Atrial Fibrillation Begets Atrial Fibrillation in the Pulmonary Veins

On the Impact of Atrial Fibrillation on the Electrophysiological Properties of the Pulmonary Veins in Humans

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Objectives
Our purpose was to investigate the impact of short-lasting atrial fibrillation (AF) on the electrophysiological properties of the atria and pulmonary veins (PVs) in patients devoid of AF.

Background
The presence of AF is associated with electrical remodeling processes that promote a substrate for arrhythmia maintenance in the atria, which has been termed "AF begets AF." However, it is unclear whether those electrical alterations also occur in the PVs.

Methods
Thirty-five patients with a left-sided accessory pathway and without a prior history of AF were included. After successful ablation, the effective refractory periods (ERPs) and conduction times of the right atrium (RA), left atrium (LA), and the PVs were determined. Afterwards, AF was induced and maintained for a period of 15 min. Thereafter, the stimulation protocol was repeated.

Results
At baseline, the PVs had significantly longer ERPs than the atria. After exposure to AF, the ERPs of both the atria and the PVs decreased significantly. The ERPs of the PVs, however, decreased by a significantly greater extent than the ERPs of the atria (PVs: 248 ± 110 ms vs. 211 ± 40 ms, p = 0.001; LA: 233 ± 23 ms vs. 214 ± 20 ms, p = 0.004; RA: 226 ± 29 ms vs. 188 ± 20 ms; p = 0.003). After AF exposure, the PVs demonstrated a significant conduction slowing whereas the atria did not (PVs: 125 ± 33 ms vs. 159 ± 37 ms, p < 0.001; LA: 129 ± 26 ms vs. 130 ± 24 ms, p = NS; RA: 192 ± 36 ms vs. 196 ± 32 ms, p = NS). Finally, AF was more frequently induced after the presence of AF, particularly by pacing in the PVs (14% vs. 49%, p = 0.001).

Conclusions
New-onset, short-lasting AF creates electrical characteristics similar to those of patients with AF. However, these alterations are pronounced in the PVs compared with the atria, indicating that "AF begets AF in the PVs" (Electrophysiological Properties of the Pulmonary Veins; NCT00530608). (J Am Coll Cardiol 2008;51:2153–60)

Atrial fibrillation (AF) results from a complex interaction of several mechanisms, which can be generally categorized as triggers, sources, and substrate. Once initiated, a variety of factors promote arrhythmia perpetuation (i.e., shortening of refractoriness, increased heterogeneity of refractoriness, and regional conduction slowing), which strengthen with the time of AF persistence (1–4). Wijffels et al. (4) observed that while induced AF was initially short lived, the artificial maintenance of AF resulted in progressive increase of its propensity to become sustained with time, providing the innovative concept of “AF begets AF.” Thus, the atria remodel to an AF promoting substrate due to the arrhythmia itself, resulting in a self-perpetuating process.

The seminal observation by Haissaguerre et al. (5) that focal electrical discharges of the pulmonary veins (PVs) are the predominant sources of AF has stimulated intensive research into PV arrhythmogenicity. The same group was the first to demonstrate that patients with AF have distinct electrophysiological characteristics of the PVs with shorter effective refractory periods (ERPs) and more pronounced decremental conduction properties as compared with patients without AF (6). However, whether those electrophys-
Methods

The study consists of 35 patients (age: 43 ± 13 years, 21 men) with a left-sided accessory pathway (AP), either pre-excitating (n = 20) or concealed (n = 15), who underwent primary catheter ablation. No patient has had a prior history of AF, and no patient received antiarrhythmic drugs before the procedure. Patients with structural heart diseases were excluded from the study. The patients’ baseline characteristics are presented in Table 1. The study protocol was approved by the Hamburg Ethics Committee.

Electrophysiological study and catheter ablation. All patients provided informed written consent. Electrophysiological study and catheter ablation were performed with the patient in a fasting state and under mild sedation with midazolam and fentanyl.

Surface electrocardiograms and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system with DVD storage for off-line analysis (Labsystem Pro, Bard Electrophysiology, Boston, Massachusetts). Intracardiac electrograms were filtered from 30 to 500 Hz, and measured with computer-assisted calipers at a sweep speed of 100 mm/s.

