

Atrial branch coronary artery stenosis as a mechanism for atrial fibrillation



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BACKGROUND The etiology of atrial fibrillation (AF) is multifactorial and incompletely understood.

OBJECTIVE The purpose of this study was to evaluate the association between coronary artery disease (CAD) affecting atrial tissue and AF.

METHODS Patients from a single center with obstructive CAD during cardiac catheterization (January 1, 2007, through December 1, 2013) were included in a matched case-control analysis on the basis of the presence or absence of new-onset AF within 12 months of catheterization. Quantitative measurements of stenosis severity were performed for the sinoatrial nodal artery, atrioventricular (AV) nodal artery, and right intermediate atrial artery (RIAA) as well as the right coronary, left circumflex, and left anterior descending proximal to the takeoff for each atrial level artery. A multivariable logistic regression model identified factors associated with AF.

RESULTS Of 1794 patients, 115 (6%) developed AF within 1 year of catheterization. The matched cohort included 110 patients with and

110 patients without AF within 12 months of catheterization. Higher odds of AF at 1 year were associated with increasing lesion stenosis severity in the RIAA (odds ratio [OR] 1.41 per 10% increase in lesion severity above 50%; 95% confidence interval [CI] 1.01–1.97; $P = .047$) and AV nodal artery (OR 1.58 per 10% increase in lesion severity above 50%; 95% CI 1.00–2.49; $P = .050$). Odds of AF diagnosis during the year after catheterization increased with the number of atrial arteries with >50% lesion (OR 1.53 for each additional artery; 95% CI 1.08–2.15; $P = .015$).

CONCLUSION In patients with obstructive CAD, disease of the AV nodal artery and RIAA as well as a higher burden of CAD within all arteries supplying blood flow to the atrial myocardium were associated with higher odds of new-onset AF at 1 year.

KEYWORDS Atrial fibrillation; Coronary artery disease; Ischemia; Coronary angiography; Arrhythmia; Cardiac catheterization

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia seen in clinical practice, and it accounts for one-third of arrhythmia-related hospitalizations.¹ The prevalence of AF in the United States is 1% overall and >10% in people older

than 80 years, with ~70% of cases in patients between 65 and 85 years of age.² As America ages, the number of patients with AF is expected to increase 150% by 2050, with >50% of patients being octogenarians or older.^{3–7} The number of patients with AF in the United States could be as high as 16 million by 2050 if the incidence of AF increases in response to rising AF risk factors, such as systemic hypertension, diabetes mellitus, heart failure, myocardial infarction, and valve disease.⁸ Notably, ~2 out of every 3 patients with AF have concomitant ischemic heart disease.¹

Despite the high prevalence and morbidity of AF, the mechanisms of the disease are multifactorial and remain poorly understood, including the influence of ischemia. Animal models of atrial ischemia have shown that there is an increase in spontaneous atrial ectopic activity and slowing of atrial conduction that favor the initiation and maintenance of AF.^{9,10} Canines with atrial ischemia develop gap junction uncoupling that also facilitates AF.¹¹ Other infarct related causes of AF include pericarditis,^{12,13} hypoxia,^{14,15} sinoatrial (SA) node ischemia,¹⁶ ventricular dysfunction,¹⁷ sympathovagal imbalance,¹⁸ and increase in atrial pressure.¹⁹ While

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myocardial ischemia promotes AF, the ventricular irregularity caused by AF can initiate or exaggerate existing subendocardial ischemia by creating a myocardial oxygen demand mismatch.²⁰ No human studies have evaluated the association of developing AF with obstructive coronary artery disease inside or proximal to the nodal arteries. Additionally, the association between angina, atrial ischemia, and AF has not been systematically evaluated.

Methods

Study population

The Duke Databank for Cardiovascular Disease (DDCD) was used to identify patients who underwent cardiac catheterization between January 1, 2007, and December 1, 2013. Data collection methods for the DDCD have been described previously.²¹ Briefly, patients undergoing cardiac catheterization at Duke University Medical Center were included in the database. Data collection included indications for the procedure; history and physical evaluation findings including medical history, signs and symptoms, laboratory measures, medications, cardiovascular risk factors; procedure details and diagnostic findings; and follow-up for clinical events collected from health system administrative records as well as a mailed questionnaire with telephone follow-up conducted at 6 months after the procedure and annually thereafter.

