Mechanism Underlying Initiation of Paroxysmal Atrial Flutter/Atrial Fibrillation by Ectopic Foci
A Simulation Study

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Background—The mechanisms underlying paroxysmal atrial flutter/atrial fibrillation initiation by ectopic foci from various locations are unclear.

Methods and Results—We used parallel computational techniques to study an anatomically accurate 3-dimensional atrial structure incorporating a detailed ionic-current model of an atrial myocyte. At the single-cell level, upregulation of the L-type Ca\(^{2+}\) current \(I_{\text{Ca,L}}\) steepened restitution curves of action potential duration and conduction velocity compared with the control. Spontaneous firings of ectopic foci, coupled with sinus activity, produced dynamic spatial dispersions of repolarization, including discordant alternans, which caused conduction block and reentry only for the elevated \(I_{\text{Ca,L}}\) case. For each foci location, a vulnerable window for atrial flutter/atrial fibrillation induction was identified as a function of the coupling interval and focus cycle length. For ectopic foci in the pulmonary veins and left atrium, the site of conduction block and reentry gradually shifted, as a function of coupling interval, from the right atrium to the interatrial area and finally to the left atrium. The size of the vulnerable window was largest for pulmonary vein foci, becoming markedly smaller for right atrial foci, especially those near the sinoatrial node.

Conclusions—These findings suggest that a mechanism of dynamically induced repolarization dispersion, especially discordant alternans, underlies the induction of atrial flutter/atrial fibrillation by atrial ectopic foci. The sites and likelihood of reentry induction varied according to ectopic focus location and timing, with the largest vulnerable window corresponding to the pulmonary vein region. (Circulation. 2007;115:2094-2102.)

Key Words: action potentials ▪ arrhythmia ▪ atrial flutter ▪ dynamics ▪ fibrillation ▪ reentry ▪ waves

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Leaves of atrial muscle that surround the pulmonary veins (PVs) are known to be the most frequent source of ectopic beats, which initiate and perpetuate atrial fibrillation (AF). Electric isolation of the PVs effectively eliminates AF in the majority of patients. The mechanism by which PV ectopic foci induce AF remains unclear. Other functional regions, such as the left atrial (LA) posterior free wall, superior vena cava, inferior vena cava, vein of Marshall, crista terminalis, coronary sinus, and interatrial septum, have also been found to play critical roles in the initiation of AF.

Recent studies indicate that atrial flutter (AFL) and AF may share common triggers located in the PV region of the LA. Furthermore, studies have linked these 2 arrhythmias by showing alternans of atrial action potentials during the spontaneous transition from typical AFL to AF. Noncavotricuspid isthmus-dependent flutters have been found in the right atrium (RA), interatrial septum and LA, or both atria in patients with or without underlying structural heart disease. Emerging evidence suggests that there may be a similar substrate or arrhythmogenic mechanism for the onset of AFL/AF and that this mechanism could be independent of the site of ectopic foci or the reentrant circuits. However, the properties of the substrate or the arrhythmogenic mechanism remain unclear.

It is the central aim of the present study to illuminate the mechanism underlying the initiation of paroxysmal AFL/AF by ectopic foci. We performed extensive numerical simulations using an anatomically accurate 3-dimensional human atrial model and parallel computational techniques.

We systematically investigated the effects of 2 parameters—(1) the coupling interval between sinus activation and the succeeding ectopic beat and (2) the cycle length of
repetitive beats from that ectopic focus—on the initiation of AFL/AF from various ectopic foci locations.

