Alternans of Atrial Action Potentials During Atrial Flutter as a Precursor to Atrial Fibrillation

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Background—The mechanisms underlying the transition of typical atrial flutter (Afl) to fibrillation (AF) remain unclear. We set out to test the hypothesis that Afl disorganizes to AF via alternans of atrial action potentials.

Methods and Results—In 38 patients with Afl, monophasic action potentials (MAPs) were recorded at the isthmus and either high or low right atrium (HRA, LRA) during overdrive pacing to 160 ms or to the initiation of AF, whichever came first. MAP duration measured at 90% repolarization was longer at the isthmus in all patients, and failed to shorten with rate, compared with the HRA (n=38) or LRA (n=5). In 20 patients who developed AF, progressive pacing first caused alternans of isthmus MAP duration and amplitude at mean cycle length of 219±45 ms, followed by AF at a mean onset cycle length of 184±38 ms. Subsets of this group showed spontaneous action potential duration alternans at the isthmus (11 of 20 patients) and 2:1 isthmus conduction block immediately preceding AF (4 of 20 patients). In the 18 patients who did not develop AF, MAP alternans was less common (9 of 18 patients; P<0.0003), and occurred only at faster pacing (cycle length=169±25 ms; P<0.05).

Conclusions—In patients with typical Afl, action potential duration rate maladaptation at the isthmus may lead to action potential duration alternans and conduction block preceding the transition to AF. These isthmus characteristics may enable the spontaneous initiation of AF through wavefront fractionation and may explain the benefits of isthmus ablation in preventing AF recurrence. (Circulation. 2002;106:1968-1973.)

Key Words: alternans ■ atrial flutter ■ fibrillation ■ action potentials ■ waves

The dynamic mechanisms through which atrial tachycardias “degenerate” into reentrant atrial fibrillation (AF) remain unclear. It is now clear that AF frequently initiates after rapid regular rhythms such as focal pulmonary vein tachycardias1 or the macroreentrant circuit of atrial flutter. However, the mechanisms underlying disorganization of these rapid regular rhythms into AF and the reasons for wavefront fractionation and conduction block caused by these rapid impulse generators are poorly understood.

We hypothesized that isthmus-dependent atrial flutter may initially disorganize into AF through progressive alternans of action potential duration (APD), leading to conduction block, then fibrillatory conduction, and then AF. This hypothesis was inspired by several observations. First, elevated heart rates may lead to alternans of the T wave,2 ventricular APD,3 and, in preliminary reports from our laboratory and others,4 atrial APD. Second, numeric simulations have elegantly described mechanisms through which rate-related APD alternans, indicating temporal heterogeneity in repolarization, may lead to reentry.5 Third, APD alternans has been shown to precipitate conduction block and initiate reentry in the ventricle,6 which may explain the value of T-wave alternans in predicting clinical ventricular arrhythmias.2,7 However, it is unknown whether APD alternans is arrhythmogenic in the atrium and whether it plays any functional role in the initiation of AF.

We set out to test our hypothesis in patients with typical atrial flutter (Afl) by studying atrial monophasic action potentials (MAPs) during pacing-induced and spontaneous transitions to AF. We chose to record MAPs from the right atrial isthmus, a zone of slow conduction critical to the maintenance of atrial flutter, and the high and low right atrium (HRA and LRA, respectively).

Methods

Patients

We recruited 38 consecutive male patients with typical (counterclockwise, isthmus-dependent) Afl refractory to antiarrhythmic medications who were referred to the Veterans Affairs Medical Center, Washington, DC, for pace termination or radiofrequency ablation. Patients were studied during sustained Afl in the Electrophysiology
Laboratory; 4 had documented paroxysmal AF (Table). Our institutional committee on human investigation approved all studies, and all patients provided written informed consent.

Patients were studied in the postabsorptive state, and all antiarrhythmic medications (Table) except for amiodarone were withheld for 5 half-lives. Left atrial diameter and left ventricular ejection fraction, %

| Left atrium diameter, mm | 41.7±5.7 | 37.4±6.6 | 0.057 |
| Duration of Afl, wk | 15.6±30.3 | 6.7±10.7 | NS |

Drugs

| Class I | 2 | 2 | NS |
| β-Blockers | 1 | 2 | NS |
| Amiodarone | 2 | 3 | NS |
| Ca2⁺ blockers | 8 | 6 | NS |
| ACE inhibitor | 8 | 9 | NS |
| Digoxin | 8 | 7 | NS |

Values are number of patients or mean±SD. NYHA class indicates New York Heart Association functional class.