Patients were included in this particular study if they had angina pectoris as the primary indication for cardiac catheterization or angina in the last 6 weeks with the presence of typical or atypical chest discomfort, at least 1 year of follow-up post-cardiac catheterization, and obstructive coronary artery disease in at least 1 vessel. Patients were excluded if they had a history of atrial flutter, AF, or heart failure; had a history of coronary artery bypass graft (CABG) surgery or acute coronary syndrome in the 6 months before cardiac catheterization; were younger than 18 years; were not black or white; were taking an antiarrhythmic medication for ventricular tachycardia at the time of cardiac catheterization; and did not have at least 2 outpatient follow-up visits (at least 1 with cardiology) at Duke University Medical Center during the 12 months after cardiac catheterization. Only the most recent catheterization for each patient was included; or for patients with AF, the latest catheterization before the first AF event was included.

Patients meeting inclusion and exclusion criteria with no missing values of the covariates who were diagnosed with AF during the 12 months after cardiac catheterization were matched to patients who did not develop AF within the same 12-month period. Matching was performed by obtaining a predicted probability of AF using logistic regression with the variables sex, race (white vs black), age, year of cardiac catheterization, history of hypertension, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation, number of diseased vessels, percutaneous coronary intervention performed during angiography, and history of diabetes. CABG within 30 days of catheterization was also included, because of

concerns about postoperative AF and the desire to balance the rates of early CABG within cases and controls. Linearity assumptions were evaluated and met for the continuous variables age, estimated glomerular filtration rate, and catheterization year. For each AF case, a matched control was chosen with a “greedy” matching algorithm using the estimated log odds value for each patient.²² A maximum difference of 0.1 on the log odds scale was allowed. Both race and CABG within 30 days were matched exactly. One control was selected for each case.

Outcomes

The primary measure was the degree of coronary artery disease affecting the atrial tissue. There were 3 separate arteries that supply blood flow to the atria and were analyzed on angiography and subsequently coded: SA nodal artery, atrioventricular (AV) nodal artery, and right intermediate atrial artery (RIAA). Quantitative measurements of stenosis severity were made for each artery by using QAngio XA (Medis Medical Imaging Systems BV, Leiden, The Netherlands).²³ Additionally, the location of the takeoff of the SA nodal artery, AV nodal artery, and RIAA was recorded, and the degree of coronary artery disease in the portion of the right coronary artery, left circumflex, and the left anterior descending proximal to the takeoff for each of the coded arteries was also measured. All coronary disease events were measured on a scale of 0%–100%, indicating the percentage of stenosis blockage.

The primary outcome was development of AF within 1 year of cardiac catheterization. AF is defined according to one of the following: electrocardiographic findings at Duke University Medical Center, or *International Classification of Diseases, Ninth Revision* code for AF (427.31) within Duke University Medical Center Administrative Data inpatient and outpatient encounters.

Statistical methods

Categorical variables were summarized as frequency and percentage, and differences between the groups (patients developing AF within 1 year vs no patients with AF) were assessed using the Pearson χ^2 test or Fisher exact test for sparse data. Continuous variables were summarized as median (Q1–Q3), and differences between the groups were determined using the Wilcoxon rank-sum test. Conditional logistic regression was used to obtain estimates of the odds ratios (ORs) for AF within 1 year of catheterization associated with atrial disease measures, presented as 10% increases in stenosis. The conditional logistic regression is designed to account for the matched pairs.

Atrial disease was analyzed in various forms, including the analysis of each of the minor arteries individually and through composite measures of disease burden. In the individual analyses, multivariable models were implemented for the AV nodal artery, SA nodal artery, and RIAA that included stenosis percentages from both the atrial level arteries and the arteries proximal to the atrial level arteries for each model.

Disease severity was coded using linear splines with a knot at 50% to account for nonlinear relationships.

In the overall analyses of disease burden, the disease severity was determined using various combinations of the arteries. The primary analyses defined *disease burden* as the number of atrial arteries with >50% blockage, as the number of atrial arteries with a blockage of >50% or a blockage of >50% in an artery proximal to the atrial arteries, and as the number of atrial arteries with a blockage of >50% and a blockage of >50% in an artery proximal to the atrial arteries. In all these models, the measures of disease burden (number of arteries) ranged from 0 to 3 and were coded continuously. In secondary analyses, the same criteria were repeated but with a 70% cutoff instead of 50%.

Finally, we estimated the association of chest pain (on the basis of symptoms within 6 weeks before cardiac catheterization) with 1 year AF by using the Canadian Cardiovascular Society angina grade definition for chest pain: non-exertional chest pain, I/V; chest pain with moderate exertion, II; and chest pain with ordinary activity, III/IV.

