Electropathological Substrate of Longstanding Persistent Atrial Fibrillation in Patients With Structural Heart Disease

Epicardial Breakthrough

Natasja M.S. de Groot, MD, PhD; Richard P.M. Houben, BSc; Joep L. Smeets, MD, PhD; Eric Boersma, PhD; Ulrich Schotten, MD, PhD; Martin J. Schalij, MD, PhD; Harry Crijns, MD, PhD; Maurits A. Allessie, MD, PhD

Background—During persistent atrial fibrillation (AF), waves with a focal spread of activation are frequently observed. The origin of these waves and their relevance for the persistence of AF are unknown.

Methods and Results—In 24 patients with longstanding persistent AF and structural heart disease, high-density mapping of the right and left atria was performed during cardiac surgery. In a reference group of 25 patients, AF was induced by rapid pacing. For data analysis, a mapping algorithm was developed that separated the fibrillatory process into its individual wavelets and identified waves with a focal origin. During persistent AF, the incidence of focal fibrillation waves in the right atrium was almost 4-fold higher than during acute AF (median, 0.46 versus 0.12 per cycle per 1 cm² (25th to 75th percentile, 0.40 to 0.77 and 0.01 to 0.27; P<0.0001). They were widely distributed over both atria and were recorded at 46±18% of all electrodes. A large majority (90.5%) occurred as single events. Repetitive focal activity (>3) happened in only 0.8%. The coupling interval was not more than 11 ms shorter than the average AF cycle length (P=0.04), and they were not preceded by a long interval. Unipolar electrograms at the site of origin showed small but clear R waves. These data favor epicardial breakthrough rather than a cellular focal mechanism as the underlying mechanism. Often, conduction from a site of epicardial breakthrough was blocked in 1 or more directions. This generated separate multiple wave fronts propagating in different directions over the epicardium.

Conclusions—Focal fibrillation waves are due to epicardial breakthrough of waves propagating in deeper layers of the atrial wall. In patients with longstanding AF, the frequency of epicardial breakthroughs was 4 times higher than during acute AF. Because they provide a constant source of independent fibrillation waves originating over the entire epicardial surface, they offer an adequate explanation for the high persistence of AF in patients with structural heart disease. (Circulation. 2010;122:1674-1682.)

Key Words: atrial fibrillation ■ conduction ■ mapping ■ reentry ■ remodeling

In the first part of this study, we demonstrated that electric dissociation of atrial muscle bundles plays a key role in the development of the substrate of persistent atrial fibrillation (AF). In 24 patients with structural heart disease and longstanding AF, the amount of intratrial block was 3 to 4 times higher than during acutely induced AF in patients with sinus rhythm. This was associated with an almost 2-fold increase in the number of wavelets from 2.5±0.8 to 4.5±0.8 per 1 cm² per AF cycle. Epicardial mapping also revealed that fibrillation waves sometimes emerged “de novo” at the epicardial surface. Recently, experimental and clinical studies have emphasized the possible importance of rapidly firing foci for the maintenance of AF. Repetitive focal patterns of activation were observed, together with a gradient of decreasing dominant AF frequencies away from these foci. It was suggested that these sites of rapid impulse formation acted as a “driver” that maintained AF, thus challenging the concept that multiple self-perpetuating wavelets are responsible for the high persistence of AF.

Clinical Perspective on p 1682

In this second part of our study, we address the question of whether patients with persistent AF exhibit a higher proportion of “focal” fibrillation waves. We collected evidence to...
determine whether these waves originate from focal activity (ectopic impulse formation or microreentry) or whether they should be regarded as epicardial breakthrough (EB) of waves propagating in deeper layers of the atrial wall. Analysis of the spatial distribution, R-wave amplitude, prematurity, and repetitive nature of these waves failed to support a focal origin. Instead, these properties were in full agreement with EB. The analysis of >6000 fibrillation maps showed that in patients with longstanding AF, the incidence of EB was 4 to 5 times higher than during acutely induced AF. Together with the earlier demonstrated increase in longitudinal dissociation,1 we consider this a second important determinant of the electrophathological substrate of persistent AF in patients with structural heart disease.

