Frequency Mapping of the Pulmonary Veins in Paroxysmal Versus Permanent Atrial Fibrillation

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Pulmonary Veins in the Maintenance of AF. ***Introduction:*** **The pulmonary veins (PVs) are a dominant source of triggers initiating atrial fibrillation (AF). While recent evidence implicates these structures in the maintenance of paroxysmal AF, their role in permanent AF is not known. The current study aims to compare the contribution of PV activity to the maintenance of paroxysmal and permanent AF.**

Methods and Results: **Thirty-four patients with paroxysmal AF (n = 20) or permanent AF (n = 14) undergoing ablation were studied. Prior to ablation, 32 seconds of electrograms were acquired from each PV and the coronary sinus (CS). The frequency of activity of each PV and CS was defined as the highest amplitude frequency on spectral analysis. The effects of ablation on the AF cycle length (AFCL) and frequency and on AF termination were determined. Significant differences were observed between paroxysmal and permanent AF. Paroxysmal AF demonstrates higher frequency PV activity (11.0 ± 3.1 vs 8.8 ± 3.0 Hz; P = 0.0003) but lower CS frequency (5.8 ± 1.2 vs 6.9 ± 1.4 Hz; P = 0.01) and longer AFCL (182 ± 17 vs 158 ± 21 msec; P = 0.002), resulting in greater PV to atrial frequency gradient (7.2 ± 2.2 vs 4.2 ± 2.9 Hz; P = 0.006). PV isolation in paroxysmal AF resulted in a greater decrease in atrial frequency (1.0 ± 0.7 vs −0.05 ± 0.4 Hz; P < 0.0001), greater prolongation of the AFCL (49 ± 35 vs 5 ± 6 msec; P < 0.0001), and more frequent AF termination (11/20 vs 0/14; P = 0.0007) compared to permanent AF.**

Conclusion: **Paroxysmal AF is associated with higher frequency PV activity and lesser CS frequency compared to permanent AF. Isolation of the PVs had a greater impact on the fibrillatory process in paroxysmal AF compared to permanent AF, suggesting that while the PVs have a role in maintaining paroxysmal AF, these structures independently contribute less to the maintenance of permanent AF.** *(J Cardiovasc Electrophysiol, Vol. 17, pp. 965-972, September 2006)*

atrial fibrillation, spectral analysis, arrhythmia mechanism, ablation, pulmonary veins

Introduction

The pulmonary veins (PVs) are a dominant source of triggers initiating atrial fibrillation (AF) in a variety of clinical scenarios.[1-7] Recently, there has been an accumulating body of evidence that demonstrates the PVs have a role also in the maintenance of paroxysmal AF. In some patients, continual "focal firing" from these structures has been observed to maintain AF.[8] Others have observed paroxysmal short cycle length activity within the PVs during ongoing AF and suggested that this may represent a continued refueling of the fibrillatory process.[9-11] This has been further corroborated by the observation that, in patients with paroxysmal AF, isolation of each PV was associated with a gradual slowing of the fibrillatory process that culminated in the termination of AF.[12] These findings suggest that the PVs have a critical role in the maintenance of paroxysmal AF. Whether the PVs have a similar role in maintaining permanent AF remains unknown.

Experimental studies have suggested a role for high-frequency activity in the maintenance of AF.[13,14] These studies have not only demonstrated that dominant frequency (DF) sites were found in the left atrium[4,15,16] but also that there was a significant left to right atrial gradient of activity.[17] Clinical studies have shown the presence of similar findings in patients with AF.[4,18-20]

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The present clinical study was designed to compare the role of PV activity in the maintenance of paroxysmal AF versus permanent AF by determining the frequency of PV activity, the relative PV to atrial frequency gradient and the effect of PV isolation on the global fibrillatory process.

Methods

Study Population

The study comprised 34 patients with symptomatic drug refractory AF undergoing ablation. These patients were selected on the basis of having spontaneous or induced sustained (>10 minutes) AF at the time of ablation. AF was paroxysmal in 20 patients and permanent (≥12 months) in 14. Baseline characteristics of these two groups of patients are presented in Table 1.

All patients gave written informed consent to the study, which was approved by the institutional Clinical Research and Ethics Committee.

Electrophysiology Study

All patients had effective anticoagulation for ≥1 month (international normalized ratio of 2 to 4) and underwent transesophageal evaluation to exclude atrial thrombus prior to the procedure. Antiarrhythmic drugs, with the exception of amiodarone, were ceased ≥5 half lives before the study. Electrophysiological study was performed in the postabsorptive state with sedation utilizing midazolam and morphine.