The conduct of the study was approved by the Duke Health Institutional Review Board and complies with the Declaration of Helsinki. All analyses were performed

using SAS version 9.4 (SAS Institute, Cary, NC). *P* values <.05 were interpreted as evidence of statistically significant associations. Because of the exploratory nature of the study, no adjustments were made for multiple comparisons.

Results

Baseline characteristics

Of the 1794 patients who underwent cardiac catheterization between 2007 and 2013 and met the inclusion/exclusion criteria, 115 (6.4%) developed AF during the subsequent year after cardiac catheterization. The matched population included 220 patients, including 110 with and 110 without AF during the subsequent year after cardiac catheterization. Baseline characteristics including age, sex, comorbidities, coronary artery disease burden, and revascularization strategies were similar for both matched cohorts (Table 1). The overall matched population had a median age of 66.0 years (58.5–74.0 years); 76 (34.5%) were female; and the median CHA₂DS₂-VASc score evaluated at the time of cardiac catheterization was 3 (2–4). The majority of the patients (n = 175 [79.6%]) had revascularization within 30 days of angiography.

Table 1 Baseline characteristics of the matched cohort

Characteristic	Overall (N = 220)	No AF (n = 110)	AF (n = 110)	<i>P</i>
Age (y)	66.0 (58.5–74.0)	66.0 (60.0–73.0)	66.0 (56.0–75.0)	.99
Female sex	76 (34.5)	40 (36.4)	36 (32.7)	.57
White	196 (89.1)	98 (89.1)	98 (89.1)	>.99
CHA ₂ DS ₂ -VASc score	3 (2–4)	3 (2–4)	3 (1–4)	.95
History of MI	36 (16.4)	20 (18.2)	16 (14.5)	.47
History of PCI	54 (24.5)	30 (27.3)	24 (21.8)	.35
Diabetes	95 (43.2)	52 (47.3)	43 (39.1)	.22
Hypertension	174 (79.1)	87 (79.1)	87 (79.1)	>.99
Dyslipidemia	161 (73.2)	82 (74.5)	79 (71.8)	.65
COPD	3 (1.4)	0 (0.0)	3 (2.7)	.123
Prior stroke or TIA	22 (10.0)	9 (8.2)	13 (11.8)	.37
Peripheral vascular disease	21 (9.5)	8 (7.3)	13 (11.8)	.25
BMI (kg/m ²)	29.3 (26.0–33.4)	29.7 (26.3–32.8)	28.7 (25.9–34.4)	.93
History of smoking	93 (42.3)	45 (40.9)	48 (43.6)	.68
eGFR (CKD-EPI) (mL/(min·1.73 m ²))	71.3 (52.8–84.8)	67.1 (51.4–84.4)	74.5 (54.0–87.0)	.18
Angina primary catheterization indication	25 (11.4)	12 (10.9)	13 (11.8)	.83
Left ventricular ejection fraction (%)	61.8 (54.8–68.4)	61.8 (54.8–70.4)	61.7 (55.4–66.9)	.73
Number of diseased coronary arteries				.78
1	46 (20.9)	25 (22.7)	21 (19.1)	
2	69 (31.4)	33 (30.0)	36 (32.7)	
3	105 (47.7)	52 (47.3)	53 (48.2)	
PCI during angiography	66 (30.0)	32 (29.1)	34 (30.9)	.77
CABG within 30 d	102 (46.4)	51 (46.4)	51 (46.4)	>.99
PCI within 30 d	73 (33.2)	35 (31.8)	38 (34.5)	.67
RCA disease	142 (69.3)	67 (65.0)	75 (73.5)	.19
LCx disease	155 (72.4)	77 (72.6)	78 (72.2)	.95
LAD disease	183 (84.3)	90 (84.1)	93 (84.5)	.93
RCA and LAD disease	118 (58.1)	54 (53.5)	64 (62.7)	.18
LAD and LCx (left main) disease	142 (66.4)	71 (67.0)	71 (65.7)	.85
RCA and LAD and LCx disease	94 (46.3)	44 (43.6)	50 (49.0)	.44

Values are presented as median (25th–75th) or n (%).

AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass graft; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; TIA = transient ischemic attack.

Table 2 Location branch point or origin of the atrial level arteries

Variable	AV nodal artery	SA nodal artery	RIAA
Proximal right coronary artery	0% (N = 0)	96% (N = 197)	62% (N = 128)
Mid right coronary artery	1% (N = 2)	0% (N = 1)	8% (N = 12)
Distal right coronary artery	88% (N = 182)	4% (N = 8)	29% (N = 60)
Left circumflex coronary artery	11% (N = 22)	0% (N = 0)	0% (N = 0)

AV = atrioventricular; RIAA = right intermediate atrial artery; SA = sinoatrial.

