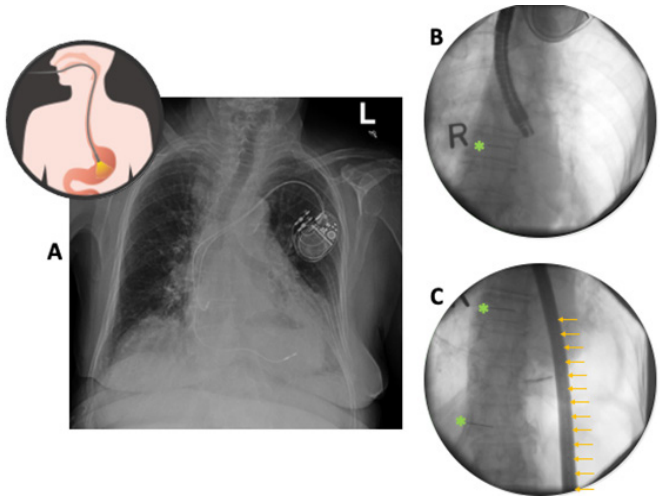

Figure 1: A. Endoscopic brachytherapy in a patient with a pacemaker. B. Insertion of endoscope to the esophageal tumour burden. C. Aligning brachytherapy seeds with radiation treatment area.

Green * = markers for distal and proximal limits of radiation treatment area in esophagus. Yellow arrows = brachytherapy seeds.

Brachytherapy remains an underutilized resource, perhaps due to limited availability of expertise. As there is growing awareness of esophageal stent-related complications in recent years[7], brachytherapy may be an increasingly popular alternative for management of dysphagia in esophageal cancer.

Similarly affected by the aging population, CIEDs are increasingly indicated in elderly patients [8]. Potential device malfunctions secondary to radiotherapy include over and under sensing, failure to capture, device mode reset, memory loss, battery depletion or complete device failure [9]. In comparison to direct external beam radiation, the effects of brachytherapy on devices are largely secondary to scatter radiation and electromagnetic interference. It is thought that scatter photon particles may cause excess electron-hole pairs in the silicon dioxide insulator causing accumulation of a net positive charge. The effect of scatter radiation on CIEDs is unclear, though small radiation doses (>2 Gy) are unlikely to result in predictable malfunction [10]. While the incidence of CIED complications due to radiotherapy is low, the rising population of patients with CIEDs requiring radiotherapy brings to attention the need for universal, evidence-based guidelines for the management of such patients[6]. A structured multidisciplinary approach involving collaboration between radiation oncology and cardiology is essential to minimize the incidence of device malfunction [11].

Conclusion

Palliative brachytherapy is likely safe for the management of dysphagia secondary to esophageal cancer in patients with CIEDs. However, further studies are required to better characterize the effect of brachytherapy on such devices..

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68 (6):394–424.
2. Enzinger PC, Mayer RJ. Esophageal cancer. N. Engl. J. Med. 2003;349 (23):2241–52.
3. Raber-Durlacher JE, Brennan MT, Verdonck-de LM, Gibson RJ, Eilers JG, Waltimo T, Bots CP, Michelet M, Sollecito TP, Rouleau TS, Sewnaik A, Bensadoun RJ, Fliedner MC, Silverman S, Spijkervet FKL. Swallowing dysfunction in cancer patients. Support Care Cancer. 2012;20 (3):433–43.
4. van der Bogt RD, Vermeulen BD, Reijm AN, Siersema PD, SpaanderM CW. Palliation of dysphagia. Best Pract Res Clin Gastroenterol. 2018;36-37 ():97–103.
5. Fuccio L, Mandolesi D, Farioli A, Hassan C, Frazzoni L, Guido A, de Bortoli N, Cilla S, Pierantoni C, Violante FS, Bazzoli F, Repici A, Morganti AG. Brachytherapy for the palliation of dysphagia owing to esophageal cancer: A systematic review and meta-analysis of prospective studies. Radiother Oncol. 2017;122 (3):332–339.
6. Yeung C, Chacko S, Glover B, Campbell D, Crystal E, Ben-Dov N, Baranchuk A. Radiotherapy for Patients with Cardiovascular Implantable Electronic Devices: A Review. Can J Cardiol. 2018;34 (3):244–251.
7. Reijm AN, Didden P, Schelling SJC, Siersema PD, Bruno MJ, Spaander MC W. Self-expandable metal stent placement for malignant esophageal strictures - changes in clinical outcomes over time. Endoscopy. 2019;51 (1):18–29.
8. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009--a World Society of Arrhythmia's project. Pacing Clin Electrophysiol. 2011;34 (8):1013–27.
9. Last A. Radiotherapy in patients with cardiac pacemakers. Br J Radiol. 1998;71 (841):4–10. [PubMed]
10. Kapa S, Fong L, Blackwell CR, Herman MG, Schomberg PJ, Hayes DL. Effects of scatter radiation on ICD and CRT function. Pacing Clin Electrophysiol. 2008;31 (6):727–32.
11. Yeung C, Hazim B, Campbell D, Gooding J, LiShirley Xl, Tam HK, Hopman WM, Chacko S, Redfearn DP, Simpson C, Abdollah H, Baranchuk A. Radiotherapy for patients with cardiovascular implantable electronic devices: an 11-year experience. J Interv Card Electrophysiol. 2019;55 (3):333–341.