The left atrium was accessed transeptally, following which a single bolus of 50 IU/kg body weight of heparin was administered and repeated only for procedures lasting ≥4 hours. The following catheters were utilized for mapping and ablation in these patients: (i) a steerable quadripolar catheter (5-5-5mm Xtrem, Ela Medical, Montrouge, France) was positioned within the coronary sinus (CS) with the proximal electrode positioned at 4–5 o'clock along the mitral annulus in left anterior oblique projection and minimizing the ventricular component of the electrogram; (ii) a circumferential mapping catheter (10-pole Lasso, Biosense-Webster, Diamond Bar, CA, USA) was introduced following transeptal access and stabilized with the aid of a long sheath (Preface multipurpose, Biosense-Webster) that was continuously perfused with heparinized glucose; and (iii) a 3.5-mm externally irrigated-tip ablation catheter (Thermocool, Biosense-Webster).

Surface electrocardiogram and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system (Bard Electrophysiology, Lowell, MA, USA). Intracardiac bipolar electrograms were sampled at 1 kHz and filtered at 30–500 Hz. All measurements were made at a sweep speed of 100 mm/sec.

TABLE 1
Patient Characteristics

	Paroxysmal AF (n = 20)	Permanent AF (n = 14)	P value
Age (years)	57 ± 8	54 ± 11	0.5
Male, n (%)	16 (80%)	10 (71%)	0.7
Sustained AF duration	11 ± 19 hours	23 ± 14 months	<0.0001
Failed antiarrhythmics (n)	3 ± 1	3 ± 1	0.5
Amiodarone use, n (%)	6 (30%)	6 (43%)	0.5
Left atrial size (mm)			
Parasternal	43 ± 8	49 ± 3	0.04
Longitudinal	49 ± 8	63 ± 5	0.0004
Transverse	39 ± 8	46 ± 7	0.04
LV dimension (mm)			
LV end diastolic diameter	53 ± 5	54 ± 6	0.4
LV end systolic diameter	33 ± 4	37 ± 8	0.5
LV ejection fraction (%)	68 ± 7	60 ± 12	0.03
Structural heart disease, n (%)	4 (20%)	4 (29%)	0.7

AF = atrial fibrillation; LV = left ventricle.

Study Protocol

Mapping during AF

Selective angiography of the PVs was performed using a NIH catheter and hand injection of 10–20 mL of contrast to provide a road map for catheter positioning. The circumferential mapping catheter was then sequentially positioned within the first 1 cm of the PV ostia for mapping. The positioning of the catheter was further confirmed in a subset with the use of intracardiac echocardiography (Acunav, Siemens Medical, Mountain View, CA, USA). Mapping acquired simultaneous electrograms from the PV and the CS for 32 seconds. Additionally, after the isolation of all veins, CS electrograms were collected for 32 seconds to determine the effect of ablation.

Signal analysis

The signal processing and spectral analysis software utilized an automated dedicated system (Bard Electrophysiology). Spectral analysis was performed by fast Fourier transformation on the bipolar recordings obtained on each bipole of the circumferential mapping catheter and also the CS catheter prior to any ablation and after PV isolation of the CS electrogram. The signals were rectified and processed with a 1–25 Hz bandpass filter. The estimation of the power spectrum was computed using the algorithm of Welch over 8,192 points in order to obtain a frequency resolution of 0.24 Hz.[21] The outcome of this procedure is the removal of inconsistent variability and enhanced weight of peaks. This was repeated over a sliding 8-second window of 8,192 points every 1 second for the entire 32-second recordings for each electrogram. Longer recordings, compared to previous studies,[20] were utilized to facilitate the identification of less frequent high-frequency activity and confirm the temporal stability of permanent AF. The averaged power spectra of each electrogram over the entire recording interval was then averaged and normalized to their total power to correct for variation in the recorded signal amplitude. The frequency of the peak with the highest amplitude in each signal was then assigned to be that signal's DF and was used for comparison between sites, as previously described.[20] The frequency of activity attributed to each PV was the highest frequency of all 10 bipoles.

In addition to the DF of each electrogram, a measure of the regularity index (RI) was calculated as the power of the DF and its harmonics, estimated by computing the area over a fixed interval of 0.73 Hz under the DF and its harmonics. The ratio of this area to the total power was defined as the RI. To control for electrograms demonstrating poor signal-to-noise ratio that may be associated with ambiguous DF, only points demonstrating an RI > 0.2 were included in subsequent analysis, as previously described.[15] In addition, in the CS, the bipole with the highest RI was utilized for comparison.

AF cycle length

The effect of PV ablation on the AF process was determined utilizing the change in AF cycle length (AFCL) within the CS, and the termination of AF, as previously described.[12]

The AFCL within the CS was determined by averaging the interval of 30 consecutive cycles before and after ablation of each PV, using automated CL monitoring software (Bard Electrophysiology). Interelectrogram intervals of <100 msec and continuous electrical activity were counted as a single interval.[12] At each time point, the automated annotation was manually verified and corrected using online calipers at a paper speed of 100 mm/sec by a single investigator.