Methods

The Single-Cell Model

We used an elaborate human atrial cell model developed recently by Courtemanche et al.4 To better account for experimental observations, we modified the original model in several ways. At a normal heart rate of 60 bpm, the action potential duration (APD) of the Courtemanche model is too long (>280 ms). This is mainly due to the heart rate of 60 bpm, the action potential duration (APD) of thenormal model in several ways. At a normal heart rate of 60 bpm, the action potential duration (APD) of the Courtemanche model is too long (>280 ms). This is mainly due to the maximum conductance of the inward rectifier K⁺ current being too small (gK₁ = 0.09 nS/pF). The small value of gK₁ yields a high-input membrane resistance (~174 MΩ). Note that with different isolation procedures, which affect isolation-sensitive currents such as I_{K1}, the reported values for the input resistance of human atrial cells can vary in a large range.4 We increased gK₁ by 200% so that gK₁ = 0.27 nS/pF, which is close to the measurement of human atrial cells reported by Koumi et al.5 To initiate AFL/AF, the key parameter that we have altered is the maximum conductance of the L-type Ca²⁺ current g_{Ca,L}. Recent observations showed that blockade of L-type Ca²⁺ channels suppressed discordant alternans clinically for AF patients.6 On the basis of these studies, we set g_{Ca,L} = 0.1857 nS/pF; an increase of 50% of the control (Figure 1A). Note that the modifications of gK₁ and g_{Ca,L} are within the physiological ranges suggested by Courtemanche et al.4 With these modifications, the resulting APDs at a heart rate of 60 bpm for the control and the case, in which L-type Ca²⁺ current I_{Ca,L} was elevated, are APD_{0} = 210 ms and APD_{1} = 235 ms (Figure 1B), respectively. Both are within the range of atrial refractory periods in humans7 and are comparable to previous modeling studies of atrial arrhythmias.8

Restitution Properties

Restitution, which refers to the relationship between electrophysiological properties of a propagating wave and the previous diastolic interval, was quantified with the use of the standard S1-S2 protocol.9–11 After pacing with 100 S1 beats at cycle length = 500 ms, the APD and conduction velocity restitution (Figure 1C to 1F) were measured in a 1-dimensional atrial fiber (Figure I in the online-only Data Supplement) by varying the S2 timing. The conduction velocity was calculated from the time required for the activation wave to propagate a distance of 1 cm within a 2-cm-long atrial fiber.9–11

Atrial Anatomic Structure

We used a detailed human atrial geometry first proposed by Harrild and Henriquez.12 The model is 3-dimensional with both LA and RA (Figure IIA in the online-only Data Supplement). Major muscle bundles of the atria include the crista terminals, pectinate muscles, limbus of the fossa ovais, and Bachmann’s bundle (Figure IIB in the online-only Data Supplement). Other anatomic obstacles are as follows: the tricuspid annulus, mitral annulus, inferior vena cava, superior vena cava, 4 PVs, coronary sinus, and fossa ovais (Figure IIC to IIF in the online-only Data Supplement). The LA and RA are connected through 3 interatrial connections: the Bachmann’s bundle, fossa ovais, and coronary sinus as observed with simultaneous biatrial noncontact mapping in humans.13

By assigning different diffusion coefficients, as suggested previously,8,12 we obtained heterogeneous conduction regions in the atria (Figure IIB in the online-only Data Supplement). Specifically, the conduction velocities were 65 cm/s in the bulk tissue, 120 cm/s in the fast bundles, and 36 cm/s in the slow-conduction region. These values were measured from a 1-dimensional atrial fiber (Figure I in the online-only Data Supplement).

These conduction velocities are within, or very close to, realistic conduction velocities (normal, 60 to 75 cm/s; fast, 150 to 200 cm/s; slow, 30 to 40 cm/s).8,12 With these assignments, it takes ~110 ms for a sinus wave to activate the whole atria, with the last activation occurring in the lateral posterior region of the LA, where 3 wave fronts converge (Movie I in the online-only Data Supplement). The results are comparable to the observations from previous experiments8 and simulation studies.8,12

Pacing Protocol

Sinus beats or ectopic beats were induced by an instantaneous voltage stimulus with an amplitude of 30 mV. The stimulus was approximately twice the diastolic threshold and was applied to a cube of 9×9×9 nodes. The pacing protocol was as follows: deliver a stimulus from the sinoatrial node (at 60 bpm); then, after a coupling interval following the sinoatrial nodal stimulus, a train of at least 10 (with the exception of Figure 2) ectopic foci were delivered from the ectopic focus location of interest (eg, the PVs of the LA) at a cycle length. The ectopic focus firings were stopped if no reentry was induced within 10 ectopic beats. The protocol is similar to the real process during which paroxysmal AF can be triggered by repetitive ectopic beats.8
Isochronal Maps
Isochronal maps, which depict the activation sequence within a local region, were constructed by calculating the time elapsed since a given temporal reference point (e.g., time 0 in Figure 2) at which the propagating wave front (defined with a threshold of −30 mV) passes through each spatial location.

