The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/88722

Please be advised that this information was generated on 2017-11-20 and may be subject to change.
Electropathological Substrate of Long-Standing Persistent Atrial Fibrillation in Patients With Structural Heart Disease

Longitudinal Dissociation

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

Background—The electropathological substrate of persistent atrial fibrillation (AF) in humans is largely unknown. The aim of this study was to compare the spatiotemporal characteristics of the fibrillatory process in patients with normal sinus rhythm and long-standing persistent AF.

Methods and Results—During cardiac surgery, epicardial mapping (244 electrodes) of the right atrium (RA), the left lateral wall (LA), and the posterior left atrium (PV) was performed in 24 patients with long-standing persistent AF. Twenty-five patients with normal sinus rhythm, in whom AF was induced by rapid pacing, served as a reference group. A mapping algorithm was developed that separated the complex fibrillation process into its individual elements (wave mapping). Parameters used to characterize the substrate of AF were (1) the total length of interwave conduction block, (2) the number of fibrillation waves, and (3) the ratio of block to collision of fibrillation waves (dissociation index). In 4403 maps of persistent AF, no evidence for the presence of stable foci or rotors was found. Instead, many narrow wavelets propagated simultaneously through the atrial wall. The lateral boundaries of these waves were formed by lines of interwave conduction block, predominantly oriented parallel to the atrial musculature. Lines of block were not fixed but continuously changed on a beat-to-beat basis. In patients with persistent AF, the total length of block in the RA was more than 6-fold higher than during acute AF (median, 21.1 versus 3.4 mm/cm²; \( P < 0.0001 \)). The highest degree of interwave conduction block was found in the PV area (33.0 mm/cm²). The number of fibrillation waves during persistent AF was 4.5/cm² compared with 2.3 during acute AF, and the dissociation index was 7.3 versus 1.5 (\( P < 0.0001 \)). The interindividual variation of these parameters among patients was high.

Conclusions—Electric dissociation of neighboring atrial muscle bundles is a key element in the development of the substrate of human AF. The degree of the pathological changes can be measured on an individual basis by electrophysiological parameters in the spatial domain. (Circ Arrhythm Electrophysiol. 2010;3:606-615.)

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

Although experimental studies have provided extensive insights into the various mechanisms that can explain perpetuation of atrial fibrillation (AF), it is unknown which electropathological changes are relevant for the development of a substrate of persistent AF in humans.¹ Clinical mapping data are scarce and often limited to part of the atria or a small number of beats.²⁻¹⁴ Yet, it is the only presently available technique that can accurately elucidate abnormalities in conduction and impulse formation responsible for perpetuation of AF. High-density mapping of AF can tell us why, at a given point in time, AF becomes refractory to drugs and why only extensive ablation procedures can terminate the arrhythmia. Intra-atrial recordings have shown that during persistent AF, the human atria are activated in a highly complex manner.¹⁵ Because of this spatiotemporal complexity, mapping of long-lasting persistent AF is certainly not an easy task. To enable quantitative analysis of the heterogeneous activation patterns during AF, we developed a mapping algorithm that divides the fibrillatory process into its individual elements (wave mapping). In 24 patients with structural heart disease and persistent AF, a large number of fibrillation maps were recorded from the right and left atria. An existing database of 25 patients with normal sinus rhythm, in whom AF was induced by rapid atrial pacing, served as a reference...
group. Differences between acute and long-standing AF and between right and left atria were evaluated by quantifying the spatiotemporal characteristics of the fibrillatory process. In this first of a series of reports, we focus on the incidence and spatiotemporal dynamics of intra-atrial conduction block during AF. This analysis shows that electric dissociation between atrial muscle bundles plays a key role in the development of the substrate of persistent AF in humans.

Methods

Study Population

Twenty-four patients with structural heart disease and long-standing persistent AF were studied. All patients (14 male; age, 64±9 years) were in persistent AF for longer than 1 year. The indications for surgery were mitral valve disease (n=13), aortic valve stenosis (n=1), coronary artery disease (n=3), concomitant mitral valve and coronary artery disease (n=5), aortic valve stenosis and coronary artery disease (n=1), and surgical isolation of the pulmonary veins (n=1). The average left atrial anteroposterior dimension was 58±9 mm (range, 47 to 72), with a left ventricular ejection fraction of 50±12% (range, 32 to 66). None of the patients had clinical symptoms of overt heart failure; the majority had valvular heart disease. Sixteen patients used 1 or more antiarrhythmic drugs, including digoxin (n=13), sotalol (n=10), verapamil (n=2), flecaïnide (n=1), and amiodarone (n=1) and were not discontinued before surgery. The protocol was approved by our institutional review board, and all patients provided written informed consent.