If AF terminated during ablation to flutter or sinus rhythm, the AFCL was determined prior to termination. To avoid transitional changes in cycle length, the AFCL was determined 10 cycles before termination. Termination of AF was defined as previously described, as direct transition to sinus rhythm or to flutter.[12] For the purpose of the study, AF was defined by the beat-to-beat variability in CL and morphology, while atrial flutter was defined as a rapid regular atrial rhythm with stable CL, morphology, and activation sequence.

Ablation of AF

All patients underwent PV electrical isolation as the first step of the ablation procedure. Following this, in patients with persistent or inducible sustained AF (>10 minutes), additional atrial ablation was performed targeting focal activity, areas of fractionated electrograms, or by linear ablation. In addition, all patients underwent cavotricuspid isthmus ablation.

PV electrical isolation

Electrical isolation of all PVs was performed as previously described.[22] In brief, isolation was performed individually without any attempt to identify potentially arrhythmogenic PVs at the time of the procedure. Ablation performed during AF, commencing 1 cm from the ostium of both right PVs and for the posterior and superior aspects of the left PVs. Isolation of the anterior aspect of the left PVs required energy to be delivered at the border of the vein to achieve catheter stability. RF energy was delivered for 30 seconds at each point, and this application was prolonged for 1–2 minutes when a change occurred in morphology or sequence of the PV potentials as determined by circumferential mapping. The procedural endpoint was either the complete elimination or dissociation of PV potentials. Radiofrequency energy was delivered with power limited to 25–35 W using irrigation rates of 5–20 mL/min (0.9% saline via Cool Flow; Biosense-Webster) to achieve the desired power delivery. Temperature was limited to 50°C.

Additional atrial ablation

Linear ablation of the cavotricuspid isthmus was performed in all patients with an endpoint of bidirectional conduction block. Left atrial substrate modification was undertaken using previously described techniques of linear ablation to join anatomical structures,[23,24] or ablation of fractionated electrograms.[25] The endpoint of linear ablation was the demonstration of complete linear block with continuous online double potentials with an activation detour that was confirmed by differential pacing techniques. Radiofrequency energy was delivered with power limited to 30–40 W using irrigation rates of 5–60 mL/min to achieve the desired power delivery. Temperature was limited to 50°C.

Statistical Analysis

Continuous variables are reported as mean ± standard deviation and assessed for normality utilizing the Shapiro–Wilk test. Data that were normally distributed were compared using the paired or unpaired Student's *t*-test. Data that were not normally distributed were compared using the Wilcoxon signed-rank or rank-sum test, for paired and unpaired data, respectively. Sequential data measurements were analyzed by repeated measures of analysis of variance followed by Newman–Keuls test for multiple comparison. Categorical variables are reported as number and percentage, and compared using the Fisher's exact test. Statistical significance was established at $P < 0.05$.

Results

Patient Characteristics

Patients had either paroxysmal AF (n = 20) or permanent AF of long duration (n = 14) and were undergoing AF ablation after having failed 3 ± 1 antiarrhythmic agents (including amiodarone in 12). Thirteen patients with paroxysmal AF had spontaneous arrhythmia for 15 ± 21 hours (median 8 hours, range 2–72 hours) prior to the procedure; in the remaining seven patients it was induced by burst pacing and persisted for >10 minutes prior to the commencement of mapping. Patients with permanent AF had documented arrhythmia for 23 ± 14 months (median 24 months, range 12–60 months) (Table 1).

Frequency of PV Activity

The PVs of patients with paroxysmal AF demonstrated a significantly higher frequency of activity (11.0 ± 3.1 Hz) compared to patients with permanent AF (8.8 ± 3.0 Hz; P = 0.0003) with each PV observed to have a higher frequency activity: left superior PV, 11.8 ± 3.0 Hz versus 9.5 ± 3.0 Hz (P = 0.04); right superior PV, 10.5 ± 3.5 Hz versus 8.5 ± 3.1 Hz (P = 0.09); left inferior PV, 10.5 ± 2.7 Hz versus 9.2 ± 3.2 Hz (P = 0.3); and right inferior PV, 11.1 ± 3.0 Hz versus 8.1 ± 2.8 Hz (P = 0.006; Figs. 1 and 2). A greater number of PVs per patient were found to have a frequency of activation ≥10 Hz in patients with paroxysmal AF (3.0 ± 1.3) compared to those with permanent AF (1.6 ± 1.5; P = 0.009).

