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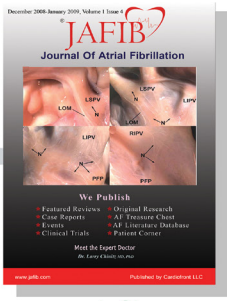

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Extra Atrial Disease in Patients with "Lone" Atrial Fibrillation.

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Abstract

Aims: Lone atrial fibrillation (LAF) is considered by some to be a primary atrial electrophysiologic disorder. However, we have frequently observed evidence of "extraatrial" diseases - atherosclerosis and associated metabolic disorders - in our LAF patients. We sought to characterize and quantify extraatrial disease burden in LAF patients, and to correlate this burden with features of the arrhythmia including pattern (paroxysmal versus persistent) and response to catheter ablation.

Methods and Results: Forty-six consecutive patients with non-familial LAF underwent assessment for evidence of atherosclerosis (computed tomographic vascular calcification and elevated arterial pulse wave velocity) and associated metabolic diseases (dyslipidemia, insulin resistance and inflammation), and then catheter ablation.

The cohort had a significant incidence of atherosclerosis (57%) and metabolic (70%) diseases. Patients with persistent AF tended to have a greater extraatrial disease burden than those with paroxysmal AF. A significant inverse relationship between the rate of ablation success and extraatrial disease burden was demonstrated.

Conclusions: Extraatrial disease was common in this LAF cohort. Correlations between extraatrial disease burden and features of the arrhythmia would, if verified, challenge the notion that LAF is a "primary" electrophysiologic disorder.

Key words: atrial, atrial fibrillation, atherosclerosis, dyslipidemia, ablation, metabolic syndrome, diabetes mellitus

Introduction

The term "lone atrial fibrillation" (LAF) was introduced over 50 years ago to characterize afflicted patients who were younger and without typical comorbidity.[1] It is, by some, conceptualized as a "primary" electrophysiologic disorder.[2-4] Although rather unusual, LAF has been represented prominently in many catheter ablation cohorts, including ours.[5]

Computed tomographic imaging is used routinely for cardiac imaging prior to catheter ablation of atrial fibrillation.[5,6] Despite a strong bias toward selecting patients for this procedure who were "well," we have observed in these images a high incidence of vascular calcification, indicating substantial atherosclerosis.[7] This surprised us, particularly in LAF patients given their youth and absent comorbidity, and prompted consideration

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as to whether in these patients the arrhythmia could be linked to the atherosclerosis or entities which were likely associated with atherosclerosis. In the present report, we summarize the results of a prospective, single-center examination of consecutive LAF patients for evidence of atherosclerosis as well as for metabolic diseases known to be associated with atherosclerosis, including dyslipidemia, insulin resistance, and inflammation. We hypothesized that these "extraatrial" diseases would be correlated with features of the arrhythmia, including the presenting AF syndrome (paroxysmal versus persistent) and the response to catheter ablation.

Methods

This study was approved by the Institutional Review Board of the University of Pittsburgh Medical Center.

Patients

During the 5 year period in which the study cohort, detailed below, was accumulated, 567 patients were referred to our center for consultation regarding candidacy for catheter ablation of AF. Of these, 181 patients were considered suitable. We did not offer the procedure to 386 patients for reasons which we have detailed previously, primarily age and known comorbidity.[5] From among the 181 patients who were considered suitable, 163 agreed to the procedure. From among these patients, we culled the 46 patients with LAF, who comprise the study cohort. We defined LAF using the current American College of Cardiology/American Heart Association criteria, which include: 1. age <60; 2. no hypertension by history nor a blood pressure measurement of >130 mmHg systolic or 85 mmHg at the initial consultation; and 3. no echocardiographic evidence of significant ventricular or valvular disease; 4. no infection, endocrinopathy, or recent surgery[3,4] The remaining 117 patients who underwent the ablation procedure were excluded from this study because they did not meet these criteria, due (non-exclusively) to: 1. age >60 (n=107); 2. hypertension (n=93); and/or 3. echocardiographic abnormalities (n=41).

