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Atrial Conduction Slows Immediately Before the Onset of Human Atrial Fibrillation

A Bi-Atrial Contact Mapping Study of Transitions to Atrial Fibrillation

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Objectives The aim of this study was to determine whether onset sites of human atrial fibrillation (AF) exhibit conduction slowing, reduced amplitude, and/or prolonged duration of signals (i.e., fractionation) immediately before AF onset.

Background Few studies have identified functional determinants of AF initiation. Because conduction slowing is required for reentry, we hypothesized that AF from pulmonary vein triggers might initiate at sites exhibiting rate-dependent slowing in conduction velocity (CV restitution) or local slowing evidenced by signal fractionation.

Methods In 28 patients with AF (left atrial size 43 ± 5 mm; n = 13 persistent) and 3 control subjects (no AF) at electrophysiological study, we measured bi-atrial conduction time (CT) electrogram fractionation at 64 or 128 electrodes with baskets in left (n = 17) or both (n = 14) atria during superior pulmonary vein pacing at cycle lengths (CL) accelerating from 500 ms (120 beats/min) to AF onset.

Results Atrial fibrillation initiated in 19 of 28 AF patients and no control subjects. During rate acceleration, conduction slowed in 23 of 28 AF patients (vs. no control subjects, $p = 0.01$) at the site of AF initiation (15 of 19) or latest activated site (20 of 28). The CT lengthened from 79 ± 23 ms to 107 ± 39 ms ($p < 0.001$) on acceleration, in a spectrum from persistent AF (greatest slowing) to control subjects (least slowing; $p < 0.05$). Three patterns of CV restitution were observed: 1) broad (gradual CT prolongation, 37% patients); 2) steep (abrupt prolongation, at CL 266 ± 62 ms, 42%); and 3) flat (no prolongation, 21% AF patients, all control subjects). The AF initiation was more prevalent in patients with CV restitution (17 of 23 vs. 2 of 8; $p = 0.03$) and immediately followed abrupt reorientation of the activation vector in patients with broad but not steep CV restitution ($p < 0.01$). Patients with broad CV restitution had larger atria ($p = 0.03$) and were more likely to have persistent AF ($p = 0.04$). Notably, neither amplitude nor duration (fractionation) of the atrial signal at the AF initiation site were rate-dependent (both p = NS).

Conclusions Acceleration-dependent slowing of atrial conduction (CV restitution) precedes AF initiation, whereas absence of CV restitution identifies inability to induce AF. Conduction restitution, but not fractionated electrograms, may thus track the functional milieu enabling AF initiation and has implications for guiding AF ablation and pharmacological therapy. (J Am Coll Cardiol 2012;59:595–606) © 2012 by the American College of Cardiology Foundation

Premature atrial complexes or rapid tachycardias might trigger human atrial fibrillation (AF) (1,2) yet likely interact with dynamic mechanisms ("substrates") to do so, because most triggers do not cause AF. Plausible mechanisms include conduction velocity (CV) and repolarization (3,4) dynamics. Slowing of atrial CV might result from atrial fibrosis on magnetic resonance imaging (5) (with its surrogate of low voltage) (6), yet structural elements are constant and thus do not per se explain why AF initiation is dynamic and typically rate-related.

We hypothesized that AF initiation requires the emergence of slow conduction at fast rates that might not be evident at slow baseline rates and that this might arise dynamically at the precise onset site of AF. Although prior studies have shown slow atrial CV at slow rates in AF patients (7,8), even those with "lone" AF (9), regionally slow baseline CV might also occur in patients without AF (10,11). Notably, prior work has examined CV at limited

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Abbreviations and Acronyms

AF = atrial fibrillation
APD = action potential duration
CFAE = complex fractionated atrial electrograms
CL = cycle length (of pacing)
CT = conduction time
CV = conduction velocity
ECG = electrocardiogram/electrocardiographic
LA = left atrium/atrial

rates without defining its rate response (restitution), has rarely studied CV in the context of a spectrum of AF vulnerability (i.e., persistent AF, paroxysmal AF, and control subjects without AF), and has not studied the very rapid rates most relevant to AF initiation.

