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Isolated Atrial Microvascular Dysfunction in Patients With Lone Recurrent Atrial Fibrillation

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Objectives The purpose of this study was to assess atrial myocardial perfusion in patients with lone recurrent atrial fibrillation (LRAF).

Background Although acute atrial ischemia has been implicated in the pathogenesis of atrial fibrillation, there are few data concerning human atrial myocardial perfusion and none for patients with LRAF.

Methods Sixteen patients with LRAF and 15 control subjects with suitable coronary anatomy underwent time-averaged peak coronary blood flow velocity (APV) measurements (cm/s), using a Doppler guidewire in the proximal left circumflex coronary artery (LCx) and in the left atrial circumflex branch (LACB), at baseline (b) and after adenosine administration to achieve maximal hyperemia (h). Coronary flow reserve was defined as h-APV/b-APV.

Results Although there were no statistically significant differences in b-APV between patients with LRAF and control subjects or between the LACB and LCx, there were significant group ($p = 0.002$), artery ($p = 0.001$), and interaction ($p < 0.001$) effects at maximal hyperemia. In patients with LRAF, the h-APV and coronary flow reserve of the LACB (30.4 ± 9.5 cm/s and 2.2 ± 0.4, respectively) were significantly lower than in the LACB of the control subjects (45.8 ± 12.8 cm/s [$p < 0.001$] and 2.9 ± 0.5 [$p = 0.001$], respectively) or in the patients' LCx (43.0 ± 10.9 cm/s [$p = 0.001$] and 3.1 ± 0.6 [$p < 0.001$], respectively).

Conclusions This study confirms for the first time isolated atrial myocardial perfusion abnormalities in patients with LRAF and coronary flow reserve impairment, indicating that microvascular dysfunction is a pathophysiological substrate associated with this arrhythmia. (J Am Coll Cardiol 2008;51:2053–7) © 2008 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality (1).

Many different factors are involved in the onset, perpetuation, and relapse of AF. A substantial proportion of patients have no detectable cardiopulmonary disease, and the underlying pathophysiological mechanisms remain obscure. Nevertheless, atrial fibrosis and loss of atrial muscle mass are the common pathoanatomic changes that have been observed (2–5) and which may precede the onset of AF (6). Given that these anatomic changes closely resemble those in ventricular myocytes in the hibernating myocardium (7,8), atrial ischemia has been implicated in the pathogenesis of AF.

Although there are animal studies indicating a direct effect of acute atrial ischemia on AF pathogenesis (9), no studies have examined this pathophysiological relationship in humans.

The use of intracoronary Doppler has made flow velocity measurements feasible in the atrial branches, and data concerning atrial myocardial perfusion have been reported recently from our department (10).

The purpose of the present study was to assess atrial myocardial perfusion in patients with lone recurrent atrial fibrillation (LRAF).

Methods

Patients and control subjects. The study assessed 42 patients with LRAF and suitable coronary anatomy who consented to undergo functional assessment of coronary circulation after the completion of programmed routine cardiac catheterization at least 1 month after the last episode of AF.

Suitable coronary anatomy means that the patients had a left atrial circumflex branch (LACB) at least 0.5 mm in

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Abbreviations and Acronyms

AF = atrial fibrillation

APV = time-averaged peak coronary flow velocity

b-APV = time-averaged peak coronary flow velocity at baseline

CFR = coronary flow reserve

h-APV = time-averaged peak coronary flow velocity after maximal hyperemia

LACB = left atrial circumflex branch

LCx = left circumflex coronary artery

LRAF = lone recurrent atrial fibrillation

diameter, originating without an obtuse angle from the left circumflex coronary artery (LCx). The LACB was defined as any branch that originated to the left of the LCx and the coronary sinus, in the right anterior oblique view.

Lone recurrent AF was defined as 2 or more episodes of AF over the last year without evidence of cardiopulmonary disease. The following patient groups were excluded: patients with other than sinus rhythm, significant coronary artery disease (stenosis diameter >40%), stenotic coronary artery lesions of any severity of the LCx, previous myocardial infarction, congenital, valvular, or hypertensive heart disease, chronic obstructive pulmonary disease, thyroid disease, left atrial diameter >40 mm, and left ventricular ejection fraction <50%.

Fifteen patients without a history of AF who had coronary angiography for clinical indications with coronary arteries free of stenotic lesions and suitable coronary anatomy constituted the control group. The same exclusion criteria as for the LRAF patients were applied to this group.