Evaluation

The following data were collected:
1.Height and weight.
2.Serology: patients were asked to refrain from tobacco or alcohol consumption for at least one week prior to the evaluation, and were fasted for 12 hours prior to blood accession for the following commercial assays:
A.high-sensitivity C-reactive protein (CRP).
B.glucose, fasting and at 2 hours after oral glucose challenge.
C.total, LDL and HDL cholesterol
D.triglycerides.
3.Computed tomography of heart and thoracic aorta: imaging was performed using a commercial 64-detector scanner (VCT, General Electric Healthcare, Milwaukee, WI, USA), as previously described.[8] Images were examined by radiologists who were highly experienced in CT angiography, and who were not aware of the identity of the study patients from among the broader cohort of patients undergoing routine pre-ablation imaging.[5] For assay of vascular calcification, the multidetector technique has been shown to correlate well with the more commonly reported electron beam technique.[9] The burden of coronary calcification was defined using the method of Agatston.[7,10] Aortic calcification, defined in this cohort as either present or absent, was always discrete and punctuate, consistent with an intimal location and involvement in an atherosclerotic plaque.[11]
4.Pulse Wave Velocity: elevated arterial stiffness is mechanistically related to atherosclerosis in the age range of the study cohort, and given the limited imaging window of computed tomorgraphy (thorax only), we included an assay for stiffness as a means to enhance sensitivity for atherosclerosis detection.[12] Stiffness was measured using brachial-ankle pulse wave velocity (baPWV), primarily an assay of large conduit arteries, via a commercial device (VP-1000, Colin Medical Inc., San Antonio, TX, USA).[13] This device recorded electrocardiogram, phonocardiogram and pulse volume data simultaneously, and calculates the time delay of the pulse to obtain the pulse wave transmit time (PTT). The device can measure pulse wave velocity in the right brachium (La) and right/left lower limbs (Lb, Lc). Calculation of baPWV was performed using the following formula: baPWV (right) = (Lb-La)/PTT; baPWV (left) = (Lc-La)/PTT. In individual pa-

tients, we defined arterial stiffness to be elevated when the baPWV value (average of right and left side values) was >2 standard deviations above community-derived values similar age and gender.[13,14]

Catheter Ablation

Each patient underwent this procedure, which has been characterized in detail previously.[5] In the present study, a "successful" outcome was defined at 1 year after a single ablation procedure by the

Table 1 Comparison of Patients with BB Prophylaxis Versus without Prophylaxis

N	**46**
Male gender (% of pts)	78
Age (years)	51±6 (36-60)
Presenting with paroxysmal AF (% of pts)	67
Left atrial volume/m2 of body surface area	29±8
BMI (kg/m2)	29.7±6.2 (20.6-44.6)
Obesity (% of pts)	39
Fasting glucose (mg/dL)	99±11 (86-143)
Stimulated (2 hour) glucose (mg/dL)	126±41 (58-226)
Insulin resistance (% of pts)	48
Total cholesterol (mg/dL)	193±38 (121-303)
LDL cholesterol (mg/dL)	118±33 (71-219)
HDL cholesterol(mg/dL)	47±14 (25-81)
Triglycerides (mg/dL)	172±179 (38-1129)
Dyslipidemia (% of pts)	43
Presence of metabolopathy (% of pts)	70
Metabolic Syndrome (% of pts)	9
Coronary calcium score (Agatston units)	61±152 (0-694)
Coronary calcification present (% of pts)	33
Aortic calcification present (% of pts)	26
Coronary or aortic calcification present (% of pts)	41
Brachial-ankle pulse wave velocity (cm/sec)	⌀1499±255 (952-2016) ⌀1510±250 (1208-1888)
Elevated pulse wave velocity (% of pts)	39
Presence of atherosclerosis (% of pts)	57
FRS (%)	5.7±5.3 (0-30)
Elevated FRS (% of pts)	37
CRP (mg/dL)	0.71±1.1 (0.1-6.4)
Inflammatory phenotype (% of pts)	2
Ablation success (% of pts)	76