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Atrial Fibrillation and Atrial Flutter Ablation – an Unconventional Approach

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Abstract

Background: Radiofrequency cathether ablation (RFCA) of Atrial Fibrillation (AFib) and typical atrial flutter (AF) is traditionally performed via femoral vein approach and all devices are designed to be delivered via inferior access. In rare cases of congenital or iatrogenic obstruction of inferior vena cava (IVC), RFCA of arrhythmias is performed via transhepatic approach.

Case report: 87 year old male patient with history of IVC filter placement for recurrent deep venous thrombosis and AFib on amiodarone developed symptoms with worsening Afib burden resulting in deterioration of left ventricular ejection fraction.

Due to highly symptomatic pharmacological uncontrolled AFib, RFCA was decided in order to achieve long term success in restoring normal sinus rhythm. Transesophageal echocardiography on the day of procedure excluded clot or thrombus. Right femoral vein cannulation was performed, but advancing the guidewire through the IVC was extremely difficult. Peripheral venography revealed complete occlusion of the venous system with no flow through the IVC filter.

We present you a case report of pulmonary vein isolation succesfully performed via the left sublcavian.

Conclusion: To the best of our knowledge, this is the first case report of the following: (a) successful transseptal puncture in a patient with persistent AFib and complete iatrogenic obstruction of the IVC using a Baylis wire through superior access without any complications, (b) PVI and typical AF ablation via superior approach using a bidirectional contact sensing ablation catheter; monitoring of the contact force in this case being extremely practical and (c) use of Vascade sheath for closure of the left axillary vein.

Introduction

Radiofrequency Ablation (RFA) has become a well-recognized non-pharmacological treatment strategy for many cardiac arrhythmias [1] because of a high success rate and low risk of complications. RFA is recommended as first-line therapy in patients with paroxysmal or persistent AF with minimal structural heart disease [2].

Atrial Fibrillation (AFib) is the most common chronic rhythm disorder encountered in clinical practice [3]. Besides being often symptomatic due to high ventricular rates, it is responsible for functional limitation and cardiomyopathy induced by tachycardia [4]. In 1996, the Bordeaux group [5] noted that AFib is initiated by rapidly firing triggers located in the pulmonary veins. Pulmonary vein isolation (PVI) via catheter ablation via femoral approach is a widely applied technique.

Typical Atrial Flutter (AF) is generated by a large, counterclockwise reentry circuit in the right atrium and can be successfully eliminated by RFA of cavotricuspidisthmus (CTI) area which is slowly conducting. The success rate was shown to be more than 90% and the recurrence rate was less than 10% when complete block of the isthmus was achieved [6].

These procedures are typically performed via femoral vein approach and all devices are designed to be delivered via inferior access [7]. In rare cases of congenital or iatrogenic obstruction of inferior vena cava (IVC), RFA of arrhythmias are performed through a transhepatic approach.

Case Report

We present a case report of PVI and Posterior Wall Isolation performed via the left subclavian access. A 87 year old male patient with a history of recurrent AFib, coronary artery disease (CAD), IVC filter placement for recurrent deep venous thrombosis, essential hypertension (HTN) and cardiomyopathy (ejection fraction (EF)=40%) delete who was referred for an EP consult. Despite being on amiodarone, the patient developed symptomatic, persistent AFib (limitation in daily activities) with worsening AFib burden resulting in deterioration of left ventricular left ventricular EF. ECG recordings

Key Words

Atrial Fibrillation, Superior Vena Cava approach, Ablation, Atrial Flutter.

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during the office visit revealed AFib with aberrant conduction as supported by previous Holter monitoring.

The patient was scheduled for transesophageal echocardiography (TEE) cardioversion on amiodarone, but he spontaneously converted into normal sinus rhythm (NSR) and his symptoms improved. He continued to have bouts of breakthrough AFib and hence was referred to us for ablation.

Due to highly symptomatic pharmacological uncontrolled AFib, RFA was decided in order to achieve long term success in restoring NSR.TEE on the day of procedure excluded clot or thrombus. Right femoral vein cannulation with modified Seldinger technique was performed, but advancing the guidewire through the IVC was extremely difficult. Peripheral venography revealed complete occlusion of the venous system with no flow through the IVC filter. We discussed the options we had with the patient's family: transhepatic

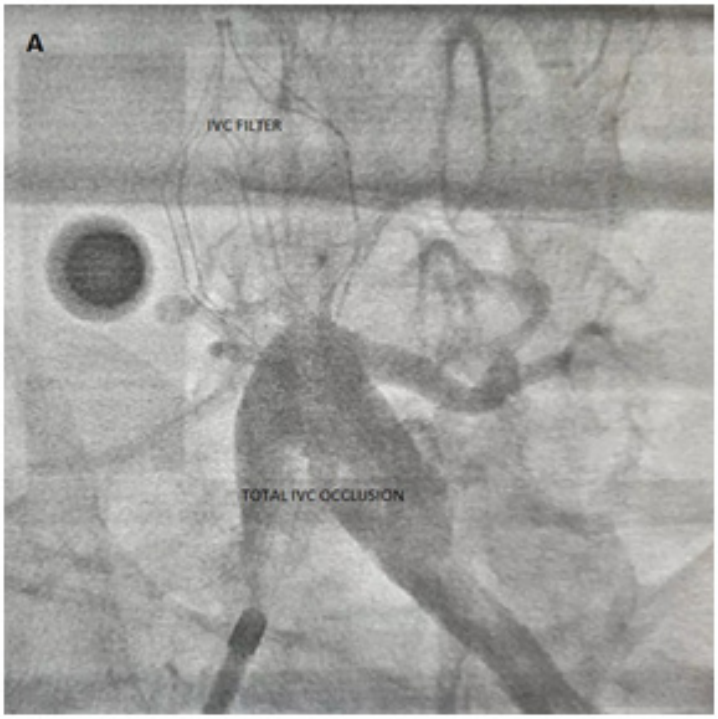

Figure 1: Peripheral venography revealed no flow through the IVC filter

access, subclavian access or referral for epicardial approach.