All cardioactive medications were continued except for antiarrhythmics, which were discontinued at least 3 days before the study.

Table 1 Clinical Characteristics for Patients With LRAF and for Control Subjects

Variable	LRAF (n = 16)	Control (n = 15)	p Value
Male/female	7/9	8/7	NS
Age (yrs)	59 ± 8	64 ± 8	NS
Current or ex-smokers	7 (44%)	6 (40%)	NS
Hypertension	5 (31%)	4 (27%)	NS
Dyslipidemia	7 (44%)	8 (53%)	NS
Total cholesterol (mg/dl)	192 ± 43	203 ± 45	NS
Triglycerides (mg/dl)	138 ± 47	146 ± 41	NS
Diabetes mellitus	1 (6%)	0 (0%)	NS
Beta-blockers	3 (19%)	4 (27%)	NS
Calcium-channel blockers	2 (13%)	3 (20%)	NS
ACE inhibitors	2 (13%)	1 (7%)	NS
Statins	5 (31%)	4 (27%)	NS
LA diameter/BSA (mm/m^2)	19.4 ± 2.4	18.5 ± 2.6	NS
Number of AF episodes	3.4 ± 1.3	—	
Duration of AF history (months)	26 ± 15	—	
Time from last episode of AF (days)	74 ± 41	—	
Duration of last documented AF episode (h)	20 ± 18	—	

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; BSA = body surface area; LA = left atrium; LRAF = lone recurrent atrial fibrillation; NS = not significant.

Table 2 Doppler and Other Parameters Recorded From the LACB and LCx for Patients With LRAF and for Control Subjects

	Control		LRAF	
	LCx	LACB	LCx	LACB
HR (beats/min)	69 ± 11	71 ± 12	71 ± 13	70 ± 14
SBP (mm Hg)	128 ± 16	127 ± 17	119 ± 14	120 ± 12
DBP (mm Hg)	70 ± 11	69 ± 12	67 ± 10	68 ± 9
b-APV (cm/s)	17.1 ± 4.8	16.5 ± 5.4	14.8 ± 5.3	13.7 ± 3.9
h-APV (cm/s)	49.9 ± 14.7	45.8 ± 12.8	43.0 ± 10.9	30.4 ± 9.5*†
CFR	3.0 ± 0.6	2.9 ± 0.5	3.1 ± 0.6	2.2 ± 0.4*†

*p = 0.001 compared with control subjects. †p < 0.001 compared with patients' LCx.
b-APV = time-averaged peak flow velocity at baseline; CFR = coronary flow reserve; DBP = diastolic blood pressure; h-APV = time-averaged peak flow velocity after maximal hyperemia; HR = heart rate; LACB = left atrial circumflex branch; LCx = left circumflex coronary artery; LRAF = lone recurrent atrial fibrillation; SBP = systolic blood pressure.

All patients and control subjects gave their written informed consent to participation in the study. The study protocol was approved by the hospital's ethics committee.

Coronary flow velocity measurements. Immediately after coronary angiography, the left coronary artery was selectively engaged with a diagnostic catheter. A 0.014-inch 15-MHz Doppler guide wire (FloWire, Volcano Therapeutics, Rancho Cordova, California) was advanced through the catheter to the proximal LCx and to the LACB. Frequency analysis of the Doppler signals was carried out in real time by fast Fourier transform using a velocimeter (FloMap, Volcano Therapeutics).

Once baseline flow-velocity data had been obtained, a 30-μg bolus injection of intracoronary adenosine was given to obtain data during hyperemia. To confirm that maximal hyperemia had been achieved, doses that were incrementally larger by 30 μg were infused until a plateau in flow velocity was reached.

Time-averaged peak coronary flow velocity (APV) was measured and coronary flow reserve (CFR) was determined as the ratio of APV at maximal hyperemia (h-APV) to APV at baseline (b-APV).

Pre-treatment and measurements were done as previously described (10).

Statistical analysis. Data are expressed as mean ± SD. The 2-tailed *t* test for independent samples was used to compare continuous variables between the 2 groups. Repeated-measures analysis of variance within drug (baseline, adenosine-induced maximal hyperemia) and artery (LACB, LCx) factors and between groups was used to assess main and interaction effects on APV. The 95% confidence intervals (CIs) were also computed to obtain a better idea about the magnitude of the effects. A p value of <0.05 was considered to be statistically significant.