- BMI = body mass index; Obesity was defined as a BMI >30.
- CRP = c-reactive protein; inflammatory phenotype defined as CRP>3.
- Insulin resistance defined as a fasting glucose of >100 mg/dL or a stimulated glucose of >140 mg/dL.
- Dyslipidemia defined as currently receiving hypolipidemic pharmacotherapy and/or at least 2 of the following: LDL > 130 mg/dL; HDL <40 mg/dL (men) or <50 mg/dL (women); TG >150 mg/dL.
- FRS = Framingham risk score. Elevated FRS was defined as a score >5%.
- Atherosclerosis defined as presence (Agatston score >0) of vascular (coronary and/or thoracic aortic) calcium and/or an elevated pulse wave velocity reading.
- Metabolopathy defined as dyslipidemia and/or insulin resistance. Metabolic Syndrome was defined more strictly by BMI ⌀30 + insulin resistance + dyslipidemia.

absence of electrocardiographic or symptomatic atrial fibrillation, as well as type I/III antiarrhythmic agents for at least 6 months.[5]

Calculations and Definitions

Using the foregoing data, we performed the following calculations and assayed individual patients for each of the following definitions (shown in bold):

1.Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Obesity was defined by a BMI ≥ 30 kg/m2.
2.Inflammatory Phenotype was defined as a CRP >3 mg/dL.[15]
3.Insulin Resistance was defined as a fasting glucose of >100 mg/dL or a stimulated glucose of >140 mg/dL.[16]
4.Dyslipidemia was defined as currently receiving hypolipidemic pharmacotherapy and/or at least 2 of the following: LDL > 130 mg/dL; HDL <40 mg/dL (men) or <50 mg/dL (women); TG >150 mg/dL.[17]
5.Metabolopathy was defined as evidencing dyslipidemia and/or insulin resistance. Metabolic Syndrome was defined as BMI ≥ 30 + insulin resistance + dyslipidemia.[18,19]
6.Atherosclerosis was defined as vascular (coronary and/or thoracic aorta) calcification and/or elevated arterial stiffness.
7.Framingham Risk Score (FRS): in that this score has been widely applied to estimate 10-year risk of "hard" coronary events (myocardial infarction and coronary death) in middle-aged patients without known heart disease, we thought that its inclusion in this report would provide useful context.[20] The FRS was calculated using patient age, gender, total and HDL cholesterol values, cigarette smoking within the past month, and systolic blood pressure recorded at the initial consultation. In the present study, a score of <1 was recorded as 0, and an "elevated FRS" was defined as >5[20]

Analytical Methods

Continuous data were compared using a Mann-Whitney rank sum test or a Kruskal-Wallis analysis of variance on ranks, as appropriate. Categorical data were compared using a chi-square test or Fisher Exact test, as appropriate. Multivariable analysis was performed using stepwise logistic regression. For each test, significant differences were assumed if the p value was <0.05. Data are reported as mean ± standard deviation, unless otherwise noted.

Results

Characteristics of the study cohort are summarized in Table 1. All patients resided in western Pennsylvania or contiguous West Virginia, and all but 1 patient was Caucasian. No patient reported a primary relative with AF. Each patient had an established syndrome of paroxysmal (all symptomatic episodes terminate spontaneously within 2 days; n=31) or persistent (at least 1 episode exceeding 1 month in duration and requiring direct-current cardioversion; n=15) AF, defined within 1 year of ablation in the antiarrhythmic drug-free state. Twenty-eight patients described a historical "vagal" preponderance to AF triggering, 9 patients an "adrenergic" preponderance, and 9 a "mixed" pattern.[21] Each patient had undergone prior treatment with at least 1 (mean 1.9) type I/III antiarrhythmic drugs, which had failed due