Taking into consideration that our patient was in therapeutic INR (for transhepatic approach the INR is vital to be within normal range) and, furthermore, that the patient's family required the procedure to be done as scheduled, it was decided to move forward with right subclavian access through which a deflectable catheter was advanced and positioned in the coronary sinus (CS) for left atrial (LA) pacing and recording purposes. Left subclavian venous access was found to be appropriate after peripheral venography. Left axillary vein was cannulated and a 10-French sheath and an Agilis sheath were advanced and positioned. Intra-cardiac Echo (ICE) catheter was advanced and positioned. Intravenous heparin bolus (100U/kg) was given to maintain active clotting time (ACT) between 250-300. ICE images were reversed (superior to inferior) in order to visualize the septum as coming from the IVC. We advanced a Baylis needle into the Agilis sheath. As we would advance the needle, the sheath would fall off the septum despite curve changes. Since extreme difficulty was faced to maintain the needle at the septum, we decided to use the Baylis wire instead of the needle. The Baylis wire was placed the septum and the transseptal puncture was performed. The puncture site was relatively superior on the septum. A 0.035mm caliber wire was advanced through the transseptal puncture site. It was difficult to get the dilator and the Agilis sheath across the septum so we exchanged the Agilus with the SL1, which was unfruitful too. The SL1 was replaced with a Vizigo sheath.

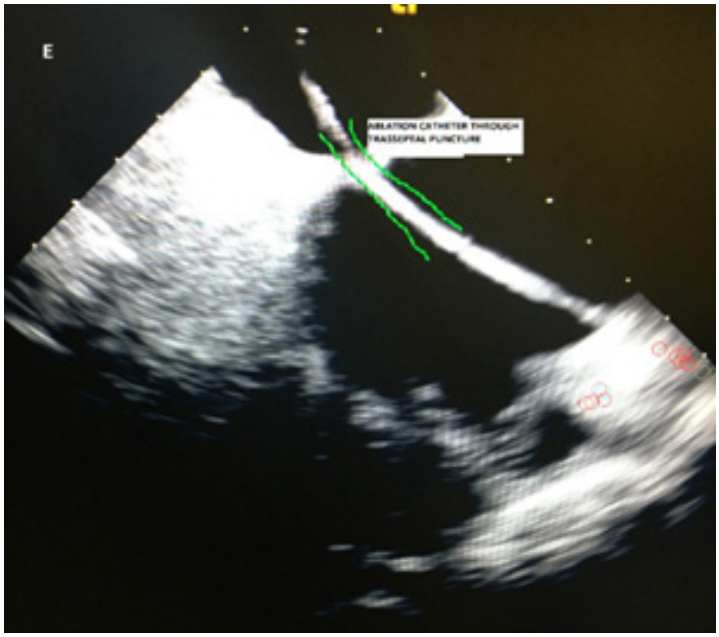

Figure 2: ICE image showing the bidirectional Ablation Catheter through the transseptal puncture.

Positioning the Vizigo Sheath right at the septum proved to be successful, following which a bidirectional ablation catheter was used to create a map (with Carto mapping system) of the LA. Following movement of the ablation catheter, patient developed AF, which appeared typical with proximal to distal activation. Patient was cardioverted to maintain stability during mapping. Superior and inferior pulmonary veins and the LA appendage were identified. Once the activated coagulation time was noted to be therapeutic, left superior and inferior pulmonary veins were isolated in pairs followed by the Right Superior and Inferior Pulmonary Veins. Fractionated electrograms and abnormal voltages were noted on the posterior wall during LA mapping; hence a posterior box isolation was done as well. Since the Vizigo sheath was right at the septum a circular catheter could not be advanced to confirm exit block. Pacing around every ablation lesion to ensure loss of capture was done followed by Adenosine testing.

Since the patient had developed Isthmus-dependent AF, the sheath was pulled back to the RA and under ICE guidance was positioned at the CTI. The bidirectional contact sensing ablation catheter was dropped at the CTI and ablation lesions extended from the tricuspid valve all the way to the IVC.