Among the 220 matched patients included in the case-control analysis, the origin of the AV nodal artery, SA nodal artery, and RIAA could be determined in 206 (94%), 206 (94%), and 205 (93%) patients, respectively (Table 2). The AV nodal artery originated from the distal right coronary artery (RCA) in 88% (N = 182) of patients. The SA nodal artery originated from the proximal RCA in 96% (N = 197) of

patients, and the RIAA originated from the proximal RCA in 62% (N = 128) of patients. Of the 220 patients with known coronary artery disease, 138 patients (67%) had at least 1 obstructive lesion >50% and 44 (21%) had at least 1 obstructive lesion >70%, impairing flow in ≥1 of the atrial level arteries (Figure 1).

Association between atrial level coronary artery disease and AF

The distribution of lesion severity within the AV nodal artery, SA nodal artery, and RIAA (Figure 2) demonstrates a higher proportion of patients with lesions of ≥80% within the AF cohort. Using a multivariable model in which the lesion severity (above 50%) was treated as a continuous variable, increasing lesion severity >50% within the RIAA was associated with higher rates of AF at 1 year (OR 1.41 per 10% increase in lesion severity above 50%; 95% confidence interval [CI] 1.01–1.97; *P* = .047) (Figure 3). Similarly, a 10% increase in lesion severity above 50% in the AV nodal artery was associated with AF at 1 year (OR 1.58 per 10% increase in lesion severity above 50%; 95% CI 1.00–2.49; *P* = .050).