Methods

The Database of Fibrillation Maps

The same patient population was used as described in the first part of our study.1 It consisted of 24 patients with structural heart disease and longstanding persistent AF and a reference group of 25 Wolff-Parkinson-White patients with normal sinus rhythm. The patients with persistent AF (14 men; age, 64±29 years) had a dilated left atrium (LA); anteroposterior dimension, 52±9 mm) and a ventricular ejection fraction of 49±13%. The reference group consisted of 16 men and 9 women (age, 32±11 years) with a normal LA size of 39±6 mm. Sequential epicardial mapping of the right atrium (RA) and LA was performed after sternotomy and before cardiopulmonary bypass. The lateral walls were mapped with a spoon-shaped electrode containing 244 unipolar electrodes (diameter, 3.6 mm; inter-electrode distance, 2.25 mm). For the posterior LA wall, a smaller rectangular array of 8×8 electrodes was used (inter-electrode distance, 2.5 mm). Fibrillation electrograms were recorded with a custom-made 256-channel mapping system (bandwidth, 0.5 to 500 Hz; sampling rate, 1 kHz; resolution, 12 bits). In the patients with sinus rhythm, paroxysms of AF were induced by rapid atrial pacing. In total, >6000 fibrillation maps were analyzed. They were divided into 4 groups: Groups 1 and 2 contained maps of the RA during acute and longstanding AF (2226 and 1401 maps), and groups 3 and 4 contained maps of patients with persistent AF recorded from the lateral LA (1854 maps) and posterior LA (1148 maps). The anterior (aortic) parts of the RA and LA, including the Bachmann bundle, and the interatrial septum were not mapped.

Detection of EB

We previously introduced a new mapping technique for the analysis of AF (wave mapping).1 Following the methods of Rogers et al,15 an algorithm was developed that decomposed the complex spatiotemporal activation during AF into its individual elements (multiple fibrillation waves). Three types of fibrillation waves were distinguished: peripheral waves, which enter the mapping area from outside; EB waves, which appear at the epicardial surface inside the mapping area; and discontinuous conduction fibrillation waves, which start at the lateral boundary of another fibrillation wave with a time delay of 13 to 40 ms.

The following criteria had to be met to classify a fibrillation wave as originating from EB. First, the EB site had to be activated earlier than all surrounding electrodes. If a neighboring electrode was activated at the same time as the EB site, this electrode should be activated earlier than its surrounding electrodes. Second, the EB site had to be activated earlier than its surrounding electrodes. Third, electrograms in the breakthrough region should not be distorted by large QRS complexes or artifacts. Fourth, if an EB occurred along the lateral border of another wave, the time delay between that neighboring wave and the moment of EB must be 40 ms. Otherwise, the wave was assigned as originating from discontinuous conduction from the lateral boundary of that wave. All wave maps were inspected carefully by 2 investigators and edited as necessary. A spatial resolution of 1 to 2 mm has been shown to be appropriate for the quantitative analysis of the epicardial activation patterns during ventricular fibrillation.12 Given a space constant of atrial myocardium of ~2 mm, the effective spatial resolution of 2.0 to 2.2 mm used in our study makes it highly unlikely that EBs could have actually originated from undetected narrow epicardial wave fronts.

Characteristics of EB

The incidence of EB was measured by shifting a rectangle of 5×5 electrodes (sample size, 0.81 cm²) over the mapping area. Samples that contained <15 electrodes with adequate recordings were excluded from analysis. In each sample, the number of EBs was counted and normalized per AF cycle and 1 cm² surface area. The median of all samples was taken as the incidence of EB in the whole mapping area. This approach enables the comparison of fibrillation maps of different size and frequency.

To help distinguish EB from ectopic focal discharges, the amplitude of the unipolar R wave at the EB sites was measured. Electrograms with an unstable baseline or with large superimposed ventricular far-field complexes were excluded. In the case of focal activity, a unipolar electrogram recorded at the site of ectopy should have an S-wave morphology, whereas in the case of EB, it is expected to exhibit a small R wave. The degree of prematurity of “focal” fibrillation waves was determined by comparing their coupling interval with the average AF cycle length (AFCL) at the site of origin. To identify a rapidly firing focus, the repetitivity of fibrillation waves with a focal spread of activation was measured. To account for small movements of the atria under the mapping electrode, the incidence of repetitive “firing” was also measured in areas of 3×3 electrodes (4.5×4.5 cm).