Patients presented with Afl mean CL of 243±27 ms. The experimental protocol induced AF in 20 patients at mean pacing CL of 184±38 ms. The remaining 18 patients remained in Afl despite overdrive pacing to CL of 160 ms. Two patients in each group had prior documented AF (Table) but were otherwise similar to others in their groups. There was a nonsignificant trend for shorter Afl CLs in AF-inducible (219±22 ms) than noninducible (240±28 ms; P=NS) patients. There were almost-significant trends for patients paced into AF to have worse NYHA functional class and larger left atria. Patient demographics are shown in the Table.

The MAPD-CL Relationship at the Isthmus and RA Free Wall

Figure 1 shows that MAPD₀⁻ was longer at the isthmus than the HRA or LLA. MAPD was longer at the isthmus than the HRA or LLA (labeled HRA) in all patients. Isthmus MAPDs in AF-inducible patients were longer than in patients without AF (P<0.05 for CL of 260 ms and for all CLs together) and failed to shorten at the shortest pacing CL. Isthmus MAP in patients who did not develop AF and MAPD at nonisthmus sites in both groups increased monotonically with pacing CL.

Groups. The χ² test was applied to contingency tables. A probability level of 5% (P<0.05) was considered statistically significant.

Results

Patients presented with Afl mean CL of 243±27 ms. The experimental protocol induced AF in 20 patients at mean pacing CL of 184±38 ms. The remaining 18 patients remained in Afl despite overdrive pacing to CL of 160 ms. Two patients in each group had prior documented AF (Table) but were otherwise similar to others in their groups. There was a nonsignificant trend for shorter Afl CLs in AF-inducible (219±22 ms) than noninducible (240±28 ms; P=NS) patients. There were almost-significant trends for patients paced into AF to have worse NYHA functional class and larger left atria. Patient demographics are shown in the Table.

The MAPD-CL Relationship at the Isthmus and RA Free Wall

Figure 1 shows that MAPD₀⁻ was longer at the isthmus than nonisthmus sites (HRA and LRA pooled) for all CLs,
although this was not statistically significant. MAPD did not differ significantly between the HRA and LRA at any CL. In AF-inducible patients, isthmus MAPD\(_{90}\) was longer than in patients without AF \((P<0.05\) for CL of 260 ms and for all CLs together; \(n=20\)). At nonisthmus sites, MAPD did not differ significantly between patients with or without AF.

Isthmus MAPD decreased little with decreasing CL in patients who developed AF, whereas MAPD decreased monotonically with shorter CL at nonisthmus sites and in other patients (Figure 1). Differences in MAPD-CL between the isthmus and RA free wall were even more apparent in individual patients. Figure 2 shows rate maladaptation of isthmus MAPD, relative to the HRA, in a patient induced into AF. This was seen in all AF-inducible patients.

MAPD Alternans

MAPD alternans occurred in all patients (20/20) who developed AF, but in only 9 of 18 patients who did not \((P=0.0003)\). Figure 3 shows MAPD during decremental pacing from CL of 260 ms in a patient who developed AF. MAPD was longer at the isthmus than the HRA. Faster pacing initiated APD alternans at the isthmus, reflected by the separation of MAPD into 2 populations (labeled A and B) occurring every other beat. Figure 4A shows electrograms of pronounced alternans of isthmus MAP duration and amplitude in another patient who developed AF. The magnitude of APD alternans at the isthmus in AF-inducible patients was \(24.8\pm11.1\) ms at 220 ms, \(20.0\pm10.4\) ms at 200 ms, and \(30.4\pm22.3\) ms at 180 ms pacing (differences \(P=NS\)).

In patients who did not develop AF, MAPD alternans occurred in 9 of 18 patients, but it required faster pacing (CL \(189\pm25\) ms versus CL \(219\pm45\) ms; \(P<0.05\)). In both groups, alternans was consistent at the isthmus (Figure 4A) but was also seen at nonisthmus sites (Figure 4B). When alternans was recorded at multiple atrial sites, it was sometimes out of phase between them (discordant alternans; Figure 4B).