Vortex Filaments
In a 2-dimensional atrial tissue, spiral wave reentry can be characterized by tracing the tip trajectory. In a 3-dimensional atrial anatomy, spiral waves become scroll waves, and, correspondingly, spiral tips become vortex filaments. Vortex filaments, which represent the number of scroll wavelets, were detected by calculating the intersection of 2 successive isovoltage lines (−30 mV) arising from the propagating wave front. Moreover, they can indicate atrial regions where wave break occurs by showing the birth of new vortex filaments.

Results

L-Type Ca\(^{2+}\) Current and Restitution Properties
Through increasing the maximum conductance of the L-type Ca\(^{2+}\) current \(g_{Ca,L}\) (see Methods), the L-type Ca\(^{2+}\) current \(I_{Ca,L}\) upregulation lengthened the APD (Figure 1A and 1B). Compared with the control, the APD had a steepened restitution curve for the elevated \(I_{Ca,L}\) case, with the maximum slope of the APD restitution slightly >1 within a range of diastolic intervals between 175 and 185 ms (Figure 1C and 1D). In addition, conduction velocity had a steepened restitution curve in a lower diastolic interval between 0 and 50 ms for the elevated \(I_{Ca,L}\) case compared with the control (Figure 1E and 1F).

To illuminate the spatiotemporal dynamics of the atrial cell model, a 1-dimensional atrial fiber was investigated for the control and the elevated \(I_{Ca,L}\) cases. Transitions from discordant alternans to conduction block in the atrial fiber were found only for the elevated \(I_{Ca,L}\) case, when it was paced with a cycle length from 200 to 160 ms. Figure 1 in the online-only Data Supplement shows such an example when cycle length=180 ms, at which discordant alternans was most prominent.

Dynamic Repolarization Dispersion and Conduction Block
Using the anatomically accurate 3-dimensional human atrial model, we performed extensive numerical simulations by exploring 2 parameters: (1) the coupling interval between sinus activation and the succeeding ectopic beat and (2) the cycle length of repetitive beats (≥10) from that ectopic focus. In our simulations, we found that ectopic foci, coupled with sinus activity, produced dynamic spatial dispersion of repolarization, which caused unidirectional block and reentry only for the elevated \(I_{Ca,L}\) case. Typically, the unidirectional block and reentry were found around the cavotricuspid isthmus of the RA (Figure 2A) or the left PVs of the LA (Figure 2B), preceding the onset of AFL/AF (Movies I and III in the online-only Data Supplement).

Note that dispersion of APDs, including discordant alternans (Figure 3A), could be observed at multiple recording sites in the atria. (Although in a rigorous sense the term “alternans” requires several beats [≥4] to be fully developed, we apply the term to the 2-beat pattern here because of the analogous APD versus diastolic interval long-short dynamics, the analogous mechanism of spatial discordance, and the demonstration of sustained alternans in the same cycle length range in the atrial fiber simulations of Figure 1 in the online-only Data Supplement.) Furthermore, within the range for which transient discordant alternans occurred (160≤ cycle length ≤200 ms; Figure I in the online-only Data Supplement), AFL/AF could be initiated by rapid firings of ectopic foci (Figure 4 and Table II in the online-only Data Supplement).

Figure 3 shows that ectopic firings from the left superior PV-induced conduction block and reentry in the cavotricuspid isthmus of the RA (Figure 3A) and left PVs (Figure 3B) for short and long coupling intervals, respectively. Specifically, when the coupling interval between the sinus beat and the first ectopic excitation was short (Figure 3A), the ectopic...
excitation had a short APD. This short APD allowed a longer subsequent diastolic interval before the second ectopic excitation, which therefore had a longer APD due to APD restitution. As the first ectopic wave propagated toward and into the RA, its preceding diastolic interval and therefore its APD gradually lengthened because the wave traveled against the repolarization gradient of the preceding sinus wave (Figure V in the online-only Data Supplement; this effect is known as “symmetry breaking”\cite10,\cite14). The APD lengthened to the extent that the second ectopic wave blocked in the cavotricuspid isthmus of the RA. Alternatively, when the coupling interval of the first ectopic excitation was long (Figure 3B), the ectopic excitation had a long APD. This long APD permitted only a short subsequent diastolic interval before the second ectopic excitation, which therefore had a shorter APD due to APD restitution. In fact, the diastolic interval was so short that conduction block occurred almost immediately in the region near the PVs. These 2 cases clearly demonstrate that both the orientation and timing of the ectopic beats relative to the preceding sinus beat are critically important for when or where conduction block will occur. Furthermore, these simulation results are consistent with predictions from Equation II in the online-only Data Supplement that relates conduction block with APD and conduction velocity restitutions and the spatial dispersion of diastolic interval of the first ectopic beat (see Conditions for Conduction Block in the online-only Data Supplement).