Statistics

We chose the electrode, not the patient, as the unit of our main analyses. Thus, each patient contributed >1 observation to the analysis data set. As far as the description of the end point parameters is concerned, these data were merged together on group level (acute AF versus chronic AF) and are presented as mean±SD and as median values and interquartile range (25th [P25] and 75th percentiles [P75]).

Differences in the specified end point parameters between patients with acute AF and chronic AF were analyzed by linear regression analysis with 1 treatment factor (which is equivalent to 1-way ANOVA). We realize that the electrode measurements within a patient are correlated and thus not (entirely) independent. Therefore, we used the generalized estimating equation to fit the model parameters. The generalized estimating equation method is developed to adjust for clustering (ie, the hierarchical structure) of data, in this particular case, clustering of the specified end-point parameters within a patient. Visual inspection of the residual plots demonstrated no major deviations of the assumptions underlying ANOVA (ie, a normal distribution of the residuals with a mean value of 0 and homogeneity of variances of the residuals).

We sought to confirm the results of the electrode-based analyses by analyses on the patient level. The median value of the end point parameter was determined for each patient. These median values were then compared between patients with acute AF and those with chronic AF by unpaired Student t tests. A value of P<.05 was considered statistically significant.

Results

Incidence of EB

Figure 1 shows examples of EB in 4 patients with longstanding persistent AF. The 2 maps at the top were recorded from the lateral wall of the LA; the maps at the bottom were recorded from the right side. Each color represents a separate fibrillation wave according to their sequence of appearance in
the mapping area (color scheme is given at the bottom). In the top left map, a single breakthrough occurred (yellow). The wave was conducted in 4 directions and collided with 2 other fibrillation waves entering the mapping area from the outside (red and light green). The top right panel exhibits 4 fibrillation waves, 3 entering from the periphery and 1 originating from the EB (yellow). In this case, expansion of the EB was obstructed in the upper direction by a line of conduction block, and this area was activated a little later by the light green wave. The 2 fibrillation maps at the bottom show a more complex pattern of activation. In the bottom left map, 10 fibrillation waves were present during 1 cycle of 149 ms. Three of them emerged as EB (asterisks). Two (red and purple) occurred close to each other (the red EB at t=0 ms and the purple one at t=66 ms). The breakthrough in the top part of the map (light green) resulted in 2 separate waves propagating in opposite directions. The wave map in the bottom right panel shows the presence of no fewer than 13 fibrillation waves in a time window of 171 ms. The waves were quite narrow and propagated predominantly in a top-right to bottom-left direction (or vice versa), coinciding with the known orientation of the large pectinate muscles in the RA. Four waves appeared as EB (asterisks). The blue and olive waves expanded in 3 directions, whereas the other 2 (yellow and dark green) propagated in only 1 direction.

In Figure 1, the incidence of EB is given for all patients. The top panels show the pooled histograms of the 4 groups. During acutely induced AF, the median incidence of EB in the RA was 0.11 per cycle per 1 cm² (P25, 0.02; P75, 0.25). The distribution was highly skewed to the left because, in many cases of acute AF, EB was rare. In the group with longstanding persistent AF, the median incidence in the RA was considerably higher (0.47 per cycle per 1 cm²; P25, 0.31; P75, 0.72). Because there were no patients with persistent AF in whom EB was rare or absent, the histogram showed a much more gaussian distribution. The tail at the right side was caused by 2 patients with the highest incidence of breakthroughs. The number of EBs in the lateral wall of the LA (median, 0.45; P25, 0.26; P75, 0.72) was not higher than in the RA. The highest incidence of EB was found in the area around the pulmonary veins (PVs; median, 0.54 per cycle per 1 cm²; P25, 0.18; P75, 0.84).