An existing database of 25 Wolf-Parkinson-White (WPW) patients (16 male; age, 32±11 years) undergoing surgical interruption of the accessory pathway(s) was used as a reference group. None had structural heart disease or dilated atria (left atrial [LA] diameter, 39±6 mm). In these patients without a history of persistent AF, fibrillation was induced by rapid atrial pacing. Mapping was limited to the right atrium (RA), and the first and last 12 seconds were excluded from analysis. The average median AF cycle length (AFCL) during acute and persistent AF was 156.5±23.9 and 177.7±37.6 ms, respectively (P<0.003).

Epidermal Mapping

After median sternotomy, epicardial mapping was performed during normothermia and before cardiopulmonary bypass was instituted. The lateral wall of the RA was mapped with a spoon-shaped electrode (diameter, 3.6 cm) containing electrodes (diameter, 0.3 mm; interelectrode distance, 2.25 mm) positioned on the midpart of the RA. The angle of the electrode relative to the atrial anatomy was controlled by placing the leads in the same direction toward the atrial appendage. Recordings of the posterior wall of the left atrium (PV) were made with a smaller rectangular array of 8×8 electrodes (interelectrode distance, 2.5 mm). The left lateral wall was mapped with either of the 2 electrode arrays. The different regions of the atria were mapped sequentially with a 256-channel computerized mapping system (bandwidth, 0.5 to 500 Hz; sampling rate, 1 kHz; resolution 12 bits). Far-field QRS complexes were subtracted from the unipolar fibrillation electrograms by a coherent averaging procedure. For each atrial electrogram, an individual template of the ventricular complex was created by averaging time windows of 70 ms centered around the R waves. Subtraction of these individual QRS templates from the fibrillation electrograms considerably reduced the ventricular far-field potentials. The steepest parts of the intrinsic negative deflections were taken as local activation times. In the case of fractionated potentials, the local activation time was derived from the components with the highest peak-to-peak amplitude.

The data were divided into 4 groups. Groups 1 and 2 consisted of fibrillation maps of the RA recorded during acute and long-standing AF. Groups 3 and 4 contained maps of persistent AF from the lateral and posterior left atrium. No maps from the Bachmann bundle or the interatrial septum were recorded. In total, 313 seconds of acute AF and 598 seconds of persistent AF were analyzed, yielding 2226 RA maps of acute and 4403 maps of long-standing AF (RA, 1401; LA, 1854; PV, 1148) (Table). Because of poor contact of the edge of the mapping array, the number of recorded fibrillation electrograms could be smaller than the number of electrodes. Although this reduced the effective mapping area, it did not affect the spatial resolution of the maps.

Wave Mapping

Especially in diseased and dilated atria, activation during AF can become so disorganized that conventional isochronal maps are difficult to interpret. To facilitate quantitative analysis of complex AF, we divided the spatiotemporal process into its individual elements (wave mapping). The algorithm was based on the techniques introduced by Rogers et al17 for the analysis of ventricular fibrillation. Separate fibrillation waves were defined by interelectrode conduction times of >12 ms along their boundaries. The choice of 12 ms as the cutoff value represents a lower limit of 19 cm/s. Because this is less than 20% to 30% of the normal conduction velocity in atrial myocardium, it is unlikely that this threshold overestimates the number of wavelets. For demarcation of fibrillation waves, the lower limit of 19 cm/s should be fulfilled along the entire boundary of the wave. Therefore, this does not exclude the possibility of slow conduction within parts of the fibrillation waves, and intrawave conduction times of >12 ms were frequently observed. Based on heuristic rules, an algorithm was developed that automatically demarcated the fibrillation waves. The earliest site of activation was taken as the starting point of the first wave. Then the whole mapping area was scanned in steps of 1 ms. For all electrodes activated during each time step, the shortest time difference with the 8 neighboring electrodes was calculated. In the case that the conduction time was ≤12 ms (17 ms for oblique distances), the electrode was added to the territory of the wave. To prevent directional bias in the assignment of electrodes to the surrounding waves, the mapping area was scanned in random order. Sites of early activation that were completely surrounded by later activation times were identified as starting points of separate wave fronts. To allow for small variations in activation times, a delay of 5 ms was used before an early activated site was accepted as the start of an independent fibrillation wave.

