Introduction and objectives. Ectopic activity originating inside the pulmonary veins has been associated with paroxysmal atrial fibrillation in some patients. However, the roles played by the pulmonary veins and the posterior wall of the left atrium in maintaining atrial fibrillation are not well understood.

Methods. Our aim was to determine whether there is a correlation between the refractory period of either the lateral wall of the right atrium, the lateral wall of the left atrium, the posterior wall of the left atrium, or the pulmonary veins, and the inducibility of atrial fibrillation in an experimental swine model. We assessed atrial fibrillation inducibility using programmed atrial stimulation before and after intravenous administration of a high dose of methacholine in 20 pigs.

Results. Atrial fibrillation was induced in 17 out of the 20 pigs. Univariate analysis showed that there were negative correlations between all refractory periods and atrial fibrillation inducibility. A short refractory period was associated with greater inducibility. In the multivariate analysis, only the refractory periods of the posterior wall of the left atrium and the pulmonary veins were associated with inducibility. We also investigated the relationship between the local atrial fibrillation cycle length and refractory period; the only significant correlation was with the refractory period of the lateral wall of the right atrium (Pearson correlation coefficient 0.97).

Conclusions. In an experimental swine model, the inducibility of atrial fibrillation is associated with both the pulmonary veins and the posterior wall of the left atrium.

Key words: Atrial fibrillation. Mechanisms. Physiology.
ABSTRACT

Fernández-Lozano I et al. Pulmonary Veins and Atrial Fibrillation Inducibility

INTRODUCTION

Medicine has been aware of atrial fibrillation (AF) for centuries. However, initial theories concerning the causes and mechanisms were merely speculative. It has only been in recent years that the development of animal models and analysis of patients have allowed the understanding of this arrhythmia to be approached scientifically.

The main limitations associated with the first studies of AF were the ability to obtain stable animal models and the difficulty of mapping the arrhythmia.1-3 Inducing AF is extremely difficult in standard laboratory animals and generally requires additional factors such as the use of arrhythmogenic drugs, vagal stimulation, rapid atrial pacing, heart failure, or inflammation.

In 1914, Garrey7 performed the first scientific study of the mechanisms underlying this arrhythmia and established the concept of critical mass. By continuous electrical stimulation at the tip of the atrial appendix, he observed that upon isolation of the appendix from the rest of the atrial myocardium the fibrillation disappeared in the appendix, while the rest of the atrial myocardium continued to fibrillate. Based on those observations, he concluded that a minimum amount of myocardium is necessary for the atrium to sustain AF. Based on his results and those of Mayer3 and Mines,5 he proposed that the mechanism responsible for AF involved a series of ring-shaped circuits of varying location and multiple complexity. Subsequently, Lewis13 proposed a similar model. According to that model, in AF there is a single main circuit whose location and frequency varies over time.

In the 1940s, Weiner and Rosenblueth9 used data on conduction velocity to calculate that certain anatomic orifices such as the pulmonary veins were too small to sustain a reentry circuit. However, they speculated that the orifice of the inferior vena cava could be the source of the atrial flutter and that the smaller orifice of the superior vena cava could sustain AF. An important point that these studies have in common with those of Garrey and Lewis is that they assume that a circuit could exist whose conduction velocity is so high that it cannot be followed in a 1:1 ratio by the rest of the atria. This is the concept that we currently know as fibrillatory conduction.

Scherf10-12 proposed the focal origin theory. The theory was based on a series of animal studies in which acute transection was injected into the atrium, leading to a rapid and regular rhythm consistent with flutter at the injection site and an irregular rhythm in the rest of the atrium consistent with AF.