Table 2 Cohort parsed by presenting AF syndrome

	Paroxysmal	Persistent	P
N	31	15	NS
Male gender (% of patients)	74	87	NS
Age (years)	50±5	52±7	NS
Obesity (% of patients)	39	47	NS
Atherosclerosis (% of patients)	58	67	NS
Metabolopathy (% of patients)	65	80	NS
Elevated FRS (% of patients)	32	47	NS
Ablation success (% of patients)	84	60	NS

Abbreviations and definitions as per Table 1.

Table 3 Cohort parsed by extraatrial disease burden

	Atherosclerosis NOR Metabolopathy	Atherosclerosis Metabolopathy	OR	Atherosclerosis AND Metabolopathy	P
N	8	18		20	-
Male gender (% pts)	63	72		90	NS
Age (years)	48±5	51±5		51±7	NS
Paroxysmal AF (% pts)	75	72		60	NS
Obesity (% pts)	38	39		40	NS
Elevated FRS (% pts)	13	28		55	NS
Ablation success (% pts)	100	83		60	.053

Abbreviations and definitions as per Table 1.

to inefficacy and/or intolerance. Blood pressure averaged 119/77 mmHg, and no patient had a recorded pressure in excess of 130/85 mmHg. A significant minority of patients were obese. Eight of the 10 women were post-menopausal at the time of evaluation, by a mean of 4 (range 2-12) years. Seven patients had smoked cigarettes within a month prior to evaluation, and an additional 16 patients had smoked in the past. A previous diagnosis of diabetes mellitus had been made in 3 patients, none of whom were receiving hypoglycemic pharmacotherapy, and of dyslipidemia in 13 patients, 11 of whom were receiving hypolipidemic pharmacotherapy. Each patient had produced normal resting and stress-nuclear cardiac images within 6 months of the ablation procedure. Each patient had produced normal transthoracic echocardiographic images, with the exception of LA enlargement (defined as an LA volume >30 cc/m2 body surface area and observed in 25 patients) within 3 months of the ablation procedure. Although dyslipidemia and insulin resistance were common, few patients met criteria for the metabolic syndrome and the Framingham Risk Score was generally low. Also common were coronary artery calcification, aortic calcification, and elevated arterial stiffness. Only 1 patient demonstrated an inflammatory phenotype.

A description of patients parsed by presenting AF syndrome is summarized in Table 2. Although patients with persistent AF tended more commonly to atherosclerosis and metabolopathy, these relationships were not statistically significant. A description of patients parsed by extraatrial disease burden is summarized in Table 3. Despite similar ages, patients with neither vascular nor metabolic diseases were more likely to experience a successful ablation outcome, and success diminished as burden increased; this relationship was statistically significant. The following variables were entered into a multivariable analysis of associates of a successful ablation outcome: age, gender, obesity, presenting AF syndrome, LA enlargement, dyslipidemia, insulin resistance, metabolopathy, elevated Framingham Risk Score, vascular calcification, and atherosclerosis. Atherosclerosis (P=.015) and persistent AF (P=.049) were each significantly (inversely) associated with ablation success.

Data regarding the presence and nature of the discovered extraatrial diseases were routinely communicated to referring physicians, and their subsequent treatment decisions were not controlled for this study. A post-hoc assessment did not suggest that pharmacotherapies (including hypoglycemic, hypolipidemic, and renin-angiotensin system inhibition) initiated subsequent to the ablation procedure interacted significantly with its outcome.