The following catheters were introduced via a right and/or left femoral vein access: 1) 2 nonsteerable quadripolar catheters (Inquiry 5-F, Josephson, IBI, Irvine, California) were positioned in the high right atrium (RA) and the right ventricular apex; 2) a nonsteerable decapolar catheter (Inquiry 5-F, Courand, IBI) in the His position; standard quadripolar or decapolar electrode catheter was placed in the coronary sinus (CS); and 3) a 3.5-mm externally irrigated-tip ablation catheter (Celsius ThermoCool, Biosense Webster, Diamond Bar, California) was used for mapping and ablation. All APs were approached from the left atrium (LA), which was accessed either by passage of a patent foramen ovale or by transseptal puncture. A single bolus of 50 IU/kg heparin was administered after accessing the LA. Mapping and ablation of APs was performed by the use of established criteria (7). Radiofrequency catheter ablation was performed using a power setting between 30 and a maximum of 40 W.

Study protocol. The study protocol was carried out within a 30-min waiting period after successful ablation of the AP, which is routinely performed in our institution for the detection of early conduction recurrences.

The protocol included the following steps: 1) ERP assessment of the PVs, the LA, and the RA, respectively; 2) induction and sustaining AF for 15 min (including immediate reinduction in case of spontaneous termination and cardioversion if the arrhythmia did not terminate spontaneously after 15 min); and 3) reassessment of the ERPs of the PVs, the RA, and the LA immediately after AF termination.

The protocol discussed in the preceding text was realized as follows: first, the ERPs of all PVs, the left atrial appendage (LAA), and the right atrial appendage (RAA) were determined by programmed stimulation using a basic drive cycle length of 440 ms. Pulmonary vein stimulation was performed as described previously in detail (8). Briefly, a circumferential decapolar PV mapping catheter (Lasso, Biosense Webster) was placed in an ostial position of the PVs. For PV pacing, the ablation catheter was placed in a distal position from the Lasso catheter. The Biotronik stimulator (UHS 20) was used for stimulation. The diastolic pacing threshold was measured at each site, and pacing was subsequently performed with a pacing output twice the diastolic threshold. A single premature extrastimulus was coupled (350 ms) after a basic drive train of 5 stimuli, and decremental stimulation was performed with an automatically shortened coupling interval in 10-ms steps until reaching the ERP. Two steps of subsequent stimulation trains were continued after the ERP was achieved to unmask potential ERP gap phenomena. The ERP of the PVs was defined as the longest coupling interval of a failed captured premature extrastimulus (S2) after the basic drive cycle to capture local PV musculature. The ERP of the RA and LA were defined as the longest coupling interval of a failed captured premature extrastimulus (S2) to capture local RAA or LAA musculature. In case of AF induction in response to extrastimulation, the ERP was assessed by using incremental programmed stimulation starting at a shortest coupling interval of 70 ms. All ERPs were confirmed by repeating programmed stimulation starting 30 ms above the initial measurement. Additionally, the conduction time from each pacing site (PVs, LAA, and RAA, respectively) to the earliest atrial electrogram in the CS catheter was measured at baseline at the shortest coupling interval before reaching local ERP, herein after referred to as maximal increment. After the exposure to AF, the maximal decrement was measured again by using the cycle with the identical coupling interval as compared with that in baseline conditions.

### Table 1 Baseline Patients Characteristics

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>35</td>
<td>42 ± 14</td>
</tr>
<tr>
<td>Men (n)</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>WPW syndrome</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Concealed accessory pathway</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td></td>
<td>none</td>
</tr>
</tbody>
</table>
In a second step, AF was induced by rapid atrial burst pacing, either from the LAA or RAA, up to a minimal cycle length before the loss of a 1:1 atrial capture. If induced AF terminated spontaneously, AF was reinduced immediately after termination by atrial burst pacing without permitting a single sinus beat interspersing terminated AF and burst pacing. When AF lasted for longer than 15 min, an external cardioversion was performed (strictly within 2 min) using external patch electrodes, which were placed on the patients’ chest before the procedure.

Finally, the ERPs of the PVs, the RA, and the LA were reassessed immediately after AF termination using the same protocol as described in step 1. In this step, PV stimulation has been performed in a random order.

**Statistical analysis.** All data are given as mean ± standard deviation. Statistical analysis was performed with SPSS version 11.0 (SPSS Inc., Chicago, Illinois). Paired data are expressed by use of a paired t test for parametric data and Wilcoxon log-rank test for nonparametric data. A 2-tailed p value <0.05 was considered significant. The ERPs of the PVs were averaged within subjects and then compared, with the exception of comparisons between the given PVs (i.e., left superior PV, left inferior PV, right superior PV, and right inferior PV, respectively).