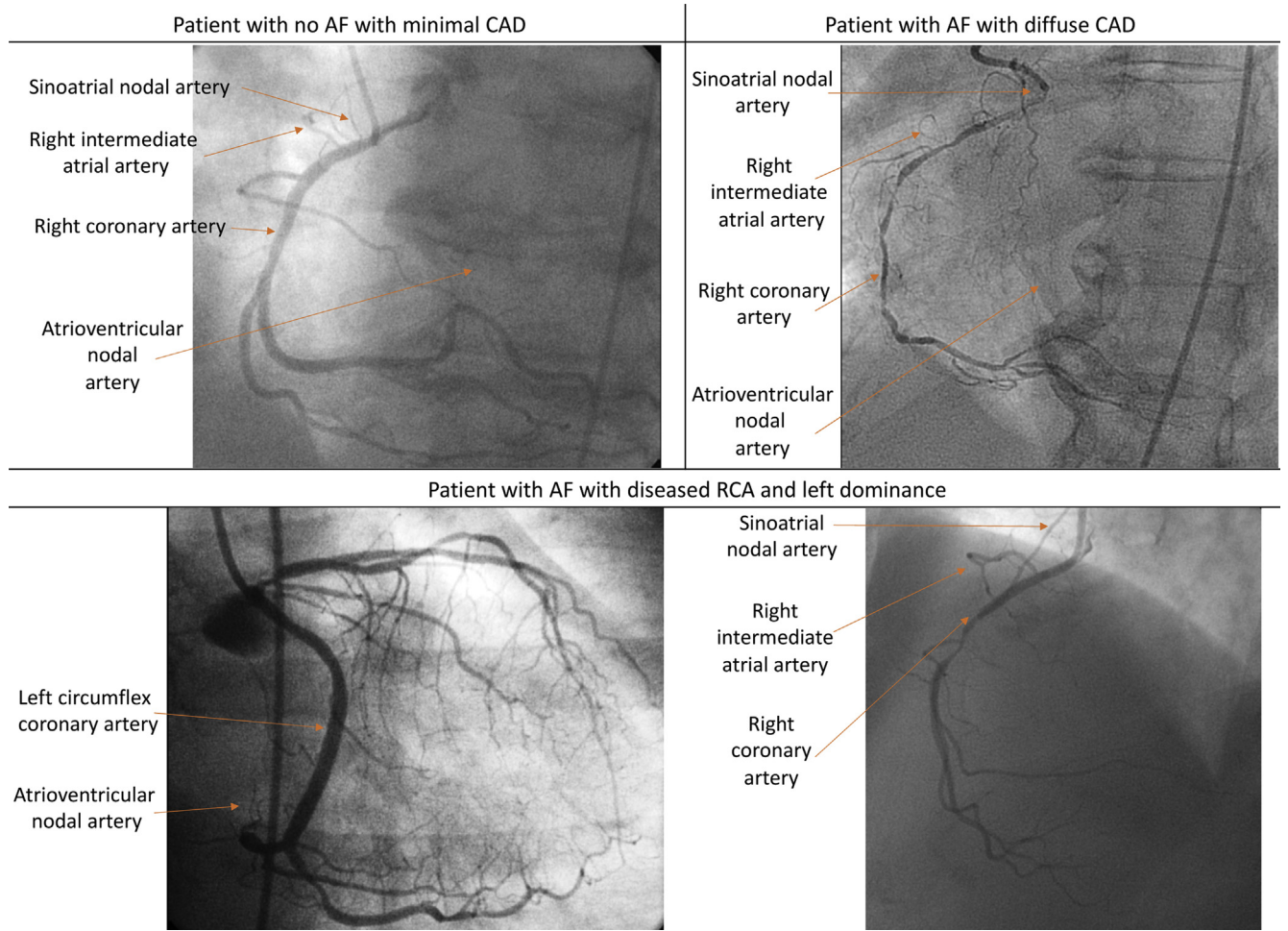


Figure 1 Examples of angiograms for patients with (1) no atrial fibrillation (AF) and minimal atrial branch coronary artery disease (CAD) (upper left corner), (2) AF and diffuse CAD involving the atrial branch vessels (upper right corner), and (3) AF in a patient with left dominance and CAD affecting the right coronary artery (RCA), sinoatrial nodal artery, and right intermediate atrial artery. These are single still frames selected to demonstrate the course of all vessels in a single frame, but interpretation in QAngio software allowed image amplification and frame-by-frame analysis to optimize the analysis of each individual vessel.

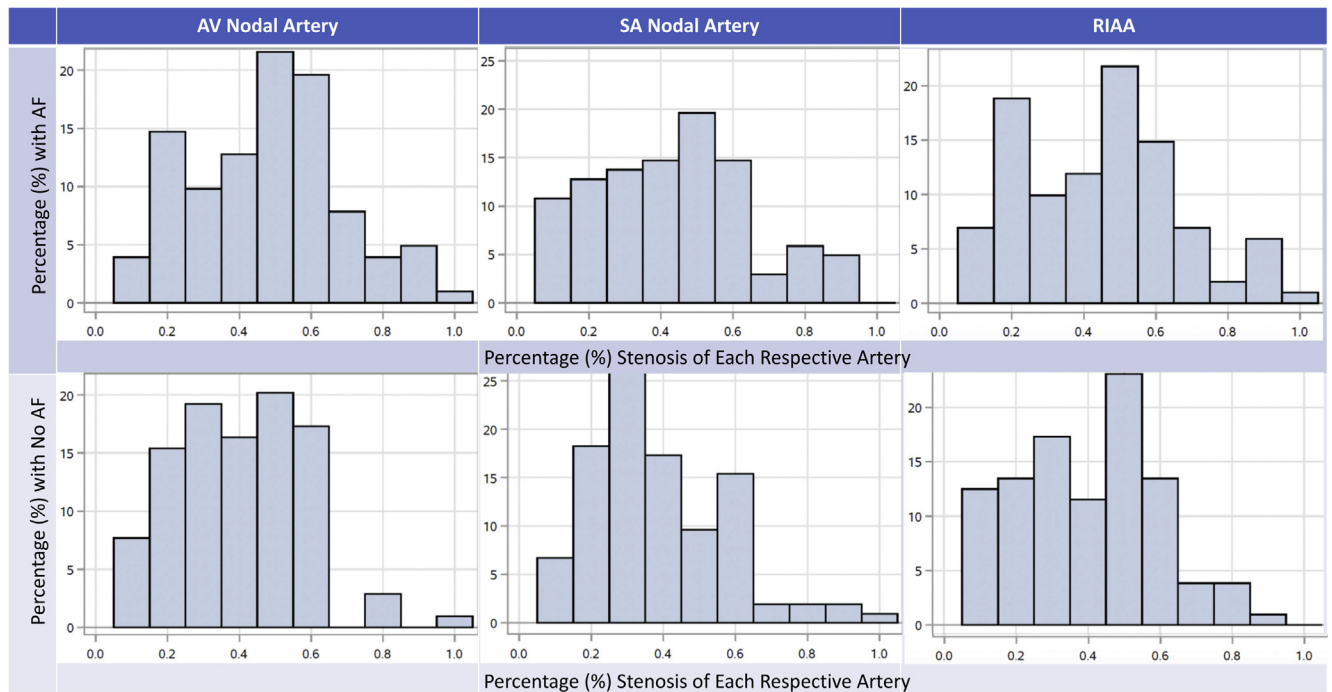


Figure 2 Distribution of the atrioventricular (AV) nodal artery, sinoatrial (SA) nodal artery, and right intermediate atrial artery (RIAA) lesion size stratified by the presence or absence of atrial fibrillation 1 year after cardiac catheterization. AF = atrial fibrillation.