Results

Of the 42 patients initially examined, 23 did not satisfy the angiographic criteria for inclusion in the study, 2 had poor-quality recordings, and in 1 the wire could not be

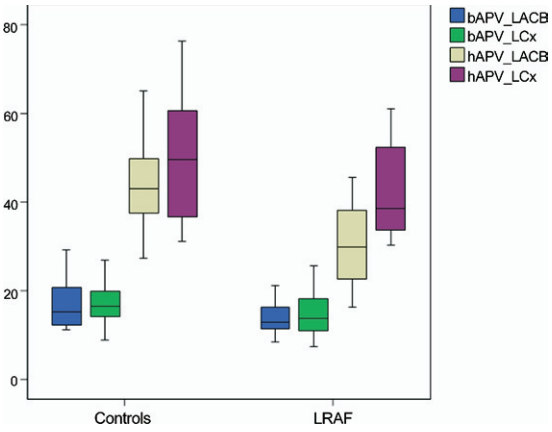

Figure 1 **Time-Averaged Peak Coronary Flow Velocity**

Box-plots of time-averaged peak coronary flow velocity at baseline (b-APV) and at maximal hyperemia (h-APV) from the left atrial circumflex branch (LACB) and the left circumflex coronary artery (LCx) in patients with lone recurrent atrial fibrillation (LRAF) and in control subjects.

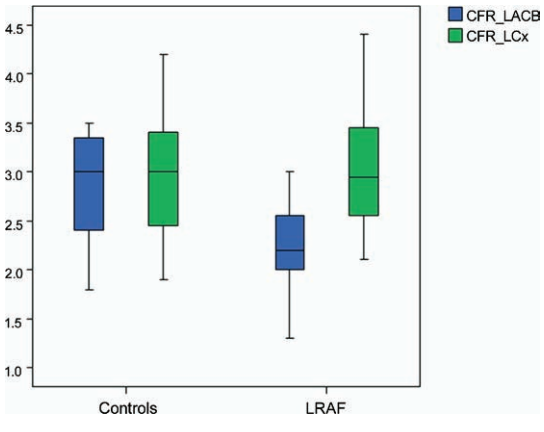

Figure 3 **CFR**

Box-plots of CFR in the LACB and the LCx for patients with LRAF and in control subjects. Abbreviations as in Figures 1 and 2.

selectively positioned in the LACB; these patients were excluded from the final analysis.

The clinical data from the remaining 16 patients and the control subjects are given in Table 1.

Heart rate and arterial blood pressure. Heart rate and systolic and diastolic blood pressures recorded during LCx and LACB Doppler measurements, in both patients and control subjects, are given in Table 2.

Coronary flow velocity measurements. The Doppler parameters recorded at baseline and at maximum hyperemia are given in Table 2.

LCx. There was a significant drug effect ($p < 0.001$) on APV but no significant group ($p = 0.14$) or interaction effects ($p = 0.21$) (Figs. 1 and 2).

The CFR was 3.1 ± 0.6 in LRAF patients and 3.0 ± 0.6 in control subjects; the difference between these values was not statistically significant ($p = 0.72$) (Fig. 3).

LACB. Although there were no significant differences in APV between patients and control subjects at baseline, there was a significant group effect ($p = 0.002$) during maximal hyperemia. There were also significant drug ($p < 0.001$) and interaction ($p < 0.001$) effects. The h-APV was significantly lower in patients with LRAF than in the control subjects (Figs. 1 and 2).

The CFR was significantly lower in patients with LRAF than in the control subjects (mean difference 0.62, 95% CI 0.97 to 0.26; $p = 0.001$) (Fig. 3). In patients with LRAF, the CFR showed no significant correlation with the number of AF episodes, the duration of AF history, the time since the last episode of AF, or the duration of the last episode.