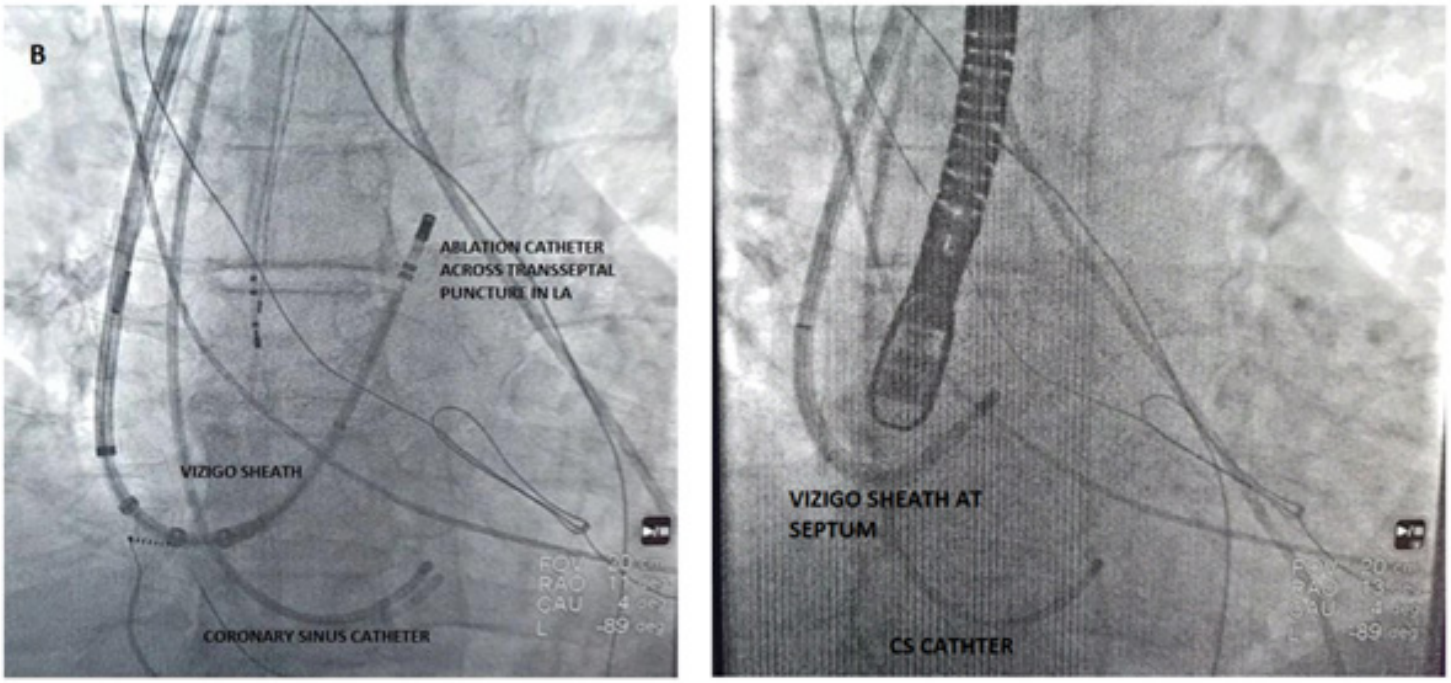

Figure 3: Fluoroscopic images showing placement of the catheters.

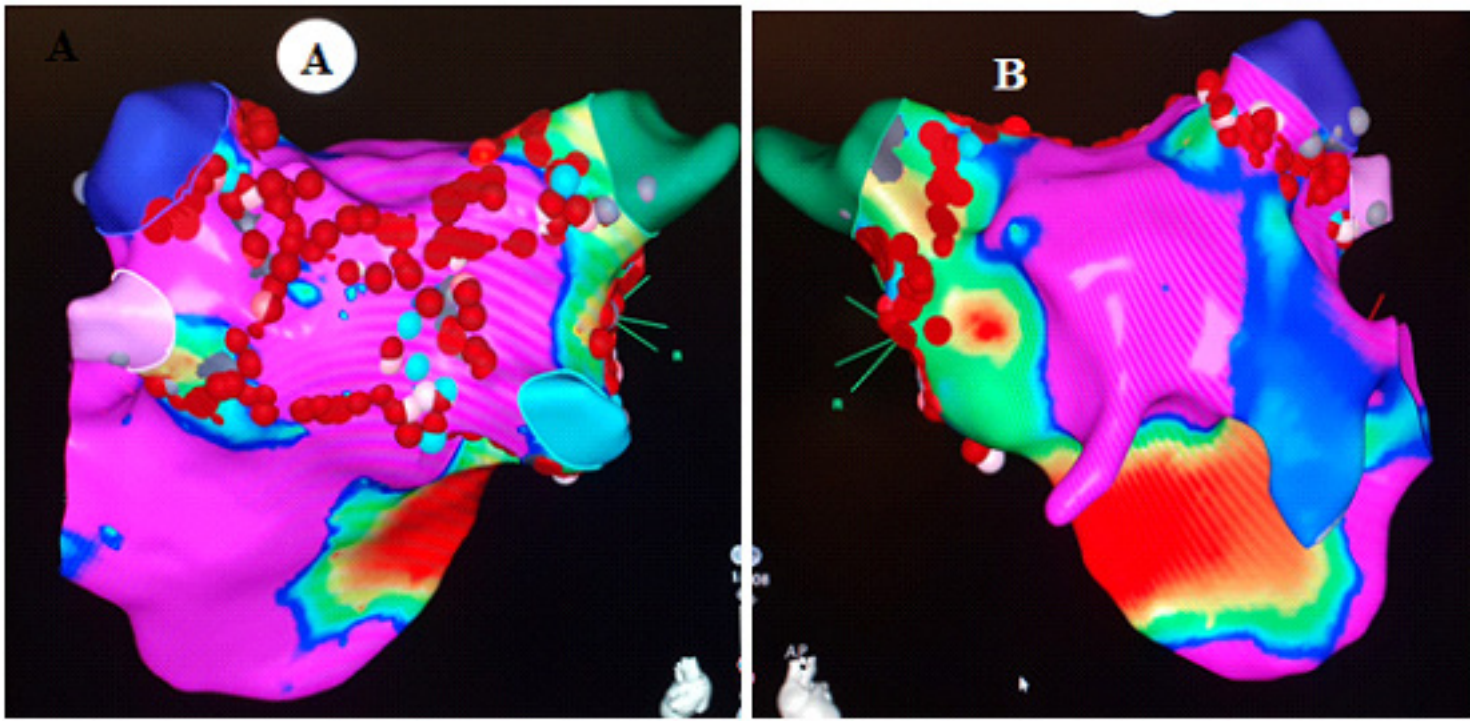

Figure 4: Electroanatomical mapping (Carto ® system) A. postero-anterior view showing PVI lines and the posterior box B. antero-posterior view