**Results**

All PVs of the 35 study patients were targeted for PV stimulation (n = 139, 1 patient had a common trunk of the left PVs). Programmed stimulation was feasible in all targeted PVs. Under baseline conditions, the PVs demonstrated significantly longer ERPs as compared with the LA (PVs vs. LA: 248 ± 27 ms vs. 233 ± 23 ms; p = 0.021) and significantly longer ERPs as compared with the RA (PVs vs. RA: 248 ± 27 ms vs. 207 ± 24 ms; p < 0.001). Notably, the mean ERP of the RA was significantly shorter than the mean ERP of the LA (207 ± 24 ms vs. 233 ± 23 ms; p < 0.001) at baseline.

**Impact of AF on ERP.** Induction of AF was feasible in all patients, lasting for at least several seconds or a few minutes. In case of spontaneous termination, AF could be reinduced immediately after termination without an interspersing sinus beat. In 6 patients, AF did not terminate spontaneously after 15 min, requiring external cardioversion to restore sinus rhythm. The mean baseline sinus cycle lengths before and after exposure to AF were not significantly different (854 ± 118 ms vs. 840 ± 127 ms, p = 0.785). A total number of 115 PVs (83%) responded to AF with an ERP decrease of at least 10 ms (mean decrease: 37 ± 34 ms). The mean ERP of all PVs (n = 139) was significantly longer at baseline as compared with the ERP assessed after 15 min of AF (248 ± 27 ms vs. 211 ± 40 ms; p < 0.001) (Fig. 1). The ERP changes due to AF of the given PVs are demonstrated in Table 2. Thus, all 4 PVs demonstrated a significantly shorter ERP after the exposure to AF as compared with their baseline ERP (Fig. 2). While the PVs demonstrated significantly longer ERPs than the atria did at baseline, this difference with regard to ERPs was abolished after the exposure to Af (PV vs. RA: 211 ± 40 ms vs. 188 ± 20 ms; p = 0.104/PV vs. LA: 211 ± 40 ms vs. 214 ± 20 ms; p = 0.265). However, the mean ERP of the RA remained significantly shorter than the mean ERP of the LA (188 ± 20 ms vs. 214 ± 20 ms; p < 0.001). There

**Table 2**

<table>
<thead>
<tr>
<th>PV</th>
<th>n</th>
<th>PV ERP (ms)</th>
<th>PV ERP Range (ms)</th>
<th>Maximum Increment (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSPV</td>
<td>35</td>
<td>245 ± 31</td>
<td>150–300</td>
<td>119 ± 35</td>
</tr>
<tr>
<td>Pre-AF</td>
<td></td>
<td>198 ± 49*</td>
<td>70–260</td>
<td>156 ± 27*</td>
</tr>
<tr>
<td>Post-AF</td>
<td></td>
<td>237 ± 26</td>
<td>170–280</td>
<td>110 ± 25</td>
</tr>
<tr>
<td>LIPV</td>
<td>34</td>
<td>201 ± 26</td>
<td>80–270</td>
<td>140 ± 29*</td>
</tr>
<tr>
<td>Pre-AF</td>
<td></td>
<td>253 ± 25</td>
<td>190–290</td>
<td>139 ± 32</td>
</tr>
<tr>
<td>Post-AF</td>
<td></td>
<td>218 ± 37*</td>
<td>70–260</td>
<td>181 ± 45*</td>
</tr>
<tr>
<td>RSPV</td>
<td>35</td>
<td>254 ± 28</td>
<td>200–320</td>
<td>131 ± 31</td>
</tr>
<tr>
<td>Pre-AF</td>
<td></td>
<td>226 ± 29*</td>
<td>140–280</td>
<td>160 ± 33*</td>
</tr>
<tr>
<td>Post-AF</td>
<td></td>
<td>232 ± 24</td>
<td>200–280</td>
<td>129 ± 26</td>
</tr>
<tr>
<td>LA</td>
<td>35</td>
<td>214 ± 20†</td>
<td>170–250</td>
<td>130 ± 24</td>
</tr>
<tr>
<td>Pre-AF</td>
<td></td>
<td>207 ± 24</td>
<td>170–270</td>
<td>192 ± 36</td>
</tr>
<tr>
<td>Post-AF</td>
<td></td>
<td>188 ± 20†</td>
<td>140–250</td>
<td>196 ± 32</td>
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</table>

*Pulmonary veins (PVs): pre-atrial fibrillation (AF) versus post-AF, p < 0.001; †Atria: pre-AF versus post-AF, p < 0.01.