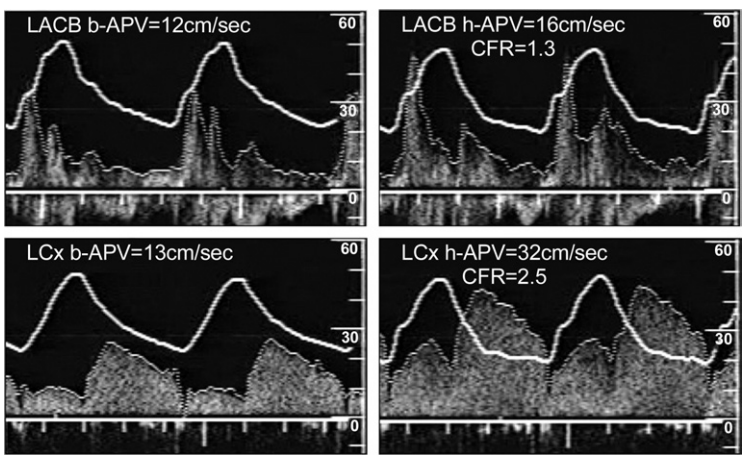

Figure 2 **CFR Recordings**

Left atrial circumflex branch and LCx b-APV and h-APV from a patient with lone recurrent atrial fibrillation. CFR = coronary flow reserve; other abbreviations as in Figure 1.

Atrial branch versus LCx. In the LRAF patients, although there were no significant differences in b-APV, there was a significant artery effect ($p = 0.001$). There were also significant drug ($p < 0.001$) and interaction ($p < 0.001$) effects. The h-APV was significantly lower in the LACB compared with the LCx (Figs. 1 and 2). The CFR was significantly lower in the LACB compared with the LCx (mean difference 0.83, 95% CI 1.16 to 0.49; $p < 0.001$) (Fig. 3).

In the control subjects, there was a significant drug effect ($p < 0.001$) but no significant artery ($p = 0.45$) or interaction ($p = 0.40$) effect. There was also no significant difference in CFR between the 2 arteries ($p = 0.28$).

Discussion

We found that the CFR of the LACB in patients with LRAF was significantly reduced compared not only with the LCx coronary artery but also with the corresponding values in the control subjects.

Atrial CFR in patients with LRAF. The microcirculation is not just a network of passive channels but is also an active site of blood flow control. At rest (baseline), the capability for blood flow regulation is high, because 60% of total myocardial vascular resistance is offered by arterioles. However, when hyperemia is induced, smooth muscle vasodilation results in dilatation of the arterioles and venules with no change in the capillaries. The total myocardial vascular resistance decreases, and the capillaries offer the most resistance to blood flow and provide a ceiling to hyperemic blood flow. Consequently, conditions that are associated with fewer capillaries are associated with reduced CFR.

Because chronic AF is associated with atrial myocardial fibrosis and vascular degeneration of atrial cells (2,3), and interstitial and perivascular isolated atrial amyloid deposition (3) and similar pathoanatomic changes have been observed in patients with LRAF (4,5), functional and/or structural changes in the microcirculation are to be expected and could explain our findings of normal coronary flow at baseline and reduced coronary flow at maximal hyperemia, as well as the reduced CFR.

Pathophysiological role of coronary flow abnormalities in LRAF. Atrial myocardium is known to have unique intrinsic characteristics. Oxygen extraction is about one-half that of the ventricle (11), and atrial myocytes are more sensitive than ventricular to flow reductions (10). This peculiarity of atrial perfusion regulation, combined with the reduced maximal blood flow found in patients with LRAF, leads to detrimental effects on atrial blood supply. In addition, the fibrillatory state in itself is a condition with high energy requirements (11).

Consequently, these patients may exhibit repeated episodes of oxygen demand/supply mismatch, atrial ischemia, chronic atrial hypoperfusion and atrial myocardial hibernation, or even fibrosis, together with a deterioration of atrial microvascular dysfunction that may further aggravate coronary blood flow abnormalities in a vicious circle. In this context of microvascular dysfunction as the pathophysiological substrate for LRAF, we may easily explain why AF begets AF (12).

Although it is not known whether atrial microcirculation dysfunction in patients with LRAF has an etiologic link or is an epiphenomenon, it may be added to the known mechanisms (13–16) that have been implicated in the pathogenesis of atrial fibrosis.

Earlier studies. Recently, 2 animal studies from the same group not only showed that acute atrial ischemia induces a substrate that supports AF maintenance (9), but also found a substrate-specific response to therapy (17). These data further reinforce the hypothesis that atrial ischemia contributes to the pathogenesis of AF.

Study limitations. The limitations of intracoronary Doppler in assessing myocardial perfusion have been analyzed in a previous report (10).

Conclusions

This study confirms, for the first time, atrial myocardial perfusion abnormalities and coronary flow reserve impairment in patients with LRAF, indicating microvascular dysfunction as an associated pathophysiological substrate.

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