Differential pacing was performed on either side of the CTI with confirmation of bidirectional line of block. Attempts to induce recurrent tachycardia with burst pacing were unsuccessful.

After confirmation of absence of any pericardial effusion, protamine was given to reverse anticoagulation. Patient was placed under observation for two days. Post-operative period was uneventful with no recurrence of tachycardia. Patient was discharged and the two month follow-up revealed no complains or complications and the patient maintained NSR.

Discussion

Interruption of the IVC due to congenital malformations or prior therapeutic procedures is a rare clinical scenario encountered during RFA of arrhythmias and represents an impediment to access the heart via traditional femoral approach. Alternative access strategies

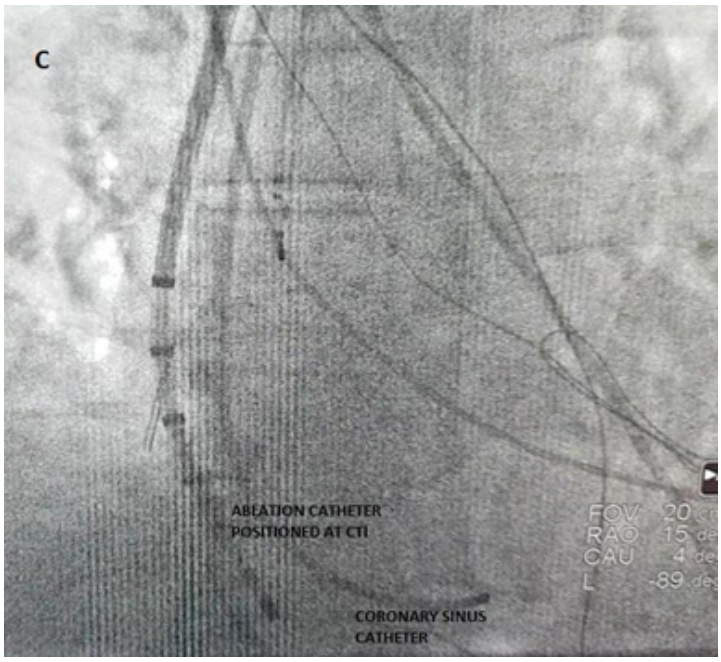

Figure 5: Fluoroscopic view of ablation catheter placement at CTI

have been outlined: Transhepatic IVC access, SVC access and the epicardial approach. [8,9] but all of them brought alongside new challenges. Need for multiple access sites for catheter placement, scarce experience with catheter manipulation, lack of stability while positioning the sheath at the transseptal puncture site and maintaining the optimal contact force during RFA are the main challenges that need to be circumvented during the superior access.

We took into consideration the transhepatic access which provides similar degrees of maneuverability and catheter manipulation as through the femoral approach [10], but it mandates INR to be within normal values. Due to limitations of our patient being in therapeutic INR, we proceeded with the SVC approach via left axillary vein.

Prime requirements included: multiple access sites for ICE placement, CS catheter, Agilis sheath (initially) and Vizigo sheath. RIJ Vein and left axillary vein were cannulated. Left subclavian vein cannulation was preferred over right subclavian vein (RSV) bearing in mind that none of the procedure instruments were designed for superior approach. Via RSV access we would need to double curve the Agilis sheath and Baylis wire in order to position them at the septum for the transseptal puncture.

Reversal of ICE images proved to be crucial during the procedure since it facilitated the visualization of the interatrial septum and LA as seen during the standard procedure via IVC approach.

Maintaining the stability of the sheath at the transeptal site while advancing the Baylis needle was difficult, as the sheath would get displaced inferiorly towards the RV/RVOT despite repeated attempts. Hence, we switched the Baylis needle with a Baylis wire for transeptal puncture. The Baylis wire has a diameter of 0.025 inch/0.635 mm; as a consequence the transseptal puncture was not wide enough for the dilator, the Agilis sheath or even the SL1 sheath to pass. Serial dilatation with larger French sheaths to finally position the Vizigo sheath at the transeptal site through which the bidirectional ablation catheter was advanced into the LA for mapping and RFCA.

All the available instruments, the Agilis sheath and Baylis needle, are curved and designed for transseptal puncture through IVC with limited degrees of maneuverability and catheter manipulation through the superior access. The Vizigo sheath was placed right at the septum maintaining appropriate contact force during RFA to ensure transmural lesions of adequate size is yet another concern during the course of the procedure. In our case, 10g of contact force was maintained on an average. This was confirmed using cartosound (ICE).