Depending on their origin, 3 types of fibrillation waves were distinguished: (1) peripheral waves, entering the mapping area from outside the electrode array, (2) epicardial breakthrough, appearing at the epicardial surface inside the mapping area, and (3) discontinuous conduction, fibrillation waves starting with a delay of 13 to 40 ms from the boundary of another wave.

In Figure 1, 4 isochrone maps are shown together with their wave maps. In the first map (acute AF), 3 broad fibrillation waves (red, yellow, and green) entered from different directions and collided in the middle. The second map, taken from another patient with acute AF, showed a more complex pattern. In addition to 4 peripheral waves (black arrows), 3 waves appeared in the middle of the mapping area (white arrows), 2 as epicardial breakthrough (asterisks) and 1 as discontinuous conduction. The 3rd and 4th maps of 2
patients with persistent AF, exhibit multiple narrow fibrillation waves, many of them originating as epicardial breakthrough or discontinuous conduction (white arrows). In the 4th map, as many as 15 fibrillation waves were present during a time window of only 151 ms.

Conduction Block and Electric Dissociation During AF

The amount of intra-atrial block during AF was quantified by measuring the percentage of conduction block around each electrode. The boundaries between fibrillation waves were plotted in so-called dissociation maps. All time differences across the boundaries were collected in a histogram. Interwave time differences of $>12\ms$ ($>17\ms$ for oblique interelectrode distances) were taken as conduction block, whereas differences $\leq12\ms$ were interpreted as fusion or collision. The Dissociation Index was defined as the ratio of block to collision of fibrillation waves. The total length of all wave boundaries was measured by multiplying the number of electrodes along the boundaries with the interelectrode distance. To enable comparison of patients with different cycle length and/or mapping areas, the length of interwave boundaries was measured in all areas of $5\times5$ electrodes $(0.81\cm^2)$. After normalization per $\cm^2/AF$ cycle, the median length of interwave block in these samples was taken as the amount of dissociation in the mapping area.

Statistics

We choose the electrode and not the patient as unit of our main analyses. Thus, each patient contributed more than 1 observation to the analysis dataset. As far as the description of the end point parameters is concerned (length of conduction block, dissociation index, wave density), these data were merged together on group level (acute AF versus chronic AF) and presented as mean values $\pm$1 standard deviation, as well as median values and interquartile range (P25, 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 (GEE) to fit the model parameters. The GEE 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 probability value of $<5\%$ was considered statistically significant.

Results

Intra-Atrial Block During Acute and Persistent AF

In Figure 2 the amount of intra-atrial conduction block is plotted for all patients. The upper panels show the pooled
histograms of percentage of RA block in 25 patients with acute and 24 patients with persistent AF. During acute AF, the median percentage of block was 6.1% (P25, 1.3; P75, 13.8). The distribution was highly skewed to the left, indicating that in many cases block of fibrillation waves was relatively rare. In patients with persistent AF, the histogram showed a more gaussian distribution with a considerably higher degree of RA block (median, 21.1% [P25, 16.6; P75, 27.5]; P<0.0001). The incidence of conduction block in the LA is given in the lower panels. In the left lateral wall, a bimodal distribution was found with a narrow peak at 3% and a broader population with a median of 23% (vertical dashed lines) (P25, 8.5; P75, 28.9). This was because in a minority of patients with persistent AF, the incidence of conduction block in the LA was still relatively low. In the posterior wall of the LA (PV area), the amount of block was highest (median, 30.5%; P<0.0001 versus RA and LA). In all parts of the atria that were mapped, conduction block was diffusely distributed, and no preferential sites of conduction block were found. In only 0.5±1.2% of all electrodes, the incidence of conduction block was higher than 3 times the average (data not shown).