Various mechanisms of AF have been demonstrated in the human heart. Haissaguerre et al14 used endocardial mapping with catheters in a group of patients with paroxysmal AF and without structural heart disease to demonstrate that in many cases the AF occurred as a result of high-frequency automatic foci. Those foci could be localized to the right atrium or the posterior wall of the left atrium, but in 94% of cases they were found inside the pulmonary veins, 2 to 4 cm from the left atrium. These types of automatic foci could also originate in other structures such as the ligament of Marshall or the superior vena cava.15

Unfortunately, no animal model is available that reproduces the findings in those patients, making it difficult to extend our understanding of the role played by the pulmonary veins in the initiation and maintenance of episodes of AF. It is not clear whether the role of these automatic foci is limited to initiation of AF in a vulnerable myocardium, whether they also play a role in the maintenance of AF, or if the 2 mechanisms alternate with each other.16,17

In addition, there is evidence that the electrical activity of the pulmonary veins depends on their interaction with the surrounding atrial myocardium.18,19 Unfortunately, no animal model is available that reproduces the findings in those patients, making it difficult to extend our understanding of the role played by the pulmonary veins in the initiation and maintenance of episodes of AF. It is not clear whether the role of these automatic foci is limited to initiation of AF in a vulnerable myocardium, whether they also play a role in the maintenance of AF, or if the 2 mechanisms alternate with each other.16,17

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METHODS

The study used 20 female 2-month-old Landrace x Large-White pigs weighing between 18 and 25 kg. Prior to use in the study, each animal was separated and housed individually and did not receive solid food for 24 hours or water for 4 hours. On the day of the study the animals were premedicated with ketamine (20 mg/kg), diazepam (1 mg/kg), and atropine (40 µg/kg), administered by intramuscular injection in the same syringe. Anesthesia was induced with isoflurane at a concentration of 5% vaporized in oxygen at 2 L/min and administered using a Hall mask placed over the snout of the animal. Anesthesia was maintained by administration of isoflurane at a concentration of 1% to 1.5% vaporized in oxygen (2 L/min).

Next, the left external jugular vein was dissected and cannulated for administration of fluid therapy, inotropic drugs, and continuous infusion of fentanyl (10 µg/kg/h) and pancuronium (0.2 mg/kg/h). In addition, the left carotid artery was dissected and an 18G catheter introduced to record arterial pressure and obtain samples of arterial blood for gasometry and analysis of acid-base equilibrium. Standard electrocardiography monitoring was used and arterial oxygen saturation was measured by pulse oximetry.

The heart was accessed by median sternotomy. After resection of the thymus, an inverted-T shaped incision was made in the pericardium. Spontaneous rhythm and atrial activation sequence were then analyzed by epicardial mapping with simultaneous bipolar recordings. Atrial signals (a maximum of 24 bipolar signals) were recorded using sutured pentapolar discs, tripolar probes, and a flexible mesh with 24 bipolar signals. The discs were sutured on the lateral wall of the right atrium, the right ventricle, the lateral wall of the left atrium, and the pulmonary veins.

The signal from the pulmonary veins and, occasionally, the posterior wall of the right atrium, was recorded with a tripolar probe. The signal from the His bundle was recorded with a 6F tetrapolar catheter introduced into the right carotid artery through a “tobacco pouch” suture and advanced until the noncoronary cusp.

Stimulation was performed as follows:

1. Recordings: temporal bipolar recordings filtered at 30 Hz or 1000 Hz obtained with epicardial electrodes.

2. Stimulation: square-wave pulses with a duration of 2 ms at twice the measured threshold.

3. Recording points:
   - Lateral wall of the right atrium.
   - Lateral wall of the left atrium.
   - Posterior wall of the left atrium.
   - Right ventricle.
   - Superior pulmonary veins.

4. Data was acquired with a 24-channel Hellige recorder (Midas System) with an analog to digital converter and an optical disc storage system.