Lesions proximal to the AV nodal artery, SA nodal artery, and RIAA were not associated with AF at 1 year.

The burden of atrial level coronary artery disease was also associated with the diagnosis of AF at 1 year. For each additional atrial artery with a severe lesion (counting $>50\%$ lesions in the AV nodal artery, SA nodal artery, or RIAA), there was an OR of 1.53 (95% CI 1.08–2.15; $P = .015$) for being diagnosed with AF during the subsequent year after cardiac catheterization (Figure 4). Similarly, the OR was 2.03 (1.14–3.62; $P = .016$) when counting $>70\%$ lesions in each of the 3 atrial level branches. There was no association between disease burden proximal to the takeoffs of the atrial level coronary arteries and AF.

Association between chest pain severity and AF

Among the matched cohort, 18 (16.4%) patients had chest pain severity scores of II (chest pain with moderate exertion) on the basis of symptoms within 6 weeks before cardiac catheterization in the no AF cohort while 21 (19.1%) had a score of II in the AF cohort. The majority of patients in the no AF ($n = 65$ [59.1%]) and AF ($n = 60$ [54.4%]) cohorts had chest pain severity scores of III/IV, consistent with chest pain with ordinary activity. Non-exertional chest pain was noted in 27 patients (24.5%) who did not develop AF and in 29 patients (26.4%) who did develop AF. There was no association between chest pain severity and the odds of AF at 1 year, including chest pain with moderate exertion (OR 1.11; 95% CI 0.47–2.62; $P = .81$) and chest pain with ordinary activity (OR 0.87; 95% CI 0.47–1.62; $P = .65$) vs patients with non-exertional chest pain.

Discussion

The underlying etiology of AF is thought to be multifactorial. Preclinical models suggest that atrial ischemia is a cause and trigger of AF. In order to determine whether atrial branch stenosis is associated with the development of clinical AF in patients with known ischemic heart disease, we conducted a matched case-control analysis of 220 patients without a history of AF at the time of cardiac catheterization. There are several important findings of our analysis. First, in patients with known coronary artery disease, the prevalence of obstructive lesions impairing atrial perfusion was 67% ($N = 138$). Second, obstructive disease of the AV nodal artery and the RIAA were associated with higher rates of new-onset AF during the subsequent year after cardiac catheterization. Finally, a higher lesion severity in all 3 atrial level arteries was associated with higher rates of new-onset AF at 1 year.

Lesion severity $>50\%$ within the RIAA (OR 1.41 per 10% increase in lesion severity above 50%) and AV nodal artery (OR 1.58 per 10% increase in lesion severity above 50%) was associated with higher rates of new-onset AF at 1 year. Prior preclinical work has suggested that atrial ischemia and infarction can promote AF. A previous study of 20 mongrel dogs evaluated burst pacing–induced AF after ligation of the RIAA.⁹ The duration of AF was longer when RIAA ischemic times were >30 minutes. After ligation, electrical conduction was significantly slower in the area of atrial tissue supplied by the RIAA when compared to baseline. When taken together, preclinical data in animal models and data from this matched case-control analysis suggest that