At the bottom of Figure 2, the incidence of EB is plotted for each individual patient. In the group with acutely induced
AF, the average median number of EBs in the RA was 0.12 per cycle per 1 cm² (P25, 0.02; P75, 0.27). During persistent AF, the incidence of EBs was significantly higher: 0.46 (P25, 0.4; P75, 0.77) in the RA, 0.48 (P25, 0.26; P75, 0.73) in the LA, and 0.59 (P25, 0.32; P75, 0.98) in the PV area (all P<0.0001). EBs occurred more frequently in the PV area (P<0.0001) compared with the RA and LA (P<0.0001).

In the bottom right graph, the patients are ranked according to the incidence of EB. In patients with persistent AF, the data from the RA, LA, and PV were pooled. Large interindividual differences were present. During acute AF, the number of EBs varied between 0.0 and 0.49 per cycle per 1 cm²; in patients with persistent AF, the number of EBs varied from 0.07 to 1.18 per cycle per 1 cm². Although during persistent AF the overall incidence of EB was almost 4-fold higher than during acute AF (0.51 [P25, 0.41; P75, 0.65] versus 0.12 [P25, 0.02; P75, 0.27]; P<0.0001), there was still some overlap between the 2 groups. The best cutoff between acute and persistent AF was an incidence of 0.30 EBs per cycle per 1 cm² (dotted line). In 3 patients with acute AF, the number of EBs was higher than this value, whereas in the persistent AF group, 2 patients showed <0.3 breakthroughs per 1 cm² surface area.

R-Wave Amplitude at Sites of EB
One way to test whether waves with an epicardial focal spread of activation originate from ectopic discharges or from EB is to measure the amplitude of the associated R waves. If a wave originates de novo, the unipolar electrogram has no R wave and should exhibit an S-wave morphology. In Figure 3, all R-wave amplitudes at the sites of EB in patients with longstanding AF are collected (n=3,656). At the bottom, some representative potentials with different R-wave amplitudes are shown. Next to the histogram, a number of wave maps are plotted to illustrate the variety in focal patterns of activation and to illustrate that there was no relationship between the pattern of epicardial activation and the amplitude of the R wave. The far majority of breakthrough potentials showed a small but clear R wave, indicating that a depolarization wave was approaching the epicardial surface. The dominant amplitude of the R wave at the site of EB was 2.5 mV.

Spatial Distribution of EB
To determine whether waves with a focal pattern of activation originated preferentially from certain sites, the spatial distribution of EBs was mapped in all patients. Figure 4 shows some representative examples. Sites of EB are indicated by asterisks, and the size of the asterisk is proportional to the number of EBs occurring at that site. The distribution of EBs in the free wall of the RA in a patient with acute AF is shown on the top left. During 8 seconds, 33 breakthroughs were recorded at 27 different sites. Only at 5 electrodes did EB occur more than once. For comparison, on the top right, the spatial distribution of EB is plotted during persistent AF. During a relatively short time period of 8 seconds, a total of 149 breakthroughs were detected at 56% of the electrodes in this patient. In addition, in the LA, EB occurred at many different sites (bottom). Occasionally, some clustering was observed (bottom left), but also in these cases breakthrough was not restricted to only a few sites. In the posterior LA (bottom right), the incidence of EB was higher than in other areas. In the whole group of patients with persistent AF, EBs in the RA occurred at 46±18% of all electrodes compared
with 30±22% during acute AF (P<0.001). In the lateral and posterior walls of the LA, they were recorded at 41±17% and 51±26% of all electrodes, respectively.

The dynamic behavior of EB, recorded in a small area of 1.25×1.25 cm between the PVs, is illustrated in Figure 5. On the right, a fibrillation electrogram of 6 consecutive seconds of persistent AF is shown (Figures 6 and 7 give more examples of electrograms covering consecutive AF cycles). During this relatively short time period of 6 seconds, 55 breakthroughs occurred at 32 of the 36 electrodes. The total incidence and spatial distribution are plotted on the top left. The individual breakthrough sites are plotted in the 42 consecutive time windows of 143 ms below the fibrillation electrograms. One complete wave map from each second is selected (solid frame), which is shown on the left. The spatiotemporal distribution of EB was heterogeneous, with no breakthrough occurring during some cycles and multiple breakthroughs during others. The sites of breakthrough changed continuously on a beat-to-beat basis without showing a fixed pattern or preferential sites of breakthrough.