Discussion

Key observations in this study included: 1. despite a diagnosis of lone AF, these patients commonly

manifested extraatrial diseases, including atherosclerosis, insulin resistance, and dyslipidemia; 2. disease burden tended to be greater in patients with persistent AF; and 3. there was a significant inverse relationship between disease burden and ablation success. To our knowledge, this is the first attempt to link extraatrial disease burden to characteristics of the atrial arrhythmia. These data suggest that the atrial disease from which AF emerges does not occur in isolation: this is not a new notion.[3,4,2] A correlation between extraatrial disease burden and characteristics of the arrhythmia might suggest an etiologic relationship.

The young age of AF occurrence in these patients could, hypothetically, be due to an atrial substrate predisposition, either intrinsic (eg. electroanatomical) or extrinsic (eg. neurological). The notion that vascular or metabolic diseases could encourage such a predisposition is well supported.[3,4,12,13,22-24] The absence of an important inflammatory component, reported elsewhere in similar cohorts, may be further testimony of predisposition.[25] If these findings can be verified, characterization of extraatrial disease burden may prove a useful tool for refining the process of patient selection for atrial fibrillation therapies, including catheter ablation.

The extraatrial disease burden which we characterize here are worrisome. Although LAF is historically associated with a benign prognosis, given evolution of culture, diet and environment it should not be assumed that present-day LAF is necessarily the same entity.[3,26,27] Although apparently at low risk for near-term vascular morbidity/mortality, these were young patients for whom multiple decades of life may be expected.[27] Whether the presence of AF betrays the need for a more aggressive or modified extraatrial disease management regimen than dictated by current guidelines is unknown. Also unknown is whether/how ablation outcome might predict or influence the course of the extraatrial disease.

We note several limitations to this work. First, the small cohort size render our observations preliminary. Optimally, characterization of extraatrial disease burden would be integrated into large arrhythmia intervention trials involving multiple centers, which will permit better insight into the robustness of their interaction, as well as the influence of other factors including gender, race, geography/nationality, cardiac and neural phenotypes, proteomics, and genomics. It is also apparent that persistent AF responds less well to catheter ablation than paroxysmal AF, possibly due to a greater amount of atrial pathology in the former, but if true to what extent this pathology precedes and/or is attributable to the AF is unclear. Second, referral and/or selection bias may have rendered this cohort not reflective of LAF in the community. For example, we note a high incidence of obesity. More broadly, although the extraatrial entities demonstrated here clearly demarcate "disease," the absence of a contemporaneous non-AF cohort derived from the same community limits our ability to place them in context. Third, our data are limited to LAF patients, and as such are not representative of the community problem of AF, which exists in an older population with more comorbidity.[3] How the extraatrial diseases demonstrated here interact with the aging process, hypertension and/or abnormalities in cardiac structure/function is unclear. Our data would support the contention that the term "lone" may have limited utility or, given its presently disarming connotation, may even be counterproductive.[26] Fourth, our data should not be viewed as representing an exhaustive search for extraatrial disease. For example, atherosclerosis, although a diffuse process, is underdetected by calcium scoring and is regionally heterogenous; a search of additional vascular beds may have increased the incidence. Similarly, our definitions of "dyslipidemia" oversimplify a field in rapid evolution, both in terms of mechanisms by which lipids associate with atherosclerosis and as to which lipid elements are sinister or beneficial. Fifth, we provide no data as to the incidence of obstructive sleep apnea (OSA), the relevance of which to AF incidence and response to catheter ablation has been demonstrated.[28,29] We did not systematically perform sleep evaluations. Finally, although we chose what we felt was a conservative tack by dichotomizing at clearly pathologic cutpoints, some would view our definitions of atherosclerosis or metabolic diseases with suspicion. Similarly, our observations are limited to the regionally limited ablation procedure which we performed, and our definition of ablation "success" is relatively short-term (1 year).

In summary, among patients with non-familial LAF, evidence for atherosclerosis and associated metabolic diseases was common, and their presence could be correlated with AF pattern and response to attempted catheter ablation. If verified, these data would challenge the notion of LAF as a "primary" electrophysiologic disorder.

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