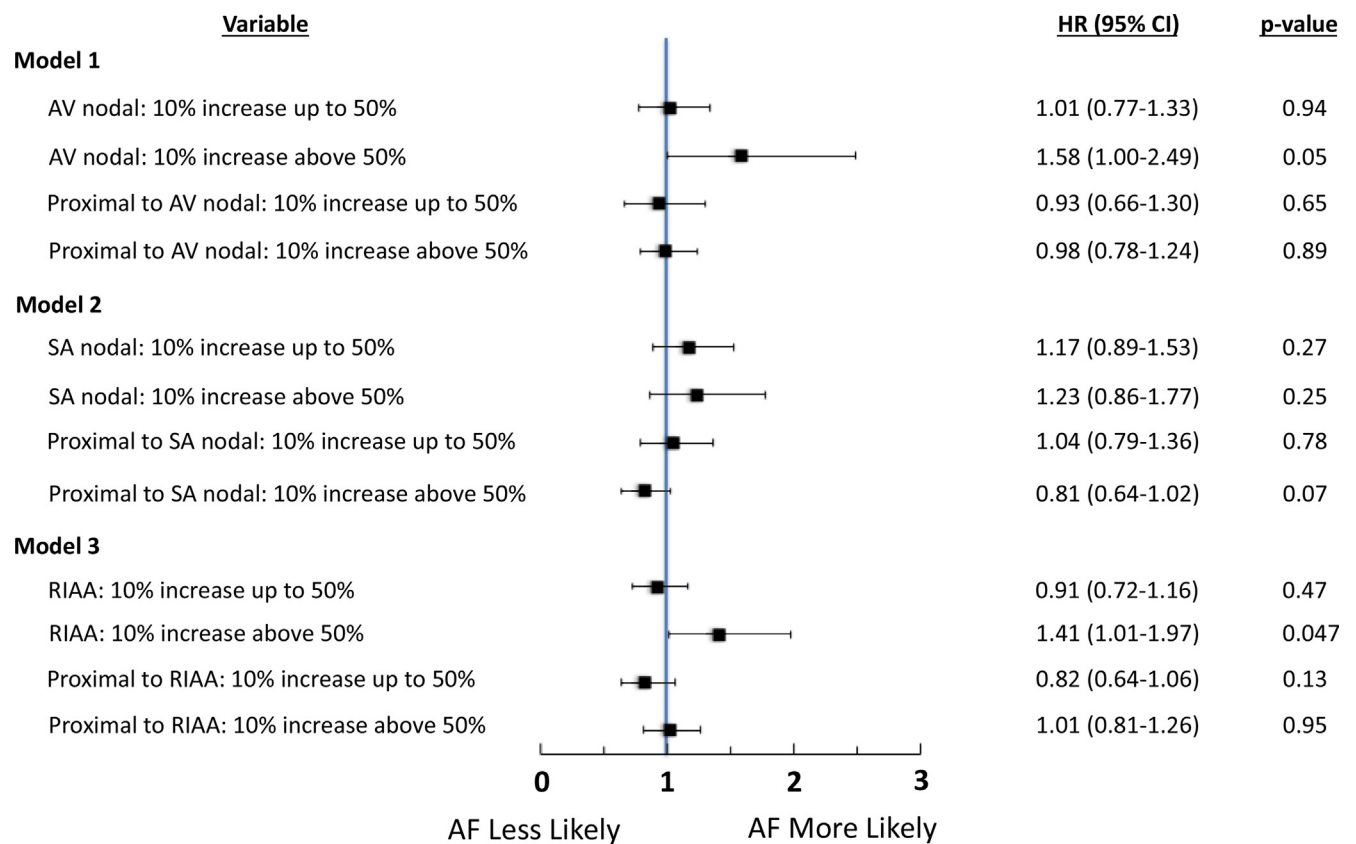


Figure 3 Association between atrial level coronary artery disease and the development of atrial fibrillation (AF) within 1 year of cardiac catheterization. Odds ratio for 10% increase in blockage, with each atrial arterial system considered separately. AV = atrioventricular; CI = confidence interval; HR = hazard ratio; RIAA = right intermediate atrial artery; SA = sinoatrial.

atrial ischemia can lead to prolonged conduction times and an increased likelihood of new-onset AF. Of course, it is likely that other mechanisms surrounding ischemia can also promote AF, including the occurrence of ectopy as well as increased dispersion of atrial refractoriness. Atrial ischemia in animal models has previously been shown to increase

heterogeneity of atrial repolarization (T-wave alternans and spatiotemporal heterogeneity) and increase susceptibility to induce AF,²⁴ and late sodium channel blockade has been shown to lower the susceptibility to ischemia-induced AF.²⁵

Patients with obstructive disease in all 3 atrial level arteries (AV nodal artery, SA nodal artery, and RIAA) had