### Prematurity of EB

The degree of prematurity of fibrillation waves with a focal spread of activation was determined by comparing their coupling interval with the average AFCL at the breakthrough sites. In Figure 6, the prematurity of all EBs (n=4,617) is plotted, together with the delta intervals of the cycles preceding and following the breakthrough interval. Like the normal AF cycles, the EB cycles showed a high degree of temporal irregularity. As a result, the coupling interval of an EB was shorter than, similar to, or actually longer than the average AFCL. On average, the breakthrough intervals were only 11 ms shorter than the normal AF cycles (P=0.04). This represents a prematurity of only 95% of the average AFCL at the sites of breakthrough. The cycle lengths before the EB interval were not longer than normal. Below the histograms, some breakthrough electrograms (asterisks) are shown, 1 with a short (131 ms), 1 with a normal (177 ms), and 1 with a long (219 ms) coupling interval.

### Is EB Repetitive?

A site with a focal spread of activation can only act as a “driver” of AF if the ectopic activity is repetitive. Therefore, we counted the number of times that EB occurred repetitively.
at the same site. The vast majority of EBs (90.5%) were not repetitive and occurred as single events. They occurred twice in only 7.1% of the cases and 3 times in a row in 1.6%. A higher degree of repetition was extremely rare and made up 0.8% of all breakthroughs. To account for small movements of the fibrillating atria under the mapping electrode, we also measured the incidence of repetitive breakthrough within areas of 3×3 electrodes (4.5×4.5 cm). But even then, repetitive breakthrough (≥3 in succession) occurred in only a minority of the cases (23%). In Figure 7, some fibrillation electrograms are shown with a different number of repetitive breakthroughs (asterisks). Note the clear R waves in most of the breakthrough potentials. The cycle length between repetitive EBs was irregular and on average not shorter than the average AFCL at these sites. The lower tracing shows an exceptional case in which EB occurred 6 times in succession at the same site. The wave maps below the tracing show that during repetitive breakthrough, the epicardial expansion was variable. Instead of causing a constant radial spread of activation, the direction(s) of activation and the territories occupied by the breakthroughs varied on a beat-to-beat basis.

Discussion

Focal Patterns of Activation During AF

The first observation of focal patterns of epicardial activation was made during acutely induced AF.17 Later, Holm et al18 mapped the free wall of the RA in patients with persistent AF. Interestingly, in this study, most focal activations were repetitive, but the cycle length did not differ from the average AFCL. In patients with persistent AF and mitral valve disease, Harada et al19,20 found regular and repetitive activations that emerged from the LA appendage. However, because of the low spatial resolution (32 electrodes; interelectrode distance, 10 mm), the associated patterns of epicardial activation could not be analyzed in detail. Repetitive patterns of focal activation, in both the RA and LA, were reported by Nitta et al.7 In the LA, focal activity emerged predominantly from the PV area. In the RA, the origin of focal waves was more variable. From these observations, the authors concluded that focal activation in the RA and LA was the driving force behind persistent AF.2 Sahadevan et al8 observed sites with rapid regular activity in some patients with persistent AF that were considered to act as drivers of AF.

Breakthrough Versus Focal Discharge

Schuessler et al21 performed simultaneous endocardial and epicardial mapping of isolated canine atria during atrial tachyarrhythmias induced by acetylcholine and premature stimulation. Focal patterns of activation were present concurrently on the endocardial and epicardial surfaces. Earliest sites of endocardial and epicardial activation were spatially discordant, with a separation of 1.5 cm between the sites of endocardial breakthrough and EB. They were ascribed to the presence of small transmural circuits, including free-running bundles connecting the endocardium and epicardium. Two later studies also provided evidence that focal patterns of activation can be due to transmural reentry.11,22 In a canine model of pacing-induced heart failure and sustained AF,
multiple foci were found in the RA and LA.\textsuperscript{23–25} The presence of delayed afterdepolarizations and the response to programmed electric stimulation suggested that these foci were due to a focal mechanism. The different frequencies of these multisite foci were held responsible for the fibrillatory process.\textsuperscript{23–25} Other experimental studies provided evidence that the initiation of AF was caused by focal activity based on enhanced automaticity or triggered activity.\textsuperscript{26,27}