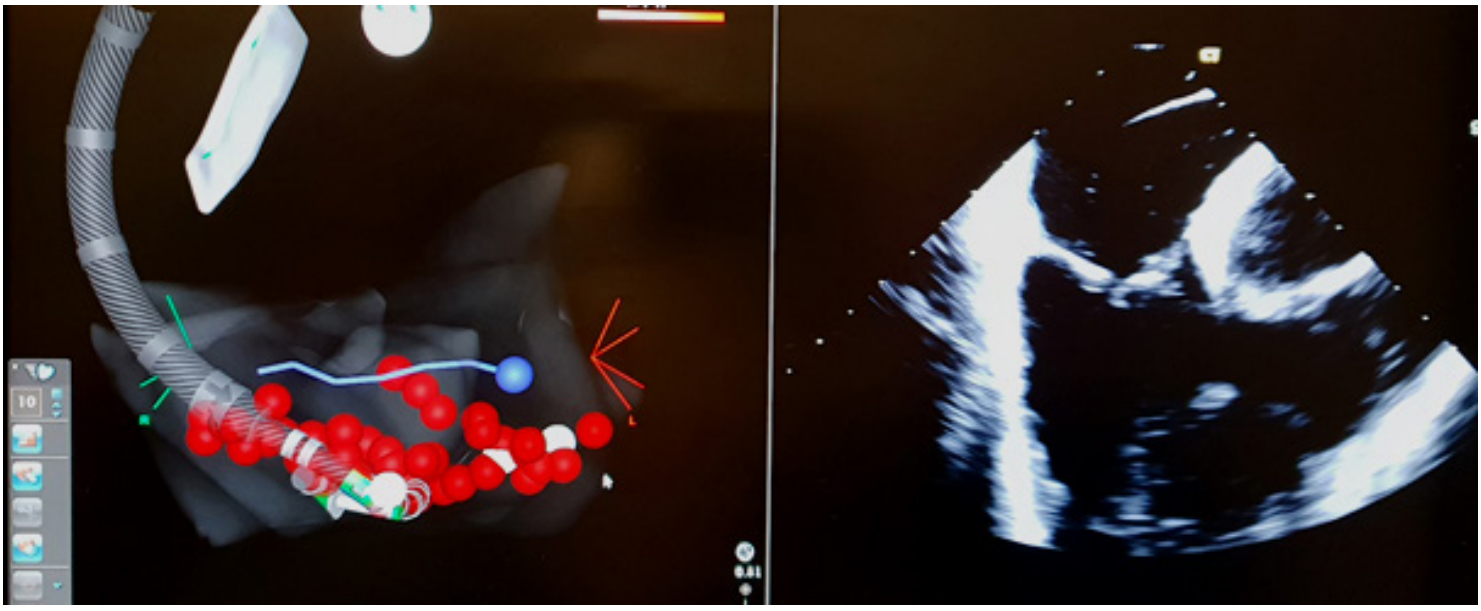

Figure 6: Left – CTI Ablation and testing of bidirectional line of block. Right- CTI as visulised on ICE.

After PVI, , ablation catheter placement at the CTI for the AF ablation was quite easy.

The subclavian vein approach provides less compressible site for haemostasis, therefore the closure of the access in patients with therapeutic INR is a serious concern in order to prevent hemorrhage and hematoma formation. Hence, two vascade sheaths were placed in the left axillary vein to successfully secure haemostasis.

Conclusion

To the best of our knowledge, this is the First case report of : (a) successful transseptal puncture in a patient with persistent AFib and complete iatrogenic obstruction of the IVC using a Baylis wire through superior access without any complications, (b) PVI and typical AF ablation via superior approach using a bidirectional contact sensing ablation catheter; monitoring of the contact force in this case being extremely practical and (c) use of Vascade sheath for closure of the left axillary vein.

References

1. Joseph JP, Rajappan K. Radiofrequency ablation of cardiac arrhythmias: past, present and future. QJM. 2012;105 (4):303–14.
2. Kirchhof P, Calkins H. Catheter ablation in patients with persistent atrial fibrillation. Eur. Heart J. 2017;38 (1):20–26.
3. Wyndham CR. Atrial fibrillation: the most common arrhythmia. Tex Heart Inst J. 2000;27 (3):257–67.
4. Grogan M, Smith HC, Gersh BJ, Wood DL. Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. Am. J. Cardiol. 1992;69 (19):1570–3.
5. Nair GM, Nery PB, Diwakaramenon S, Healey JS, Connolly SJ, Morillo CA. A systematic review of randomized trials comparing radiofrequency ablation with antiarrhythmic medications in patients with atrial fibrillation. J. Cardiovasc. Electrophysiol. 2009;20 (2):138–44.
6. Morady F. Radio-frequency ablation as treatment for cardiac arrhythmias. N. Engl. J. Med. 1999;340 (7):534–44.
7. Lim HE, Pak HN, Tse HF, Lau CP, Hwang C, Kim YH. Catheter ablation of atrial fibrillation via superior approach in patients with interruption of the inferior vena cava. Heart Rhythm. 2009;6 (2):174–9.
8. Lim HE, Pak HN, Tse HF, Lau CP, Hwang C, Kim YH. Catheter ablation of atrial fibrillation via superior approach in patients with interruption of the inferior vena cava. Heart Rhythm. 2009;6 (2):174–9.
9. Rajappan K, Sporton SC, Schilling RJ. Left atrial tachycardia and inferior vena cava thrombotic occlusion complicating atrial fibrillation ablation successfully treated from the right subclavian vein. Heart. 2007;93 (1).
10. Nguyen DT, Gupta R, Kay J, Fagan T, Lowery C, Collins KK, Sauer WH. Percutaneous transhepatic access for catheter ablation of cardiac arrhythmias. Europace. 2013;15 (4):494–500.