**Vulnerable Window and Ectopic Foci**

For certain cycle length and coupling interval combinations, AFL/AF could be initiated by rapid firing of ectopic foci (<10 beats). Each episode of AFL/AF lasted <5 seconds (Table II in the online-only Data Supplement). Figure 4 shows the induction of AFL/AF with ectopic foci from the 4 PVs, LA free wall, coronary sinus, inferior vena cava, superior vena cava, and crista terminalis, all regions from which ectopic foci have been observed clinically. However, the size and specific properties of the vulnerable window differed for different ectopic focus sites. In particular, within...
When cycle length 210 ms (see Table I in the online-only Data Supplement for details), the sequential shift-as a result of coupling interval–dependent dynamic spatial dispersion of repolarization (Figure 3). The sequential shift-gradually shifted with increasing coupling interval, from the RA (black zone) to the interatrial region (red zone) to the LA (green zone) (Table II in the online-only Data Supplement), RA (black zone) to the interatrial region (red zone) to the LA (green zone) (Table II in the online-only Data Supplement), as observed in the form of lower-loop reentry.15 Such dual-loop macroreentrant behavior involving both the inferior vena cava and tricuspid annulus is often observed in patients with typical AFL.16

Within a narrow range of intermediate coupling interval values (red zone in Figure 4A), macroreentry involved the interatrial region (Movie II in the online-only Data Supplement). After conduction block, typically at the Bachmann’s bundle or the inferior septum of the LA, macroreentry was found revolving around the interatrial region including the fossa ovalis and the inferior vena cava either clockwise or counterclockwise (Table I in the online-only Data Supplement). In this situation, the macroreentry was usually induced first (Movie I in the online-only Data Supplement). Within the vulnerable window (Table I in the online-only Data Supplement), 11 of 13 cases (85%) of RA flutter showed counterclockwise rotation around the tricuspid annulus, characteristic of “typical AFL.” Moreover, RA flutter with tricuspid annulus counterclockwise rotation could evolve not only from conduction block at the isthmus region but also after conduction block around the fossa ovalis or at the inferior vena cava. While rotating counterclockwise around the tricuspid annulus, in 5 cases reentrant waves were also found rotating around the inferior vena cava either clockwise or counterclockwise (Table I in the online-only Data Supplement and Movie I in the online-only Data Supplement), as observed in the form of lower-loop reentry.15 Such dual-loop macroreentrant behavior involving both the inferior vena cava and tricuspid annulus is often observed in patients with typical AFL.16

Atrial Flutter
After conduction block induced by left superior PV ectopic beats, different macroreentrant circuits during AFL were observed when coupling intervals were varied (see Table I in the online-only Data Supplement for details).

At shorter coupling intervals (black zone in Figure 4A), RA flutter was usually induced first (Movie I in the online-only Data Supplement). Within the vulnerable window (Table I in the online-only Data Supplement), 11 of 13 cases (85%) of RA flutter showed counterclockwise rotation around the tricuspid annulus, characteristic of “typical AFL.” Moreover, RA flutter with tricuspid annulus counterclockwise rotation could evolve not only from conduction block at the isthmus region but also after conduction block around the fossa ovalis or at the inferior vena cava. While rotating counterclockwise around the tricuspid annulus, in 5 cases reentrant waves were also found rotating around the inferior vena cava either clockwise or counterclockwise (Table I in the online-only Data Supplement and Movie I in the online-only Data Supplement), as observed in the form of lower-loop reentry.15 Such dual-loop macroreentrant behavior involving both the inferior vena cava and tricuspid annulus is often observed in patients with typical AFL.16

Within a narrow range of intermediate coupling interval values (red zone in Figure 4A), macroreentry involved the interatrial region (Movie II in the online-only Data Supplement). After conduction block, typically at the Bachmann’s bundle or the inferior septum of the LA, macroreentry was found revolving around the interatrial region including the Bachmann’s bundle, atrial septum, coronary sinus, and fossa ovalis.