Wave Mapping
In Figure 3, a number of wave maps, recorded from the RA during acute and long-standing AF, are shown together with their dissociation maps. During uniform propagation of a single broad fibrillation wave (upper left), the median inter-electrode conduction time was 3 ms (equivalent with ≈75 cm/s), and no local conduction delays were observed. In the second map of acute AF, 2 waves entered the mapping area from opposite directions, resulting in an interwave boundary running from the upper right to the lower left part of the map. Because the 2 waves entered the mapping area almost simultaneously (at t=0 and t=2 ms) most time differences across their boundary was ≈12 ms, indicating that the 2 waves collided (gray boxes). The third map of acute AF shows an example of asynchronous activation by 3 waves. The yellow and green waves entered the mapping area 55 and 63 ms, respectively, after the red one. Because of this asynchronicity, large parts of the interwave boundaries were demarcated by time differences of >12 ms (black boxes).

In the right part of Figure 3, 3 wave maps of patients with persistent AF are given. They show a much higher degree of dissociation with numerous lines of conduction block (black) and collision (gray) demarcating the boundaries of the fibrillation waves. In the upper map, 4 peripheral waves collided along 3 lines of fusion/collision. In the second map, the RA was activated by multiple narrow fibrillation waves, many of them appearing as epicardial breakthrough (asterisks). The third map illustrates that in patients with persistent AF, these narrow fibrillation waves often propagated parallel to each other. The lines of interwave block were predominantly oriented in an upper right to lower left direction, coinciding with the orientation of the large pectinate muscles in the right atrium.

Electrogram Characteristics of Longitudinal Dissociation
Figure 4 shows some unipolar electrograms recorded along the boundaries of the fibrillation waves. The RA map at the top exhibits 9 separate waves, 4 entering from the periphery (black arrows), 3 arising from epicardial breakthrough (red, yellow, dark green), and 2 originating from discontinuous conduction (blue and purple). Next to the wave map, the interwave boundaries are plotted together with some of the electrograms recorded along these boundaries. As expected, at the boundary between 2 fibrillation waves the electrograms showed double potentials with a delay equivalent to the phase difference of the waves. Although theoretically one might
expect R waves, earlier studies of Konings et al. recorded short double potentials at sites of collision. This might be due to transmural nonuniformities in conduction or collision that occur not exactly under the recording electrode. Alternatively, short double potentials could also result from sequential activation on either side of a line of block by separate waves with small phase differences.

In the lower part of Figure 4, a wave map of the posterior wall of the left atrium is shown. This map was recorded with a smaller electrode (1.75 cm) that was positioned between the right and left pulmonary veins. The PV area was highly dissociated and showed many narrow wavelets. Fractionated electrograms (encircled) were recorded at sites where multiple asynchronous wavelets were present. Each component of the fractionated potentials was associated with one of the wavelets propagating in the vicinity of the electrode.

**Dynamics of Interwave Boundaries**

In Figure 5, 2 series of consecutive dissociation maps during persistent AF are shown, 1 recorded from the RA and 1 from the posterior LA. In both atria, electric dissociation showed a highly dynamic behavior, the position of the wave boundaries changing continuously on a beat-to-beat basis. Quite strikingly, particularly in the RA, the lines of interwave block were predominantly oriented parallel to each other, coinciding with the orientation of the pectinate muscles, running parallel from the crista terminalis (upper right side of the map) to the AV groove (lower left side). However, despite this preferential direction of interwave boundaries, conduction block was not restricted to a specific area and occurred virtually everywhere in the parts of the atria that were mapped. In the posterior left atrium, the lines of block were generally shorter and more densely packed than in the right atrium. This was due to the presence of very narrow fibrillation waves in this area, often not being broader than one interelectrode distance of 2.5 mm. This fits with the atrial architecture in this area, consisting of small muscle bundles running parallel in a craniocaudal direction between the right and left pulmonary veins.