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Pulse and Gap in Greek Medicine History

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Abstract

We read and enjoyed the paper entitled "Avicenna and Tremor of the Heart" by Ghahramani et al., which expressed the viewpoints of Avicenna, which was expressed unique subjects. But there are some contradictions with our findings which list as below

Dhanvantari was not a physician, but was of the Hindu gods; nadi in Sanskrit is derived from the word ney, referring to hollow paths. On the other hand, Nadi-ha is an equivalent of the pulse, but Nadi has been popular for several hundreds of years; Accordingly, there is no trace of a book written by Dhanvantari in the books translated from Hindi to Arabic during the translation movement, Rafus of Ephesus (70-110 A.D.) had the earliest writing about pulse, and Galen (129-210 A.D.) was not the first to provide a book concerning the pulse.

Also, there was a severe breakdown in Greek medicine concerning the concept of the pulse, according to absence of pulse concept in Hippocrates works.

Dear Editor-in-Chief

We read and enjoyed the paper entitled "Avicenna and Tremor of the Heart" by Ghahramani et al., which expressed the viewpoints of Avicenna about the heart and pulse [1]. "Dhanvantari" was cited as a physician of the fifth century B.C. and the first physician to apply a checkup method using the pulse in some cardiac disorders.

Moreover, the article points out that Avicenna learned the knowledge of pulse from Galen and Dhanvantari. It was also described that Galen had introduced the heart pulse a few years after Dhanvantari did, allowing to infer that Galen was the earliest physician to refer to the issue of the pulse in ancient Greece or Rome.

According to our studies on the identity of Dhanvantari in the book Secrets of the Pulse: The Ancient Art of Ayurvedic Pulse Diagnosis, one of the references used in the article mentioned above, it is noted that:

… Dhanvantari, one who uses prana and higher states of consciousness for healing. For thousands of years the vedic literature has used the word nadi as a common word for pulse and is the most popular word for pluse throughout the healing system of Ayurveda [2].

Key Words
Pulse, Avicenna, Greek medicine.

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Additionally, it seems that Dhanvantari was one of the Hindu gods [3], not a physician.

Using this part of the book mentioned above, the author of the paper might have considered the word nadi equivalent to pulse. However, it should be noted that the word nadi in Sanskrit is derived from the word ney, referring to hollow paths. On the other hand, Nadi-ha is an equivalent of the pulse, as used in the book Secretes of the Pulse, and Nadi has been popular for several hundreds of years. The word virijananam means cognition, and the term nadi-virijananam means knowing paths through which the wind passes [4]. Therefore, it is not reasonable that, in the Vedic period, when Dhanvantari was praised as the god of medicine, nadi-virijananam would have been used to mean the recognition of the radial pulse. Pulse examination is not mentioned in the classical Ayurvedic texts [5].

Accordingly, there is no trace of a book written by Dhanvantari in the books translated from Hindi to Arabic during the translation movement. Citations are made to 12 Indian physicians in the texts remaining from the time of the relationship between Indian medicine and Islamic medicine: Canakya, Sushruta, Caraka, Astangahrdaya, Madhava, Vrnda, Manica, Salih Bin Behletül, Bahlindad, Shribhar gudate, Kanakah, and śāntah [6]. The name of Dhanvantari is not present in any text remaining from that time. For the same reason, it is unlikely that the writings of Dhanvantari have influenced Avicenna; especially, in the text of Avicenna's Canon, there is no trace of a word equivalent to Dhanvantari or the like.

It is necessary to note that Galen (129-210 A.D.) was not the first to provide a book concerning the pulse. Rafus of Ephesus (70-110 A.D.) had written a work about pulse, which survives to this day [7].

Although the issue of the pulse has been pointed out by Alcmaeon of Croton (5th century B.C.) during the golden era of ancient Greece, this issue is one of the historical unknowns [8]. However, in the works of Hippocrates, no trace is observable of the concept of the pulse [9]. The gap extends to the ancient Rome where Rafus indicated in his book that there was a severe breakdown in Greek medicine concerning the concept of the pulse, explaining that the notion had not yet been adequately explored.

References

1. Ghahramani M, Ruzieh M. Avicenna and Tremor of the Heart. J Atr Fibrillation. 2018;11 (2).
2. V Lad. Secrets of the Pulse: the ancient Art of Ayurvedic Pulse Diagnosis. 2006;
3. LH Gray. The Indian God Dhanvantari. Journal of the American Oriental Society .1922;42:323–337.
4. G Mazars. A concise introduction to Indian medicine, Motilal Banarsidass Publishe. 2006;
5. BV Subbarayappa. Medicine and life sciences in India. Munshirm Manoharlal. 2001;
6. F Sezgin. history of science and technology in the Islamic world(third volume). Frankfurt: Wolfgang Goethe Univercity. 2010;
7. Mahlooji K. Comments on the letter to the editor by Farjadmand et al., on "Galen's book on sphygmology" [Int. J. Cardiol. 221 (2016) 333-334]. Int. J. Cardiol. 2017;229 ();
8. Celesia GG. Alcmaeon of Croton's observations on health, brain, mind, and soul. J Hist Neurosci. 2012;21 (4):409–26.
9. S Kuriyama. New York: The expressiveness of the body and the divergence of Greek and Chinese medicine. www.surveymonkey.com/mp/audience. 1999;

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Dr. Airaksinen works as Professor of Cardiology in University of Turku and as Director of Heart center in Turku University Hospital,Turku, Finland. His main research interests are atrial fibrillation and anticoagulation plus antithrombotic treatment during cardiac interventions.