With further increases of coupling interval (green zone in Figure 4A), the location of conduction block and reentry quickly shifted to the LA, and LA flutter ensued (Movie III in the online-only Data Supplement). In this situation, the macroreentry was found mainly revolving around the mitral annulus (counterclockwise). For even longer coupling intervals, the conduction block moved to the left PVs, and the ensuing macroreentry revolved around the left PVs, in addition to the mitral annulus (Movie III in the online-only Data Supplement).

Atrial Fibrillation
Figure 5 shows an example of AF snapshots, in which arrows indicate directions of wave front propagation. In our simula-
tions, AF could be initiated directly by a train of ectopic beats. However, because of a relatively small and uniform initial APD dispersion produced by the normal sinus rhythm (60 bpm), in most cases (Table II in the online-only Data Supplement) AF occurred from spontaneous conversion of AFL. Once AFL was initiated, the spontaneous conversion from AFL to AF could occur in either the presence or absence of ectopic firings. Interestingly, the conversion occurred through a brief fibrillatory conduction process (mean ± SD, 570 ± 300 ms),17 during which rapid electric impulses emanating from flutter circuits interacted with functional and/or anatomic obstacles throughout the atria, leading to fragmentation and wavelet formation (Movie I in the online-only Data Supplement). Within the vulnerable window (Table II in the online-only Data Supplement), approximately one third of AFL spontaneously converted to AF, with multiple wavelets simultaneously meandering in the atria.

Figure 6 shows that AF was characterized by multiple vortex filaments, reflecting the time-varying multiple-wavelet nature of AF. Vortex filaments (red) were found dispersed across the walls of the LA, RA, and even interatrial septum (Figure 6A), indicating wave fragmentation and formation in these regions. Moreover, the number of vortex filaments during the lifespan of an episode of AF (Figure 6B) varied from as few as 1 to as many as 9, which is comparable with previous optical mapping18 and modeling studies of AF.10 Instead of randomly meandering, vortex filaments were anchored at preferential sites such as the isthmus (Figure 6C) and the PV (Figure 6D), where they were first induced. The observed ECG characteristics during the onset of AF, that is, sinus rhythm followed by repetitive firings of ectopic foci and then AF (Figure IV in the online-only Data Supplement), are comparable to those observed clinically during the induction process of paroxysmal AF (Figure 3 in Haissaguerre et al1).

Discussion

L-Type Ca²⁺ Current and Restitution Properties

It is well documented that flattening restitution curves of the APD and conduction velocity suppresses discordant alternans.14 Through increasing the maximum conductance of the L-type Ca²⁺ current gCa,L, we found that the L-type Ca²⁺ current upregulation steepened restitution curves of both the APD and the conduction velocity (Figure 1C to 1F) and thereby promoted discordant alternans, which is consistent with recent observations that blockade of L-type Ca²⁺ channels suppressed discordant alternans clinically for AF patients.6

Additionally, for the elevated gCa,L case in our studies, the maximum slope of the APD restitution is slightly >1 (Figure

![Figure 5.](http://circ.ahajournals.org/)

**Figure 5.** Snapshots of the membrane voltage (V) during AF, in which numbered arrows indicate multiple reentrant wavelets meandering in both atria from 4 different views, as annotated in the figure. AF was induced by the PV ectopic beats when coupling interval=390 ms and cycle length=190 ms. 1 indicates anterior LA free wall and Bachmann’s bundle (BB) (superior view); 2, inferior vena cava (IVC) (inferior view); 3, posterior LA free wall (FW) (inverted left posterior view); 4, isthmus (inferior view) and tricuspid annulus (TA) (right anterior view). SVC indicates superior vena cava. See Movie I in the online-only Data Supplement.