ERP = effective refractory period; LA = left atrium; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RA = right atrium; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.
were no significant differences of the ERP changes in patients who required cardioversion as compared with the patients who did not require cardioversion.

In response to AF, the mean ERP of all PVs (n = 139) showed a significantly greater decrease as compared with that seen in the atria (PVs vs. RA: 37 ± 34 ms vs. 17 ± 19 ms).
ms; p = 0.005/PVs vs. LA: 37 ± 34 ms vs. 19 ± 20 ms; p = 0.009).

**Impact of AF on conduction properties.** The changes of conduction times in response to AF are demonstrated in Table 2 for the given pacing sites (PVs, LAA, and RAA, respectively). Thus, the mean maximal increment of all PVs (n = 139) increased significantly in response to AF, whereas the atria (LAA and RAA) did not demonstrate a significantly changed conduction velocity. Interestingly, the maximal increment of the superior PVs increased by a significantly greater extent as compared with that in the inferior PVs (40 ± 28 ms vs. 30 ± 14 ms; p < 0.033).

**Impact of AF on AF susceptibility.** At baseline, programmed stimulation induced AF in 5 patients (14%). Strikingly, after the presence of AF, programmed stimulation induced AF in a significantly higher amount of patients (n = 17, 49%; p = 0.001). Of note, under baseline conditions, AF was exclusively induced by programmed stimulation from the RAA, the site with the shortest baseline ERP. After the presence of AF, the arrhythmia was more often induced from the PVs (in 10 patients) with a preferential distribution to the superior PVs (only 1 AF induction from a left inferior PV). Furthermore, the induction of AF from the PVs occurred in response to extrastimulation and during the baseline train before delivering an extrastimulus (Figs. 3 and 4).

**Discussion**

This study first demonstrates the impact of short-lasting AF on the electrophysiological characteristics of the PVs in humans devoid of AF. At baseline, the PVs display significantly longer ERPs than the atria. After a short-lasting episode of AF, the ERPs of both atria and PVs decrease significantly. However, the electrophysiological response to AF is markedly pronounced in the PVs indicated by a significantly greater extent of ERP shortening as compared with that in the atria. Moreover, the short-term presence of AF does influence the PV electrophysiology by slowing the conduction velocity, without affecting the conduction times of the atria. Finally, the susceptibility to induce AF is significantly higher after the exposure to short-lasting AF, particularly by pacing from within the PVs.

**Electrophysiological changes associated with AF.** The current knowledge on electrophysiological alterations of the heart linked to AF (electrical, structural, and mechanical) is mainly based on experimental (animal) studies (1–4). Furthermore, clinical data on AF-related electrical characteristics, including the landmark studies on AF mechanisms provided by the group of Allessie et al. (4,9,10), are derived from investigations that are confined to AF processes in the RA. However, AF inducing and perpetuating processes in humans are predominantly localized in the LA and its adjacent thoracic veins (i.e., the PVs [5] and the CS.
[11,12)], particularly in patients with self-terminating AF episodes. Accordingly, a left-to-right frequency gradient has been shown in AF-induced, Langendorff-perfused sheep hearts (13). Moreover, in the clinical setting, paroxysmal AF is associated with a PV-LA frequency gradient (14,15). The crucial role of the PVs in human AF is furthermore corroborated by their distinct electrophysiological properties, which are strikingly different from those of patients without AF (6). Additionally, it has been demonstrated that patients with AF have significantly shorter ERPs within the PVs compared with the PV-LA junction (16,17) and the atria (17). It is, however, unclear whether those electrical characteristics of the PVs are a pre-existing condition predisposing to AF or if the presence of the arrhythmia itself causes these distinct electrical alterations and thereby, starts a cascade leading to “AF domestication” (4). The observed characteristic electrophysiological properties of the PVs and atria of patients with AF are similar to those of patients exposed to short-term AF as has been shown by our study. Thus, the data of the present study demonstrate that even short-term exposure of AF to “electrically unaltered” human atria results in electrical properties characteristic of AF in conjunction with a significantly increased AF susceptibility. Thus, even patients without an AF predisposing substrate may rapidly develop an arrhythmogenic milieu similar to those of patients with AF. This observation provides evidence that the arrhythmia itself causes distinct electrical alterations associated with AF and, therefore, indicates that the process of AF induced “electrical remodeling” does not necessarily require a predisposing substrate.