**Quantification of Dissociation**

Figure 6 illustrates how we quantified the degree of electric dissociation during AF in individual patients. One case of acute AF (RA) and 1 of long-standing AF are shown (RA and left posterior wall). At the top, histograms of all time differences across the wave boundaries are plotted. The gray bars represent fusion and collision of waves. The black bars indicate conduction block. During acute AF, the fibrillation waves often fused and/or collided, resulting in a high peak of small interwave time differences. In the given example, 51.4% of the wave boundaries consisted of collision and 48.6% of conduction block (ratio, 0.95). In contrast, in the patient with persistent AF, the wave boundaries were predominantly formed by block (82.1% in the RA [ratio, 4.6] and 61.9% in the LA [ratio, 7.3]).
90.9% in the left posterior atrium \( [\text{ratio, 9.9}] \). Note that in the posterior LA, small time differences between waves were quite rare. This low incidence of collision of fibrillation waves in highly dissociated atria might even be an overestimation because part of the short interwave time differences might result from dissociated waves that, by chance, pass each other with a small time delay.

In the lower panels of Figure 6, the degree of dissociation is measured as the total length of wave-boundaries per cm\(^2\) tissue area. Again, the interwave boundaries were divided in collision (delay \( \leq 12 \) ms) and block (delay \( > 12 \) ms), and the median length of block in all samples was taken as the amount of dissociation in the whole mapping area. In the RA of the patient with acute AF, the total length of wave boundaries was 9.4 mm/cm\(^2\) per AF cycle. About half of the boundaries consisted of collision or fusion (median, 5.1 mm; P25, 4.8; P75, 6.2) and half of conduction block (median, 4.3 mm; P25, 3.8; P75, 6.2). In the patient with persistent AF, the wave boundaries measured as much as 25.2 mm/cm\(^2\), with the far majority now consisting of conduction block (median, 20.6 mm; P25, 18.9; P75, 24.2). In the posterior LA, the amount of block was even higher (median, 33.7 mm/cm\(^2\); P25, 32.5; P75, 36.3).

In Figure 7 the amount of interwave conduction block is plotted for all patients. There were large interindividual differences, both during acute and long-standing AF. During acute AF, the median length of RA interwave block ranged from 0.0 to 20.2 mm/cm\(^2\). In the persistent group, the amount of block ranged from 3.4 to 41.6 mm/cm\(^2\) in the RA, between 2.7 to 40.0 in the LA, and from 17.5 to 46.5 mm/cm\(^2\) in the PV area. In the right panel, the 4 groups are compared. During long-standing AF, the degree of RA dissociation was more than 6 times higher than during acute AF (median, 21.1 mm/cm\(^2\); P25, 19.1; P75, 23.1 versus 3.4; P25, 0.3; P75, 8.8; \( P < 0.0001 \)). In the left lateral wall, the amount of block was not higher than in the RA (21.0 versus 21.1 mm/cm\(^2\)). The highest degree of dissociation was found in the left posterior wall (median, 33.0 mm/cm\(^2\); P25, 25.1; P75, 37.4).

### Dissociation Index, Interwave Block, and Number of Wavelets

In Figure 8 the number of fibrillation waves, amount of interwave block, and dissociation index (ratio of block to collision) are plotted for each patient. In the acute AF group, the median amount of block was 3.4 mm/cm\(^2\) (P25, 0.4; P75, 8.9), with 2.3 (P25, 1.7; P75, 2.9) fibrillation waves per cm\(^2\) and a median dissociation index of 1.5 (P25, 0.6; P75, 2.3). In patients with persistent AF, the pooled data of RA, LA, and PV yielded 23.0 mm/cm\(^2\) of
interwave block (P25, 18.2; P75, 26.9), 4.5 (P25, 4.1; P75, 5.1) waves per cm², and a dissociation index of 7.3 (P25, 5.6; P75, 9.2) (all P/H11000.0001). Again notice the large interindividual differences in these parameters of the substrate of AF. About one third of patients with long-standing AF still exhibited only a moderate degree of dissociation, whereas in others major conduction defects were detected. In the acute AF group, some patients also showed a considerable degree of dissociation. However, it should be remembered that this group consisted of WPW patients, in whom atrial abnormalities cannot be excluded. The right lower panel of Figure 8 shows a statistically significant linear correlation between the dissociation index and the amount of interwave conduction block (R=0.77; P<0.0001). However, in patients with severe longitudinal dissociation, the dissociation index was often