![Figure 6.](http://circ.ahajournals.org/)

**Figure 6.** Vortex filament characteristics during AF induced by PV ectopic beats when coupling interval=390 ms and cycle length=190 ms. A, Snapshot of vortex filaments (red). B, Vortex filament fluctuation during 1 episode of AF. During AFL/AF, vortex filament trajectories are clustered around regions where conduction block first occurs, including isthmus when coupling interval=390 ms and cycle length=190 ms (C) and PVs when coupling interval=470 ms and cycle length=190 ms (D). AFL/AF has a longer duration and thus a higher density (with correspondingly smaller sampling red points for visualization) of vortex filament trajectories shown in C compared with D. Vortex filament trajectories are sampled every 5 ms. LAA indicates left atrial appendage.
AFL/AF Induction Mechanism: Discordant Alternans and APD Dispersion

We found that ectopic foci, during sinus activity, produced dynamic spatial dispersion of repolarization. Such repolarization dispersion could cause unidirectional block and initiation of reentrant AFL/AF (Figure 2). Preceding the onset of AFL/AF, a large dispersion of APDs, often manifested as discordant alternans, was observed only for the elevated $I_{CaL}$ case (Figure 3). This is consistent with recent observations in patients that discordant alternans facilitated the initiation of AF as well as the spontaneous transition between AFL and AF. In our simulations, AFL/AF could be initiated by rapid firing of ectopic foci with only a few beats (<10) (Figure 4 and Table II in the online-only Data Supplement), within the range for which transient discordant alternans occurred in the 1-dimensional fiber (160 ≤ cycle length ≤ 200 ms; Figure I in the online-only Data Supplement). In contrast, outside this range, AFL/AF could not be induced, or a train >10 beats was required to induce AFL/AF. Taken together, these results suggest a causal relationship between dynamic spatial dispersion of repolarization, notably discordant alternans, and the onset of AFL/AF.

In our simulations, AF could be initiated directly by a train of ectopic beats. More often, however, AF converted spontaneously from AFL (Table II in the online-only Data Supplement). The preference of AFL (a single macroreentrant circuit) over AF (multiple reentrant wavelets) induction by a few ectopic beats in our simulations was because of (1) a relatively small initial APD dispersion produced by sinus rhythm (60 bpm) preceding the ectopic beats and (2) a normal atrial anatomy (with no structural heart disease). Consistent with these observations, detailed mapping in AF patients showed that organized monomorphic atrial arrhythmias was more extensive in patients with structural heart disease and persistent AF compared with patients without structural heart disease or paroxysmal AF. Therefore, these results support the clinical observation that AFL is induced preferably by focal discharges for a normal spatial dispersion of atrial refractoriness, whereas AF is more likely to be induced when the dispersion is increased, such as due to atrial inflammation or structural heart diseases.

Atrial Flutter

By simply varying the coupling interval between sinus activation and the ectopic firing, our results link, through a sequential shifting phenomenon, among different AFL circuits as a function of the coupling interval is of significance for relating various AFL circuits observed clinically through a similar induction mechanism. In addition, a high percentage (85%) of the RA flutter occurred counterclockwise around the tricuspid annulus (Table I in the online-only Data Supplement), which agrees with the fact that AFL with tricuspid annulus counterclockwise rotation characteristics is “typically” observed in patients.

Preceding the induction of different macroreentry circuits in the RA, in particular for the typical isthmus-dependent AFL, functional block was found rarely in the region of the crista terminalis in our simulations (Table I in the online-only Data Supplement). This supports a similar conclusion reached in a previous analysis of human AFL.

Atrial Fibrillation

In our simulations, the existence of a vulnerable window found for ectopic foci at various clinically observed locations, including those at the 4 PVs, LA free wall, coronary sinus, inferior vena cava, superior vena cava, and crista terminalis (Figure 4), suggests that the revealed mechanism underlying the induction of AFL/AF by ectopic foci is a general one and independent of the location of the foci. Within the vulnerable window for ectopic foci from the PVs and LA (Figure 4A and 4B), the location of conduction block and reentry arose from the RA, interatrial region, or LA (Table II in the online-only Data Supplement). This is consistent with a detailed mapping study that showed that organized monomorphic atrial tachyarrhythmias induced by premature beats could first arise from the RA, interatrial region, or LA in patients with AF. Moreover, for ectopic foci in the RA, especially those closer to the sinoatrial node such as the superior vena cava and crista terminalis, the size of the vulnerable window for the induction of AFL/AF became markedly smaller than that of the PV ectopic foci (Figure 4B). The effect of increasing vulnerable window size when increasing the distance between 2 pacing sites (in this case sinoatrial node and ectopic focus) has been attributed to a physical principle known as symmetry breaking; as described in Dynamic Repolarization Dispersion and Conduction Block in Results. Our findings of larger vulnerable windows for PV ectopic foci suggest the preference of these sites for inducing AFL/AF and may help in our understanding of why the PV ectopic foci in the LA play a dominant role in inducing AFL/AF.