5. Stimulation protocol:
   - Baseline recording of spontaneous rhythm. Calculation of baseline parameters. To determine the baseline parameters, each one was measured 3 times and the mean value calculated.
   - Calculation of the corrected sinus-node recovery and atrioventricular conduction times. The stimuli used were 2-ms square-wave pulses with an amplitude of twice the threshold at each point. A Medtronic 5200® stimulator was used. The sinus-node recovery time was obtained using a 30-s pacing train at 4 different cycle lengths (400, 350, 300, and 250 ms). The correct sinus-node recovery time was obtained by subtracting the baseline interval from the maximum interval measured following pacing.
   - Calculation of the ERP of the right atrium, the lateral and posterior walls of the left atrium, and the pulmonary veins. The ERP was calculated using a train of 8 stimuli (S1) to 300 ms followed by an impulse (S2) with progressive reduction of the coupling intervals. The ERP was defined as the longest S1-S2 interval that did not generate a myocardial response. The atrial ERP was determined twice for each stimulation point.
   - Stimulation of the right atrium and the lateral and posterior walls of the left atrium according to the following protocol: a) S1-S1 (300 ms) with progressive reduction of the interval to S2 until the atrial ERP is obtained; b) S1-S1 (300 ms), S2 (atrial ERP + 20 ms), S3 (progressive reduction of the interval until the atrial ERP is reached); and c) S1-S1 bursts for 5 s, with sharp interruptions, starting at 200 ms and reducing progressively until 1:1 capture was lost. If repetitive responses were obtained, the coupling interval was only repeated once prior to continuing with the protocol.

If AF was not induced by the end of the protocol, the entire process was repeated from the second stimulation point (left atrium).

The aim of the protocol was to induce sustained AF, defined as irregular atrial tachycardia with a cycle length of less than 200 ms, spontaneous variations in
the cycle of greater than 10 ms, and a duration of more than 10 minutes from induction.

– Methacholine was then infused through a central line, initially at a low dose of 1.5 µg/kg/min and then at a higher dose of 3.6 µg/kg/min and a very high dose of 6.5 µg/kg/min.

– The stimulation protocol was repeated for the right and left atria.

Statistical Analysis

The hypothesis that the data obeyed a normal distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Student t test was used for normally distributed parametric variables. The Mann-Whitney U test was used for non-normally distributed variables. Significance at \( P < 0.05 \) was analyzed by 2-tailed test.

The relationship between inducibility of AF and the electrophysiologic parameters of the model were analyzed using the Student t test for independent samples. Correlation and multiple linear regression analysis were performed with the electrophysiologic parameters as independent variables and inducibility as the dependent variable. Multivariable analysis was performed with the electrophysiologic parameters as independent variables and inducibility as the dependent variable. The coefficient of determination \( R^2 \) indicates the proportion of the variability of the dependent variable that is explained by the independent variables.

Data were analyzed using the statistical program SPSS version 11.0.

RESULTS

At baseline, measurements were made of the cycle length and the PR, QRS, and QT intervals from the surface electrocardiogram (ECG), along with the PA, AH, and HV intervals from the His bundle electrogram. The corrected sinus-node recovery time was also determined. The values obtained for the mean, range, and SD of the variables analyzed are shown in Table 1. In addition, the ERP was determined for the lateral wall of the right atrium, the lateral and posterior walls of the left atrium, and the pulmonary veins (Table 2).

AF was induced in 17 (85%) of the 20 animals analyzed. In 75% of cases, AF was sustained with continued perfusion of methacholine, in 10% AF lasted less than 10 minutes, and in the remaining 15% AF induction was not achieved (Figure 1). Low doses of methacholine were required to maintain AF in 25% of animals, high doses in 40%, and very high doses in 20%.

Of the 17 animals in which AF could be induced, in 4 (23.5%) the AF was only inducible from the right ventricle, in 9 (53%) only from the left atrium, and in 4 (23.5%) it was inducible from both atria (Figure 2). Analysis of the stimulation point revealed greater arrhythmogenicity associated with induction from the left atrium; however, the difference was not statistically significant. The absence of statistical significance was probably due to the small sample size.

We analyzed the relationship between baseline inducibility of AF and the refractory periods obtained on the lateral wall of the right atrium, the left atrium, the posterior wall of the left atrium, and the pulmonary veins. All were negatively correlated with inducibility in the univariate analysis. The shorter the refractory period the greater the inducibility of AF.