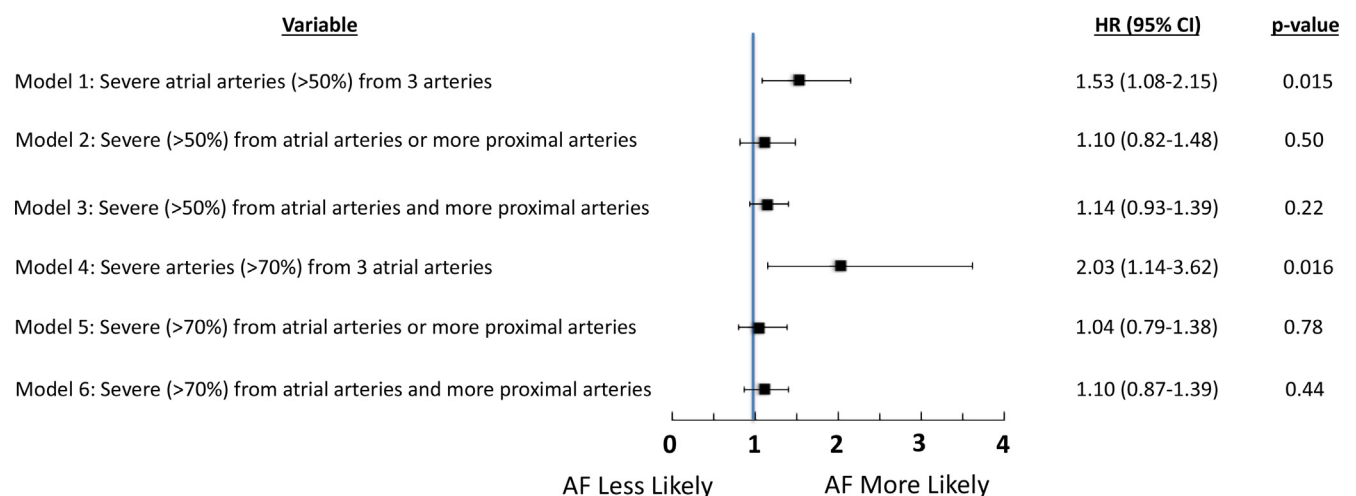


Figure 4 Association between the overall severity of atrial level coronary artery disease and the development of atrial fibrillation (AF) within 1 year of cardiac catheterization. Odds ratio for increase in 1 artery with a severe lesion. CI = confidence interval; HR = hazard ratio.

higher rates of new-onset AF at 1 year. The OR was 1.53 if all 3 vessels had >50% lesions and 2.03 if all 3 vessels had >70% lesions. These findings suggest a “dose-response” relationship between atrial ischemia and the likelihood of developing AF. There was no association between disease burden proximal to the takeoffs of the atrial level coronary arteries and AF, and this may have been related to collaterals, which developed for the larger more proximal coronary arteries. Prior investigation in humans found an association between atrial ischemia and postoperative AF after CABG.²⁶ The study compared rates of obstructive coronary artery disease in the SA and AV nodal arteries on preoperative cardiac catheterizations of patients who went on to develop AF and those who did not develop AF after CABG. There was an association between coronary artery disease of the SA nodal artery and postoperative AF. This study was limited by the fact that subjective assessment of coronary artery disease was used, which can be challenging in small arteries. The present analysis used quantitative measurements of the atrial level coronary arteries and their lesions, which improves accuracy, especially given that lesion sizes tend to be more overestimated when the surrounding vessel is smaller.²³

Clinical implications

There are several clinical implications of the findings within this study. First, given the association between ischemia within the atrial level coronary arteries and higher odds of AF, providers should consider screening for ischemic coronary artery disease in patients with AF and risk factors for coronary artery disease. Second, primary prevention of coronary artery disease with lifestyle modifications and statin therapy may contribute to the primary prevention of AF. Third, atrial level ischemia and resultant atrial repolarization heterogeneity represent a potential new target for interventions in both the prevention and the management of AF, which would need to be studied further in future trials; however, revascularization of coronary arteries proximal to the arteries supplying blood flow to the atrial myocardium was not associated with lower rates of AF.

Limitations

This analysis had several important limitations. The diagnosis of AF was made clinically and was abstracted from the medical records. Although patients included in the analysis were required to be followed within the Duke medical system and through the DDCD follow-up in order to be included in the study, the diagnosis of AF was opportunistic, as there was no standard systemic screening for AF or prespecified timing of outpatient visits before or after cardiac catheterization. The AF events were not blindly adjudicated. Patients were required to have at least 2 outpatient follow-up visits with at least 1 being with cardiology after the cardiac catheterization, so all patients had follow-up within the system for the purposes of having the opportunity to identify

AF. The atrial level branches were not the focus of the angiogram images. Therefore, only the proximal portion of each of the atrial level branches was measured in order to determine the maximum lesion stenosis in that region. Disease involving more distal aspects of the atrial level branches could not be measured or included in the analysis. Collateral flow to the atrial tissue was not measured, and atrial tissue perfusion could not be assessed. Statistical analyses were exploratory in nature and did not control the rate of possible false-positive findings beyond the nominal level of 5% used for each comparison.

Conclusion

In patients with obstructive coronary artery disease, disease of the AV nodal artery and RIAA as well as a higher burden of coronary artery disease within all the arteries supplying blood flow to the atrial myocardium were associated with higher rates of new-onset AF at 1 year. These data provide additional evidence beyond animal models that atrial ischemia may contribute to AF. Additional studies evaluating perfusion of the atrial level myocardium are needed.

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