In our group of 24 patients with longstanding persistent AF, the properties of fibrillation waves with a focal pattern of epicardial activation were as follows: First, the large majority (90.5\%) were not repetitive but appeared as solitary events. Second, they were not confined to a limited number of sites but occurred virtually everywhere in the atria, RA and LA alike. Third, the median coupling interval of these waves was only 11 ms shorter than expected (and in one third of the cases actually longer than the average AFCL) and were not preceded by a long interval. Finally, the unipolar electrograms recorded at the epicardial sites of origin of these waves showed small but clear R waves. These features do not support a focal mechanism resulting from automatic cellular discharge but are more in agreement with EB of fibrillation waves propagating in deeper layers of the atrial wall.

**Endo-Epicardial Dissociation**

The 4-fold higher incidence of EB in patients with longstanding AF implies the presence of a 3-dimensional substrate in which fibrillation waves frequently cross over from the endocardial to the epicardial layers. In Figure 8, various patterns of EB are shown schematically. For simplicity, transmural dissociation is represented by only 2 planes. On the left, the atrial wall is shown in cross section. On the top, the atrial wall is activated by a single depolarization wave, propagating in 30 ms from left to right. In the other diagrams, the 2 layers are dissociated, with an endocardial-epicardial junction in the middle. Assuming a transmural conduction time of 10 ms, the breakthrough appeared at \( t = 25 \) ms at the epicardial surface (asterisk). Depending on the spatial distribution of electrophysiological properties like strength of depolarization, excitability, electric coupling, and source-sink relations, the spread of activation from the site of EB may vary (diagrams 2 through 4). In the second diagram, the EB propagates in 2 directions. Activation in the same direction as the endocardial wave (right part of diagram) results in nearly synchronous activation of the atrial wall with the endocardium leading by only 10 ms. In contrast, epicardial activation in the opposite direction produces larger differences in
activation time between the endocardium and epicardium (left part of diagram). Such a pattern of breakthrough not only generates 2 independent waves on the epicardium but also serves as an intramural pivot point. In the bottom 2 diagrams, EB expands in only 1 direction. In diagram 3, conduction is blocked to the left, and the right part of the epicardium is activated in concordance with the endocardium. In diagram 4, expansion is blocked to the right, and the epicardial wave propagating exclusively in opposite direction makes a sharp intramural U turn. The 3-dimensional representations illustrate the arrhythmogenicity of endocardial-epicardial EB by creating independent wave fronts and causing abrupt 180° changes in direction.

The transition from a 2- to a 3-dimensional substrate has important effects on the stability of the fibrillatory process. By providing transmural bifurcation and pivot points, dissociation of the endocardial and epicardial layers will markedly increase the number of possible pathways for the wandering fibrillation waves.13,14 In the >4000 fibrillation maps of persistent AF, complete reentrant circuits in the epicardial plane were extremely rare. Absence of reentry in the epicardial plane was also noticed by Gray et al.11 Assuming that the same holds true for the endocardium, most reentrant pathways must be exclusively transmural with 1 limb in the endocardial and 1 limb in the epicardial plane. In such a situation in which reentry occurs predominantly between the endocardial and epicardial planes, the sites of breakthrough must be considered reentry points. The incidence of breakthrough then directly represents the number of reentrant circuits in the atria. Hence, in addition to longitudinal dissociation of the muscle bundles,1 we consider endocardial-epicardial dissociation the second important factor for the development of a substrate of persistent AF in humans.

Limitations
A major limitation of this study is that only the epicardial surface of the atria was mapped. Direct proof that fibrillation waves arising at the epicardial surface are due to EB has to await simultaneous epicardial and endocardial mapping of persistent AF. Somewhat arbitrarily, breakthroughs occurring within a delay of 40 ms next to the border of another wave were excluded from analysis. These waves were assigned to result from slow discontinuous conduction and will be described in a later article. Other limitations are that no recordings were obtained from the Bachmann bundle and that most of the patients with persistent AF suffered from valvular heart disease.

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Disclosures

None.

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