Multivariable analysis only showed ERP of the posterior wall of the left atrium and the pulmonary veins to be correlated with inducibility (\( R^2=0.97, P<0.001 \)) (Figure 3). The relationship between the refractory periods of the right atrium, the left atrium, the posterior wall of the left atrium, and the pulmonary

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Electrophysiologic Characteristics of the Model*</th>
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<tbody>
<tr>
<td><strong>Description Statistics</strong></td>
</tr>
<tr>
<td><strong>Minimum</strong></td>
</tr>
<tr>
<td>Cycle length</td>
</tr>
<tr>
<td>PR interval</td>
</tr>
<tr>
<td>QRS duration</td>
</tr>
<tr>
<td>QT interval</td>
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<tr>
<td>AH interval</td>
</tr>
<tr>
<td>HV interval</td>
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<tr>
<td>CSNRT</td>
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</table>

*CSNRT indicates corrected sinus node recovery time. Data based on information obtained from 20 animals.

<table>
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<tr>
<th>TABLE 2. Effective Atrial Refractory Periods*</th>
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</thead>
<tbody>
<tr>
<td><strong>Description Statistics</strong></td>
</tr>
<tr>
<td><strong>Minimum</strong></td>
</tr>
<tr>
<td>RA</td>
</tr>
<tr>
<td>LA</td>
</tr>
<tr>
<td>Posterior LA</td>
</tr>
<tr>
<td>PV</td>
</tr>
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</table>

*RA indicates right atrium; LA, left atrium; PV, pulmonary veins.
veins (independent variables) and inducibility of AF (dependent variable) was assessed (Table 3).

**Induced Atrial Fibrillation**

We went on to analyze the characteristics of the induced AF at the different recording points. The first 2 seconds of each episode of AF were excluded from this analysis and the mean cycle length determined over the next 5 seconds. The cycle length of AF was measured manually: the signals were recorded on 200 mm/s paper and 2 F waves were considered to be separate if there were 2 electrograms separated by an isoelectric interval of at least 50 ms (Table 4).

The correlation between the local cycle length of the AF and the refractory period measured at baseline was assessed. Only the cycle length of AF on the lateral wall of the right atrium and the refractory period at that point displayed a significant correlation ($r=0.97$, Pearson’s correlation coefficient). No significant correlations were observed at the other points analyzed (Figure 4).

**Figure 1.** Left: inducibility. Right: type of atrial fibrillation (AF) induced. Out of 20 animals, AF was induced in 17 (85%), 75% of the animals with sustained AF, 10% with nonsustained AF, and 15% were not inducible. Data shown on pie charts as percentages.

**Figure 2.** Inducibility in relation to stimulation site. Data shown on pie charts as percentages. n indicates the number of animals in each group.

**Figure 3.** Relationship between refractory periods and inducibility. The chart on the left shows the atrial refractory periods measured in the inducible and noninducible group. The chart on the right shows the refractory periods in the posterior wall of the left atrium and the pulmonary veins. Boxes indicate the interquartile range with the median indicated by a thick line; the extreme values are indicated by whiskers. RA indicates right atrium; LA, left atrium; post, posterior; PV, pulmonary veins; ERP, effective refractory period.
DISCUSSION

The model used here has been analyzed previously in studies demonstrating the usefulness of methacholine for the induction of AF in experimental animals.27,28 The mechanism of action of the drug is based on the reduction of the refractory periods throughout the atrial myocardium. To analyze the data obtained, nonsustained AF was considered as AF lasting between 30 s and 10 min. Sustained AF was defined as AF lasting more than 10 minutes. Consequently, repeated short-duration responses following stimulation were considered nonspecific and were not included in the analysis. A stepwise protocol

<table>
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<tr>
<th>Coefficient of Regression</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>2.06</td>
<td>1.937-2.186</td>
</tr>
<tr>
<td>ERP Poster LA</td>
<td>-0.0061</td>
<td>-0.011 to -0.002</td>
</tr>
<tr>
<td>ERP PV</td>
<td>-0.00099</td>
<td>-0.011 to -0.001</td>
</tr>
</tbody>
</table>

*ERP indicates effective refractory period; LA, left atrium; PV, pulmonary veins.