Prolongation of the electrocardiographic (ECG) P-wave, an indirect index of slow atrial conduction, is also an actuarial predictor of AF (12,13). However, ECG studies cannot localize sites of slowing within the atrium and also have not studied very rapid rates relevant to AF. As a corollary, the biophysics of charge conservation dictates that prolonged atrial electrograms from CV slowing should also exhibit reduced amplitude, comprising both "fractionated" electrograms observed during sinus rhythm (14) and AF (15). However, the relationship of fractionated electrograms to CV slowing before AF onset has also not been studied.

We tested our hypotheses by examining bi-atrial conduction time (CT) and atrial signal diminution and prolongation during incremental pacing from the superior pulmonary veins to AF initiation, at the site of AF onset defined from contact 64-128 electrode maps of left or both atria in patients with persistent AF, paroxysmal AF, and control subjects before ablation.

Methods

Patient flow. We prospectively enrolled 31 consecutive patients referred for ablation to the Veterans Affairs and University of California Medical Centers in San Diego—28 for AF (15 paroxysmal, 6 persistent, 7 longstanding persistent), and 3 control subjects (1 with left-sided accessory pathway, 1 with atrial tachycardia, and 1 with left ventricular tachycardia) without AF. In AF patients, left atrial (LA) thrombus was excluded by transesophageal echocardiography. In control subjects, pre-procedural AF was excluded by Holter monitoring and several ECGs. The study protocol was approved by our joint Institutional Review Board, and all patients provided written informed consent. Some patients were included in recent reports that action potential duration (APD) restitution slope >1 explains the initiation of paroxysmal AF from ectopic beats (3) and that APD alternans precedes AF onset (4).

Placement of recording electrodes. Electrophysiology study was performed >5 half-lives after discontinuing antiarrhythmic medications (3 patients had discontinued amiodarone >30 days prior) (Table 1). A decapolar catheter was placed in the coronary sinus via femoral venous access, and after trans-septal puncture, a deflectable 4-mm tip catheter was used to record and pace at the right or left superior pulmonary vein antra, common sites of AF-triggering ectopy or tachycardia (Fig. 1). A 64-pole basket catheter (Constellation, Boston Scientific, Natick, Massachusetts) was advanced trans-septally to the LA. Right atrial recordings were made either from a quadipolar catheter or, in 14 patients, an additional basket for a total of 138 (128 basket plus 10 coronary sinus) electrodes (Fig. 1). Baskets were manipulated to maintain optimum electrode contact with the atrial wall with fluoroscopy, electrograms, and intra-cardiac echocardiography.

Pacing protocol. Patients in AF were electrically cardioverted to sinus rhythm, and the protocol started after 15 min, prior to ablation. We delivered 74 paced beats at cycle lengths (CL) of 500 ms, 450 ms, 400 ms, 350 ms, and 300 ms, then in 10-ms steps to AF (sustained if >1 min), capture failure (n = 6), or patient intolerance, whichever came first.

Table 1 Clinical Characteristics

Characteristic	Persistent AF (n = 13)	Paroxysmal AF (n = 15)	Control Subjects (n = 3)	p Value
Age, yrs	64 ± 11*	62 ± 6*	48 ± 22	0.43
History of AF, months	74 ± 67	31 ± 30	—	0.02
Left atrial diameter, mm	46 ± 4*†	41 ± 5	37 ± 2	<0.01
LV ejection fraction, %	55 ± 11	59 ± 7	54 ± 18	0.58
CHF, n (%)	5 (38)	2 (13)	1 (33)	0.38
Coronary disease, n (%)	5 (23)	3 (33)	1 (33)	0.26
Medications, n				
ACEI/ARB	6	8	0	0.28
Statins	7	10	2	0.84
Beta-blockers	9	7	2	0.58
Class I agents	1	1	0	0.52
Amiodarone	2	0	1	0.21
Sotalol	1	5	1	0.49
Dofetilide	0	2	0	0.27

*$p < 0.05$ versus control subjects; †$p < 0.05$ versus paroxysmal atrial fibrillation (AF).
ACEI = angiotensin-converting enzyme inhibitors; ARB = aldosterone receptor blockers; CHF = congestive heart failure; LV = left ventricular; NYHA = New York Heart Association.