Exaggerated MAPD Alternans Preceded Disorganization into AF

In 11 patients, MAPD alternans was seen spontaneously during Afl. In 3 patients, spontaneous alternans became exaggerated and spontaneously disorganized into AF (Figure 5). These 3 patients had a shorter Afl CLs (238\pm15 ms) than the other 8 (254\pm13 ms; \(P=0.11\)). We observed a very similar disorganization in patients paced from Afl into AF (Figure 6). We also observed a potential mechanism for this disorganization: Progressive APD alternans progressed to 2:1 isthmus conduction block immediately before disorganization to AF both during pacing (in 4 patients; Figure 7) and spontaneously (Figure 5 and legend).

Discussion

The present study is the first to document that alternans of atrial action potentials in humans occurs during progressive disorganization of Afl to AF. During atrial flutter, we show that atrial APD is longer and shortens less with increasing rate at the isthmus than at the LRA or HRA. With progressively faster pacing, we found that this rate maladaptation leads to alternans of APD at the isthmus preceding all transitions to AF. At still faster heart rates, APD alternans led to 2:1 isthmus conduction block preceding the transition to AF. Conversely, patients who did not develop AF at our maximum paced rate exhibited significantly less APD alternans. These data suggest that APD alternans may play a role in the degeneration of typical isthmus-dependent Afl to AF, potentially via wavefront fractionation at the isthmus.

Nonuniformity and Rate Maladaptation of Atrial APD

The longer baseline APD and flattened APD-CL relationship at the isthmus versus the LRA or HRA (Figure 1) may
contribute to regional conduction block and the initiation of AF. Indeed, prior studies have associated maladaptation of atrial APD with AF in animals\textsuperscript{8–13} and humans,\textsuperscript{14,15} although not previously with AFl. Mechanistically, AF-related APD maladaptation may be associated with reduced mRNA expression for the $\alpha$-subunit of the L-Ca\textsuperscript{2+} channel,\textsuperscript{13} may reflect cytosolic Ca\textsuperscript{2+} overload,\textsuperscript{16} and is attenuated by ryanodine.\textsuperscript{12} Although these calcium-dependent mechanisms may be inhibited by L-Ca\textsuperscript{2+} antagonists, our non–AF-inducible patients (without maladaptation at these rates; Figure 1) did not have higher rates of use of such medications (Table).

Spatial nonuniformities in APD maladaptation at the isthmus (Figure 4B), which may be a corollary of its slow conducting role during AFl, versus other atrial sites may potentiate AFl or AF. Indeed, studies in canine atria emphasize that factors including spatial nonuniformity, rather than cellular electrophysiology, influence the stability of AF.\textsuperscript{12} Although the repolarization dynamics of the isthmus are poorly described, atrial effective refractory period (ERP) in post-AF cardioversion patients lengthened paradoxically at shorter CLs in the LRA than the HRA, coronary sinus, or control patients.\textsuperscript{17} It is unclear whether the isthmus was included with LRA in that study. Detailed mapping of atrial epicardium demonstrates that AF vulnerability relates to the spatial heterogeneity of effective refractory period (measured directly in dogs\textsuperscript{10} and indirectly in patients\textsuperscript{19}), and that isthmus effective refractory period are among the longest (Figure 2B of Fareh et al\textsuperscript{10}). Other atrial heterogeneities have also been reported. In dogs, the transitional cell zone of the anterior fossa ovalis showed progressive alternans of action potential magnitude, then 2:1 block during comparable pacing (CL 180 to 140 ms).\textsuperscript{19} This finding became less noticeable farther from the tendon of Todaro and was absent at the HRA and coronary sinus. Speculating on potential cellular mechanisms at the isthmus, APD rate maladaptation may represent reduced regional outward current at higher rates. Longer APD has been associated with local elevations of $I_{Ca}$ and reduced $I_{Kr}$ density in canine RA\textsuperscript{20,21} and with reduced $I_{Kr}$ which is further inactivated at higher rates, in rabbit\textsuperscript{22} and canine\textsuperscript{23} RA.