The baseline refractory periods for the posterior wall of the left atrium and the pulmonary veins show a more significant relationship with inducibility of atrial fibrillation, while the refractory periods of the right atrium and the lateral wall of the left atrium are not significant.

TABLE 3. Multivariable Analysis. Linear Regression Analysis*

TABLE 4. Analysis of Induced Atrial Fibrillation*

<table>
<thead>
<tr>
<th>Descriptive Statistics</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean±SD</th>
</tr>
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<tbody>
<tr>
<td>AF CL RA</td>
<td>145</td>
<td>185</td>
<td>160.9±10.62</td>
</tr>
<tr>
<td>AF CL LA</td>
<td>117</td>
<td>168</td>
<td>134.6±18.51</td>
</tr>
<tr>
<td>AF CL Posterior LA</td>
<td>81</td>
<td>107</td>
<td>92.7±8.60</td>
</tr>
<tr>
<td>AF CL PV</td>
<td>101</td>
<td>155</td>
<td>118.0±13.00</td>
</tr>
</tbody>
</table>

*AF indicates atrial fibrillation; CL, cycle length; RA, right atrium; LA, left atrium; PV, pulmonary veins.

Cycle length of atrial fibrillation induced in the right atrium, left atrium, posterior wall of the left atrium, and the pulmonary veins.

Figure 4. Correlation between refractory period and cycle length of induced atrial fibrillation. The graph on the top left shows the correlation between the effective refractory period of the lateral right atrium and atrial fibrillation, the only one to show a significant correlation. The central curve corresponds to the linear regression line, which is bordered on either side by the curves indicating the 95% confidence interval.

RA indicates right atrium; LA, left atrium; AF, atrial fibrillation; CL, cycle length; ERP, effective refractory period; PV, pulmonary veins.
was used involving increasing doses of methacholine and inducibility was analyzed by stimulation in both atria. AF was induced in 17 of the 20 animals analyzed: in 15 the AF was sustained (>10 min) and in the remaining 2 it was nonsustained.

Most previous experimental animal studies of AF have been performed in dogs. In addition, different criteria have been used to define sustained AF. Arrhythmia is less easy to generate in pigs than in dogs, and it is more difficult to obtain atrial fibrillation in response to any type of stimulus. This explains why, unlike in other studies, the baseline percentage of AF did not achieve 100% in our study.

Stimulation of the right atrium led to the induction of AF in 8 out of 17 animals (47%), while stimulation of the left atrium induced AF in 13 (76%) animals. Although these differences are apparently large, they were not statistically significant due to the small sample size. Both in reentry arrhythmias and in the majority of focal arrhythmias, greater proximity of the stimulation point to the tachycardia circuit favors inducibility. The strong tendency towards greater inducibility in the left atrium suggests that the mechanism underlying AF has its origin in that region in the experimental model used here. It should be noted at this point that although the model has been used by other authors, the mechanism responsible for AF has not been fully determined.

The atrial refractory periods were found to be negatively correlated with inducibility of AF: the shorter the refractory period the greater the capacity of the atrium to conduct impulses. This would facilitate the appearance and maintenance of AF, independently of the mechanism.

In the multivariable analysis, the strongest association with baseline inducibility of AF was obtained with ERP of the posterior wall of the left atrium and of the pulmonary veins. In 2000, a lower ERP in the pulmonary veins than observed in AF. Patients referred for ablation of AF have a lower ERP in the pulmonary veins than observed in subjects with no history of AF.

Thus, in dogs, the presence of microreentrant circuits is due to an abnormal shortening of the refractory periods and a reduction of the conduction velocity, leading to a wider dispersion of the refractory periods in the atrial myocardium and a shortening of the wavelength, both of which are critical for the initiation and maintenance of a reentrant mechanism.

The presence of microreentrant circuits is critical for the initiation and maintenance of AF. In the pulmonary veins, the regions containing complex fractionated potentials were localized to the pulmonary veins, the roof of the left atrium, the interatrial septum, the posteroseptal region of the mitral ring, and the ostium of the coronary sinus. The results of that study indicated that the regions associated with maintenance of AF may lie outside the pulmonary veins, many of them in the left atrium. Those findings are consistent with the results of our study: if AF is maintained through localized microreentrant wavelets in the posterior wall of the left atrium, a shorter refractory period would be expected in those areas along with a stronger association between shorter refractory periods and inducibility of AF.