Conduction Block of Fibrillation Waves

**Figure 6.** Top, Histograms of the time differences between neighboring fibrillation waves (n=2829, 4864, and 1318) recorded during 11.2 seconds of acute AF and 7.9 and 8.0 seconds of persistent AF. Gray bars represent fusion; black bars represent block along the lateral boundaries of the waves. During persistent AF, the wave boundaries mainly consisted of conduction block. The ratio of block to collision was 0.95 during acute AF and 4.6 (RA) and 9.9 (left posterior atrium) during persistent AF. Bottom, Histograms of the length of wave boundaries per cm² surface area. Gray histograms represent collision; the black histograms represent the length of lines of block. In the patient with long-standing AF, the median length of block was considerably higher than during acute AF (RA, 20.6 versus 4.3; posterior LA, 33.7 mm/cm²).

**Figure 7.** Left, All patients ranked according to the median length of interwave block per cm². (○ RA acute AF; • RA; ● LA; ▲ PV during persistent AF). Right, Amount of atrial dissociation in the 4 groups. During long-standing AF, the median length of block between fibrillation waves was more than 6 times higher than during acute AF. In the PV area, the degree of dissociation was higher than in the RA and LA (P<0.0001). Error bars indicate the interquartile range (P25 to P75).
higher than the amount of interwave block. This higher sensitivity of the dissociation index was due to a reduction of collision of wave fronts. As expected, a positive correlation also existed between the amount of interwave block and number of fibrillation waves (\( R = 0.79; P < 0.0001 \)) and dissociation index and number of waves (\( R = 0.91; P < 0.0001 \)) (data not shown).

**Discussion**

**Clinical Mapping of AF**

The first intraoperative mapping of human AF was performed in 1991 by Cox et al in 13 patients with WPW syndrome. All patients showed nonuniform conduction, lines of bidirectional conduction block, and multiple discrete wave fronts in both atria. In 6 of 13 patients, reentry circuits in the right atrium were observed involving the sulcus terminalis. In the LA, local reentry or automaticity could not be detected. In a study of 25 WPW patients, Konings et al\(^3,6\) reconstructed the excitation process during acute AF in more detail. Focal spread of activation and unstable epicardial reentrant circuits were observed only occasionally. Holm et al\(^5\) mapped the RA in patients with persistent AF. Intermittent episodes with focal spread of activation from the RA appendage were found in 4 of 16 patients. In a study by Wu et al\(^7\), the RA was activated by large wave fronts with lines of block oriented parallel to the crista terminalis and the pectinate muscles. In patients with mitral regurgitation, Roberts-Thomson et al\(^14\) showed extensive regions of conduction slowing in the posterior LA with anatomic lines of block running vertically between the right and left pulmonary veins. Kanagaratnam et al\(^8\) compared the complexity of RA activation during acute and persistent AF. In striking contrast to our present findings, no differences in complexity of atrial activation were found. In 21 patients with permanent AF, Nitta et al\(^19\) claimed that focal activations in the RA and LA were the driving force behind AF. Similarly, Sahadevan et al\(^21\) considered the occurrence of short episodes of regular rapid activity in patients with persistent AF as evidence for the presence of a “driver” of AF.

**‘Cracks in the Atrial Wall’**

The term “longitudinal dissociation” was introduced in the early 1970s.\(^{19–21}\) It was defined as “any form of asynchronous or nonuniform propagation along the longitudinal axis of a portion of the A-V conducting system.”\(^{20}\) Its importance for the pathogenesis of reentrant arrhythmias was that it “…could provide functionally independent parallel pathways within an anatomic unit … that would provide a setting for reentry.”\(^{20}\) Later, Spach et al\(^21\) provided evidence for longitudinal dissociation of the atria in patients with advancing age, showing progressive electric uncoupling of side-to-side connections between parallel-oriented atrial muscle bundles. This was thought to be due to proliferation of collagen in the extracellular matrix, resulting in an increase in number of longitudinally oriented insulated boundaries of connective tissue septa that often completely surrounded groups of atrial muscle fibers.