**Time course of AF-associated alterations.** Allessie (18) proposed 4 time domains to distinguish between the different adaptation processes linked to AF: 1) short-term, lasting for seconds to minutes with metabolic changes; 2) moderate-term (hours to days), with electrical alterations; 3) long-term, during a time period of several weeks with contractile changes; and 4) very-long-term (months to years), with anatomical consequences for the heart. While metabolic changes occurring during the initial phase of AF rapidly result in a new steady-state of intracellular ion concentrations, activity status of ion pumps, and phosphorylation of ion channels, processes other than metabolic (e.g., change of ion channel density and properties) occur after hours and days, leading to the characteristic electrical changes (18–20). Daoud et al. (21) were the first to demonstrate the effect of short-lasting AF (7 min) on the electrophysiological properties of the RA, which were characterized by ERP shortening and an increased propensity of AF induction. Their study furthermore revealed that these electrical alterations recover in a time frame of 5 to 8 min to the baseline value, while the increased AF susceptibility diminishes progressively as the elapsed time after the primary exposure to AF increases (21). The present study confirms the distinct electrophysiological response to AF in
the RA and demonstrates its similar occurrence in the LA and PVs. Thus, significant electrical changes are already induced by short-lasting AF (a few minutes) despite the absence of a predisposed substrate. Interestingly, these changes were significantly more pronounced in the PVs as compared with the atria. These findings suggest that first, the PVs are more susceptible to metabolic and subsequent electrical alterations due to AF and second, the time domains of the “AF begetting AF” process may progress more rapidly in the PVs than in the atria, which both again elucidate the crucial role of the PVs in AF.

Mechanistic and clinical impact. The findings of the present study provide new information on potential mechanisms of the electrical establishment of human AF. Continuous short-term firing from a single PV may create a susceptible substrate in other PVs (and the atria). This in turn may lead to independent offspring of arrhythmogenic processes in other PVs (and then eventually in the atria), i.e., focal electrical discharges and formation of (micro-) re-entrant circuits. This “ping-pong” effect of the PVs among themselves and between the PVs and the atria is potentially capable of maintaining the arrhythmia and, thereby, starting the vicious circle of AF.

In experimental studies, it has been shown that intracellular calcium-lowering drugs (e.g., verapamil) shorten the time course of AF-associated electrical remodeling of the atria (22,23). These experimental studies are corroborated by the clinical observation that the incidence of early AF recurrences after cardioversion is significantly reduced under an oral pre-treatment with verapamil (24). Nevertheless, it is unknown whether these effects are confined to verapamil-induced changes of the calcium current properties of the atria. However, it has been shown that an abnormal calcium regulation may underlie PV arrhythmogenicity (25). More recently, aging-related alterations in calcium regulatory proteins (e.g., ryanodine receptors) are demonstrated to increase PV arrhythmogenesis (26). Therefore, it is conceivable that verapamil also affects the electrical remodeling of the PVs.

Further studies, both experimental and clinical, are desired to reveal additional information regarding the underlying mechanisms of electrical remodeling of the PVs and the time course of its occurrence. Accordingly, exploring the mechanisms may provide a new therapeutic avenue for treatment of AF by antiarrhythmic drugs or interventional approaches in the future.

Study limitations. Besides AF-induced shortening of action potential durations and alterations of ion current activities, changes in the autonomic tone due to the onset of AF might be one factor that influences atrial and PV electrophysiology. In our study, the mean sinus cycle lengths before and after the presence of AF did not differ significantly, indicating a relatively constant degree of autonomic tone (21). Nevertheless, pharmacologic autonomic blockade is required to definitely exclude influences by a variable autonomic tone. However, since this study sought to investigate the electrophysiological response to AF as it occurs in the clinical setting, including all influencing mechanisms, we did not use an autonomic blockade.

Since programmed stimulation was performed at 6 different sites (RA, LA, and PVs, respectively), we were not able to investigate the time course of the ERP changes because repeated interruption of AF may prevent the occurrence of electrophysiological alterations, as it has been demonstrated in our study.

Conclusions

New-onset, short-lasting AF induces significant changes of electrophysiological properties of both atria and PVs and, thereby, creates electrical characteristics similar to those of patients with AF. However, these changes are significantly more pronounced in the PVs as compared with the atria, indicating that “AF begets AF in the PVs.”

Acknowledgment

The author, Dr. Thomas Rostock, would like to dedicate this work to his teacher in electrophysiology and research, Dr. Michel Haissaguerre, pioneer in clinical electrophysiology.

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REFERENCES