Regional nonuniformities in APD shortening (electrical remodeling),\textsuperscript{10} which we have described in AFl,\textsuperscript{23} promote AF and may coexist with regional rate maladaptation. The relative spatial distributions of atrial rate maladaptation and remodeling\textsuperscript{4} may increase APD dispersion to facilitate the transition to and maintenance of AF. These spatially nonuniform repolarization dynamics may help to explain why...
Atrial APD Rate Maladaptation, APD Alternans, and AF

The spatial nonuniformity of rate maladaptation in both AF and AF facilitates the development of regional conduction block and may therefore provide another mechanism through which “AF begets AF.” We hypothesize that atrial APD alternans, in combination with further rate acceleration, may precede all transitions of typical AF to AF. The facts that AF spontaneously followed APD alternans in 3 patients with rapid atrial rates, and that atrial APD alternans required faster pacing to be seen in non–AF-inducible patients, are consistent with our hypothesis: At still faster rates (CL <160 ms), these patients would likely also develop AF.

At the isthmus, attenuated APD shortening (rate maladaptation) at faster atrial rates promoted foreshortening of the diastolic interval (illustrated over a CL range in Figure 3, and at one CL in Figure 4). The encroachment of successive pacing stimuli on partially or fully refractory myocardium likely caused the smaller APD, thereby lengthening the succeeding diastolic interval and APD and initiating alternans (Figure 4). As the pacing rate was further increased, alternans increased in a “crescendo” fashion until outright refractoriness (conduction block) was encountered every other beat (Figure 7). Our results are in close agreement with the elegant recent studies by Kim et al8 who showed, in patients after electrical cardioversion from AF, that rapid atrial pacing (at very similar CL of 220 to 180 ms) also foreshortened diastolic interval to cause APD alternans and 2:1 block in HRA and posterior and septal RA (the authors did not record from the RA isthmus). Our observations during AF extend their findings and provide evidence that spontaneous (Figure 5) and paced (Figure 6) isthmus APD alternans preceded dynamic wavefront fractionation, conduction block (Figures 5 and 7), and the transition to AF. These findings are also consistent with action potential alternans reported recently in the canine atrium (anterior fossa ovalis).19

Other Causes for APD Alternans

Theoretically, ischemia could contribute to MAP alternans in the atrium, as it does in ventricle,27 although the link between atrial tachycardia or AF and ischemia is controversial. AF-related remodeling is not attenuated by IKATP inhibition with glibenclamide,16 but fibrillating atria do show glycogen deposition and ultrastructural changes akin to those of hibernating ventricle.28

Atrial stretch may also be invoked as a cause of alternans. Patients induced into AF showed near-significant trends toward larger left atrial diameters and slightly worse NYHA functional class (but similar left ventricular ejection fraction) than noninducible patients. In fact, this finding supports our hypothesis, because those patients more likely to develop AF (with worse congestive heart failure and larger left atria) were those who exhibited MAPD alternans. Experimentally, stretch has variable effects on atrial repolarization29, although some studies were unable to correlate RA pressure with electrical remodeling.18 Further studies are required to resolve this issue.

Limitations and Future Directions

We localized the isthmus reliably with the use of fluoroscopy and electrography, although greater spatial information from a Halo catheter, endocardial mapping, and left atrial recordings would provide greater insights into the significance of APD alternans and its functional relationship with the transition to AF.

Because AF most likely represents a spectrum of disorders, our results cannot be extrapolated to explain transitions to AF from other tachycardias. Work in broader populations is therefore required to study spatially nonuniform atrial APD rate maladaptation and alternans in patients with focally triggered AF and atypical forms of AF. Although only 2 patients with inducible AF had documented prior AF, there are known difficulties in accurately assessing AF burden—particularly in patients with existing AF. Further work should examine the predictive value of APD alternans for future episodes of AF.

Although MAP recordings may be technically demanding, it is unlikely that MAPD alternans was artifactual (for instance, caused by catheter movement) because our MAP signals were stable at baseline, of typical and consistent morphology, and alternans segregated with the development of AF.

Conclusions

In patients with typical counterclockwise AF, rate maladaptation of APD at the isthmus during AF led to APD alternans, which preceded every episode of disorganization to AF. These dynamic properties of the isthmus enable regional conduction block and wavefront fractionation, facilitate the transition to AF, and may help to explain the therapeutic benefits of isthmus ablation in preventing recurrences of AF.

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