There is increasing evidence that AF is essentially an arrhythmia of the left atrium. This view is supported by data obtained through optical mapping of left atrial activation and mapping with multiple epicardial electrodes. Generally, shorter AF cycles are recorded at the posterior surface of the left atrium, both in animals and humans. In addition, in recent years, the importance of the pulmonary veins and the surrounding atrial myocardium has been recognized in the induction and maintenance of AF. Recent studies have demonstrated that shortening of the refractory periods and a reduced conduction velocity in the pulmonary veins may lead to focal activity that initiates AF. Patients referred for ablation of AF have a lower ERP in the pulmonary veins than observed in subjects with no history of AF.

Microreentrant circuits tend to be located in the posterior wall of the left atrium. The presence of microreentrant circuits is due to an abnormal shortening of the refractory periods and a reduction of the conduction velocity, leading to a wider dispersion of the refractory periods in the atrial myocardium and a shortening of the wavelength, both of which are critical for the initiation and maintenance of a reentrant mechanism. AF mapping studies have demonstrated that the microreentrant circuits are not distributed completely at random but rather tend to be grouped and repeated in certain regions of the atrium where functional conduction block is present or there is delayed conduction. In addition, some studies in patients in whom ablation has been performed in the pulmonary veins have demonstrated that complete isolation is not necessary for success; modification of the left posterior artery may be sufficient.

Those findings would explain the correlation between inducibility and shorter refractory periods observed in this study in both the pulmonary veins and the posterior surface of the left atrium.

Analysis of Induced Atrial Fibrillation

Analysis of the relationship between cycle length of induced AF and refractory periods revealed a significant correlation between the mean cycle length of the lateral wall of the right atrium and the refractory period at that point (r=0.97, Pearson’s...
correlation coefficient). No significant correlations were observed between baseline refractory period and mean cycle length of induced AF at the other points analyzed. Although there is no clear explanation for this finding, it may be due to a purely anatomic phenomenon. Of all the regions analyzed, the lateral wall of the right atrium is probably the region of the atrium with the fewest obstacles to propagation of electrical impulses. Consequently, it is possible that the FF intervals show a better correlation with the refractory periods than in any other region of the atrial myocardium.

In 1998, Gaita et al. analyzed the organization of AF before and after ablation involving linear lesions in the right atrium. In general, AF was found to be more regular and slower in the lateral wall of the right atrium than in the septum; furthermore, they found that the greater the regularity the more effective the procedure.

However, in other experimental studies, a clear association has been observed between the length of local refractory periods and the cycle length of induced AF. Kim et al. observed a clear association between the minimum cycle length and the ERP in 8 isolated canine atria. The difference may be accounted for by the use of isolated canine atria, free from innervation and the influence of pressure changes; furthermore, in that study the authors analyzed minimum cycle length rather than mean cycle length as used in our study.

Morillo et al. and Sih et al. also found a clear association between the atrial ERP and the cycle length of AF. However, they used a canine model involving chronic high-frequency stimulation. That model leads to dilation of both atria and that could explain, at least in part, the differences observed.

LIMITATIONS

This study was performed in a specific model using methacholine to induce and maintain AF. Consequently, care should be taken in extrapolating the results to other models. In addition, the results are based only on epicardial recordings, thereby limiting the interpretation of the data.

Furthermore, the use of only 5 seconds of recording to calculate the cycle length of AF may represent a further limitation. Finally, the group in which AF was not inducible only contained 3 animals. This could have limited the reliability of the statistical analysis.

CONCLUSIONS

Various surgical and ablation techniques have been described for the treatment of AF, with different percentage success rates. However, the insight they have provided into the mechanisms underlying AF has been very limited. This study reveals the importance of both the pulmonary veins and the posterior wall of the left atrium for the inducibility of AF in a swine model.

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