Our results showing that for certain cycle length and coupling interval combinations, AFL/AF could be initiated with just a few (<10) ectopic beats (Table II in the online-only Data Supplement) agree with clinical observations on the initiation of paroxysmal AF. Remarkably, the range of coupling interval for AFL/AF induction for our simulations (330 to 470 ms; Figure 4A and 4B) is consistent with that observed in patients with paroxysmal AF (Figure 2 in Jensen et al14). In addition, the range of cycle length to induce AFL/AF in our simulations (160 to 210 ms; Figure 4A) falls within that of clinical observations (110 to 270 ms; mean, 175 ms). The result of AFL/AF induction as a function of the coupling interval (Figure 4 and Table II in the online-only
Data Supplement) is supported by a preliminary clinical study that found that the coupling interval of atrial premature beats played a critical role in the inducibility of AFL or AF. These results could be used to resolve one of the most intriguing issues related to paroxysmal AF: how it can be triggered by short coupling atrial ectopic beats during normal heart rate in patients with structurally normal hearts, including children and adolescents.

Note that the effects of remodeling were not the main focus of the present study. However, it has been shown that once AFL/AF was initiated, its duration could be prolonged by introducing ionic remodeling. Additionally, we found that ionic remodeling through 25%, 25%, and 35% reductions of the normal conductance values of $g_{ion}$, $g_{Kas}$, and $g_{Ca,L}$ respectively, as suggested in Courtemanche et al., shortened the normal conductance values of $g_{ion}$, $g_{Kas}$, and $g_{Ca,L}$ respec-
tively, as suggested in Courtemanche et al.,4 shortened the APD at the cellular level, shortened the wavelength of the activation wave, and led to a prolonged duration of AFL/AF for > 10 seconds.

Study Limitations
Electrophysiological studies on PVs have revealed that many factors such as specialized conduction cells, abnormal Ca$^{2+}$ regulation, and the autonomic nervous system could contribute to PV arrhythmogenic activity. However, the purpose of the present study was not to investigate generating mechanisms for ectopic beats. Thus, we did not incorporate such effects in our modeling studies of AFL/AF. In fact, the rapid pacing scheme used here enabled us to flexibly pick the site of an ectopic focus and vary the coupling interval of the foci relative to the sinus beat and the firing cycle length. Furthermore, recent observations have shown that whether atrial tachyarrhythmias were induced by rapid pacing or spontaneously initiated, their properties were indistinguishable.

Conclusion
We have found that interactions between atrial structure, site of stimulation, and stimulus timing created dynamic dispersion of repolarization and conduction block that cause reentrant AFL/AF. Our findings show that a single focus can initiate different reentrant AFL circuits and suggest a mechanism whereby the atria are more vulnerable to premature beats that originate in the PVs than the RA.

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Disclosures
None.

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**CLINICAL PERSPECTIVE**

Atrial fibrillation and atrial flutter are initiated by premature atrial beats or runs of atrial tachycardia in susceptible people. Atrial ectopic foci that can initiate reentry causing atrial fibrillation/atrial flutter have been found to originate from various locations, including the pulmonary veins, left atrial free wall, superior/inferior vena cava, crista terminalis, and coronary sinus. Ectopic beats are common and increase with age. Why some ectopic beats trigger atrial fibrillation and others do not is difficult to study in humans. In the present study we use parallel computational techniques to study an anatomically accurate 3-dimensional atrial model incorporating a detailed atrial ionic-current model to investigate the relation of the timing and location of atrial foci to the initiation of reentry. We found that the timing and location of the atrial focus influence the dispersion of action potential duration across the atria. Firing that induced reentry initially caused discordant alternans, in which the duration of repolarization in one region alternated out of phase with that in another region, leading to conduction block and reentry. Our findings show how the characteristics of an atrial focus can influence initiation of atrial fibrillation/atrial flutter and suggest a unifying mechanistic picture of the induction of atrial fibrillation/atrial flutter.