Our present study provides the first quantitative analysis of intra-atrial conduction disturbances during human AF (with the exception of the Bachmann bundle and the interatrial septum). In a total of >2000 epicardial maps of acute AF and >4000 maps of persistent AF, we failed to find any rotors or foci that could explain the persistence of AF. Instead, the main feature of the substrate of long-standing AF was a significant increase in longitudinal dissociation, consisting of lines of block running parallel to the atrial musculature. We quantified the degree of longitudinal dissociation by measuring the total length of wave boundaries per cm\(^2\) surface area. During long-standing AF, the amount of dissociation was more than 6 times higher than during acutely induced AF. Whereas during acute AF, fibrillation waves were broad and often collided or fused, during persistent AF fibrillation, waves were narrow and were predominantly bounded by conduc-
tion block. Lines of interwave conduction block showed a highly dynamic behavior and shifted continuously in position. Yet, wave boundaries were not randomly distributed but their orientation seemed to be determined by the underlying atrial architecture. In the RA, they were predominantly oriented parallel to the large pectinate muscles. Also, in other studies, lines of block were found along the long axis of the crista terminalis and large pectinate muscles. In the posterior LA wave boundaries were predominantly oriented in a craniocaudal direction. This is in agreement with the studies of Markides et al and Roberts-Thomson et al, who observed lines of conduction delay running vertically between the pulmonary veins parallel to the fiber orientation. In a study by Sanders et al, no systematic direction of lines of block was found in the left atrial appendage, where the trabeculae are known to be oriented more randomly. Altogether, this provides convincing evidence that in humans with persistent AF, the course of the fibrillation waves is largely determined by the underlying architecture of the atrial musculature. However, it remains to be proven that the changes, identified as main parameters of the substrate of AF, are directly responsible for the maintenance of AF. Also, the effect of age on these electrophysiological parameters must be evaluated.

Interindividual Variation
The large interindividual differences in the substrate of AF, found in the group of patients with persistent AF, is of clinical interest. It raises the question whether it is due to preexisting differences in atrial architecture or genetic predisposition or whether it represents different stages in the development of a substrate of AF. Because of the transverse nature of our study, we cannot answer this question. Nevertheless, it is tempting to speculate that the degree of longitudinal dissociation, which we regard as a key element of the substrate of AF, expresses the progression of pathological changes in the atria over time. It is conceivable that chronic atrial stretch, caused by mitral valve regurgitation or increased ventricular end-diastolic pressure, progressively disrupts the delicate lateral connections between neighboring muscle bundles. Shear stress caused by asynchronous contraction of the atrium during AF may further add to this process. In that case, quantification of the degree of electric dissociation would provide an estimate of the stage of progression of structural atrial remodeling. In the future, such a diagnosis of the electrophathological substrate of AF could become a valuable tool for an individualized treatment of AF and to evaluate the effects of certain prevention measures.

Limitations
Our study has several important limitations. First, it should not be regarded as a controlled clinical study. Our population of patients with long-standing AF was heterogeneous and mainly comprised patients with valvular heart disease. It therefore remains unknown whether our findings also relate to AF of different etiologies such as old age, hypertension, ventricular hypertrophy, or congestive heart failure. Atrial activation from both atria was mapped sequentially and no recordings were obtained from the Bachmann bundle. Another limitation is that the relationship between lines of intra-atrial block and the architecture of the atrial musculature is based on the general knowledge of the fiber orientation in different areas of the atria and not on a direct individual comparison. Finally, the reference group of 25 WPW patients should not be considered as a true control group. Although in none of these patients the atria were dilated, the presence of some degree of atrial pathology cannot be completely excluded.

Acknowledgments
Participation of the department of cardiothoracic surgery of the Maastricht University Medical Center is gratefully acknowledged.

Sources of Funding
This study was supported by a grant of the Royal Netherlands Academy of Sciences to Dr Allessie.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

The pathophysiologic changes that create the substrate for persistent atrial fibrillation (AF) are not completely understood, and extensive mapping data are limited. In the present study, findings from detailed atrial epicardial mapping in patients with valvular disease undergoing cardiac surgery were compared with those during induced AF in patients without a history of AF. In persistent AF patients, there were more excitation wave fronts, and the AF demonstrated more lines of conduction block, oriented parallel to the atrial muscle bundles. The findings suggest that electric dissociation of neighboring atrial muscle bundles is an important element in the development of the substrate of human AF. Furthermore, it is feasible to measure the degree of electric dissociation that may reflect the underlying pathophysiology in individuals, offering the potential to improve individual characterization of the AF substrate.