Dr. Samuel J. Asirvatham, MD, FACC, FHRS

Attended Christian Medical College in Vellore, Tamil Nadu, India, followed by internship at Columbia University Hospital in New York City. Dr. Asirvatham was chief resident at the University of Wisconsin in Madison and completed fellowships at the University of Oklahoma Health Sciences Center in Oklahoma City and Mayo Graduate School of Medicine at Mayo Clinic in Rochester, Minnesota. He is currently professor of Medicine and vice chair of the Division of Cardiology (Innovations) in the Department of Medicine and a consultant in Cardiac Electrophysiology in the Department of Pediatric Cardiology, Division of Pediatric and Adolescent Medicine. Currently, Dr. Asirvatham is also Program Director for the Clinical Cardiac Electrophysiology Training Program at Mayo Clinic - Rochester.

Dr. Andre d'Avila, MD , PhD

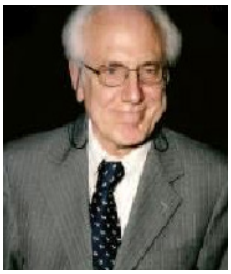
Dr. d'Avila served as an Assistant Physician at University of Sao Paulo at the Cardiac Arrhythmia Services of University of Sao Paulo and at Massachusetts General Hospital, and as Co-Director of the Cardiac Arrhythmia Service at University of Miami and at Mount Sinai Hospital in NY. He is currently serving as the Director of the Arrhythmia Service at Hospital Cardiologico Florianopolis, Brazil, as Associate Professor of Medicine at Mount Sinai Medical School and as Visiting Professor at University of Coimbra, Portugal. His main research interest is focused on AF and VT ablation especially on the role of epicardial ablation having published over 200 original scientific contributions and 18 book chapters.

Dr. Raffaele Corbisiero, MD, FACC

Dr. Raffaele Corbisiero is the Chair of Pacing and Electrophysiology and Director of the Electromechanical Therapy Institute at Deborah Heart and Lung Center in Browns Mills NJ. He received specialty training in interventional cardiology at New York Medical College, and Electrophysiology training at Baystate Medical Center, western campus of Tufts. His research efforts include implantable defibrillators, cardiac resynchronization, and pacemakers and has published in multiple journals. He recently participated on an international panel on heart failure and CRT therapy

Dr. Prashanthan Sanders, MBBS, PhD

Professor Prash Sanders is Director of the Centre for Heart Rhythm Disorders at the South Australian Health and Medical Research Institute (SAHMRI), University of Adelaide and Royal Adelaide Hospital in Adelaide, Australia. He undertook electrophysiology training in Melbourne and Bordeaux before establishing his own group. He now leads a team of clinicians, researcher and students with a focus on all aspects of understanding and treating atrial fibrillation.



Dr. Antonio Fasano, MD

Antonio Fasano is a physicist, Professor Emeritus at the University of Florence, Italy, and a member of the National "Lincei" Academy in Rome. After his retirement, in 2011, he took on the position of Scientific Manager and Director of the R&D Department of the Company FIAB, based in Vicchio (Florence). He has developed models in a variety of fields (chemistry, food industry, oil industry, glass industry, material sciences, water management, monuments preservation, volcanology, etc.) and most recently in Medicine (hematology, angiology, tumor growth, dialysis, electrophysiology). For further details Please visit: http://web.math.unifi.it/users/fasano/home.html

Dr. Yasuo Okumura MD

Associate Professor, Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

Dr. Jonathan Beaudoin , MD

Dr Jonathan Beaudoin is a cardiologist at Quebec Heart and Lung Institute, and assistant professor in medicine at Laval University, Quebec, Canada. Clinical and research interests include multimodality cardiac imaging, cardiovascular physiology and valvular heart disease.

Dr. Damian Redfearn , MD

Dr Damian Redfearn was recruited to Queen's University in Kingston, Ontario in 2006 and was appointed Director of the Heart Rhythm Service in 2007. He has overseen the growth of the electrophysiology program at Kingston General Hospital with the addition of complex ablation and the delivery of a full spectrum of electrophysiology services and procedures to the south eastern Ontario region. Dr Redfearn is a clinician scientist with a special interest in applied computer science holds several peer reviewed research grants to investigate the mechanisms of atrial fibrillation and ventricular arrhythmia through advanced signal processing.

Dr. Avishag Laish-Farkash, MD, PhD

Dr. Laish-Farkash is an electrophysiologist at Rambam Medical Campus in Haifa and a lecturer at Ben-Gurion University of the Negev in Israel. A graduate of Tel Aviv University, she completed a residency in internal medicine and Cardiology at Sheba Medical Center in Israel and fellowship in Electrophysiology at Sunnybrook Health Science Center, University of Toronto, ON, Canada. She has a PhD degree in basic electrophysiology from the Sackler Faculty of Medicine, Tel-Aviv University in Israel.

Dr. Ayman Morttada Abd ElMoteleb Mohamed

Dr. Ayman Morttada Abd ElMoteleb Mohamed,Assisstant professor of Cardioloy,,Intervention cardiologist and electrophsiologist, Ain Shams University