PV to Left Atrial Gradient

The frequency of left atrial activation, as determined within the CS, was significantly lower in patients with paroxysmal AF (5.8 ± 1.2 Hz) compared to patients with permanent AF (6.9 ± 1.4 Hz; P = 0.01). This was also corroborated by a longer baseline AFCL in patients with paroxysmal AF (182 ± 17 msec; Fig. 1) compared to permanent AF (158 ± 21 msec; P = 0.002; Fig. 2). As a result of these differences in PV and left atrial activity, patients with paroxysmal AF demonstrated a greater frequency gradient between the PV and the left atrium (7.2 ± 2.2 Hz) than patients with permanent AF (4.2 ± 2.9 Hz; P = 0.006). All patients with paroxysmal AF demonstrated a gradient of PV to left atrial activation ≥3 Hz,

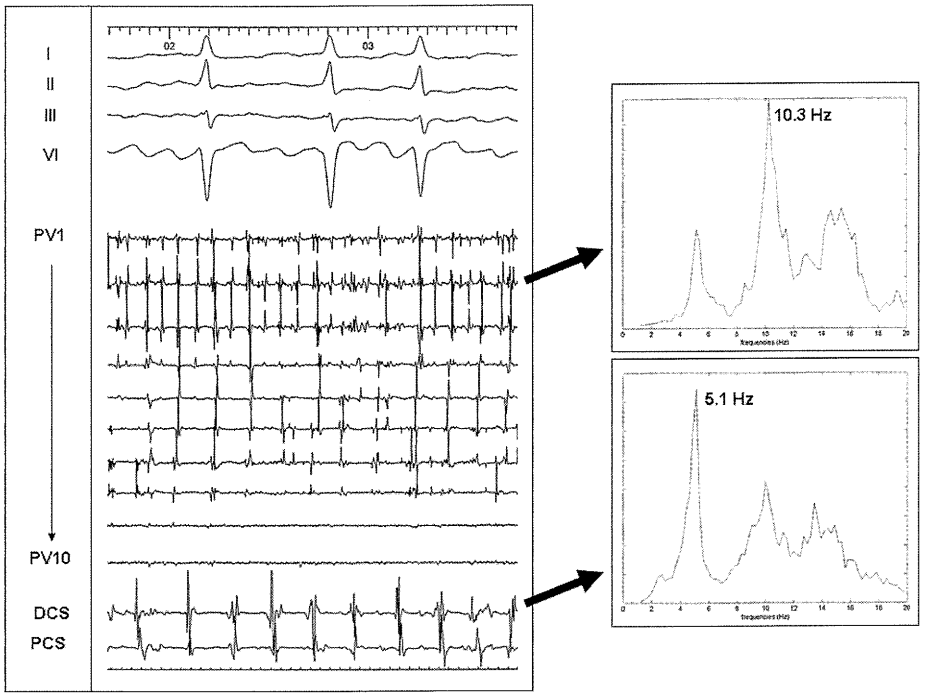

Figure 1. *PV and CS activities in a patient with paroxysmal AF. In this patient, the atrial activity in the CS demonstrates discrete activity with rapid activity observed within the PV. The frequency spectra of the highest frequency PV activity (bipole 2–3) are shown with a frequency of 10.3 Hz. In contrast, the frequency spectra of the CS demonstrate much slower activity (5.1 Hz).*

while 5 of 14 patients (36%) with permanent AF did not (P = 0.007).

Effect of PV Electrical Isolation

With ablation there was a progressive cumulative prolongation in the AFCL in patients with paroxysmal AF but not in patients with permanent AF. In paroxysmal AF, the AFCL increased from 182 ± 17 to 223 ± 41 msec (P < 0.0001; Figs. 3 and 4) and was associated with a significant decrease in the atrial frequency of activation from 5.8 ± 1.2 Hz to 4.9 ± 0.7 Hz (P = 0.0001; Fig. 5). In contrast, in patients with permanent AF, the AFCL (158 ± 21 to 164 ± 22 msec; P = ns; Figs. 3 and 4) and atrial frequency of activation (6.9 ± 1.4 to 6.8 ± 1.3 Hz; P = ns; Fig. 5) demonstrated no significant change with PV ablation. At each stage of the PV ablation, patients with paroxysmal AF had a longer AFCL than patients with permanent AF (P < 0.0001; Fig. 4): at baseline, 182 ± 17 msec versus 158 ± 21 msec (P < 0.01); after ablation of the first PV, 193 ± 20 msec versus 158 ± 21 msec (P < 0.01); after the second PV, 212 ± 36 msec versus 159 ± 22 msec (P < 0.01); after the third PV, 203 ± 18 msec versus 162 ± 22 msec (P < 0.01); and after the fourth PV, 233 ± 41 msec versus 164 ± 22 msec (P < 0.01). The total change in AFCL

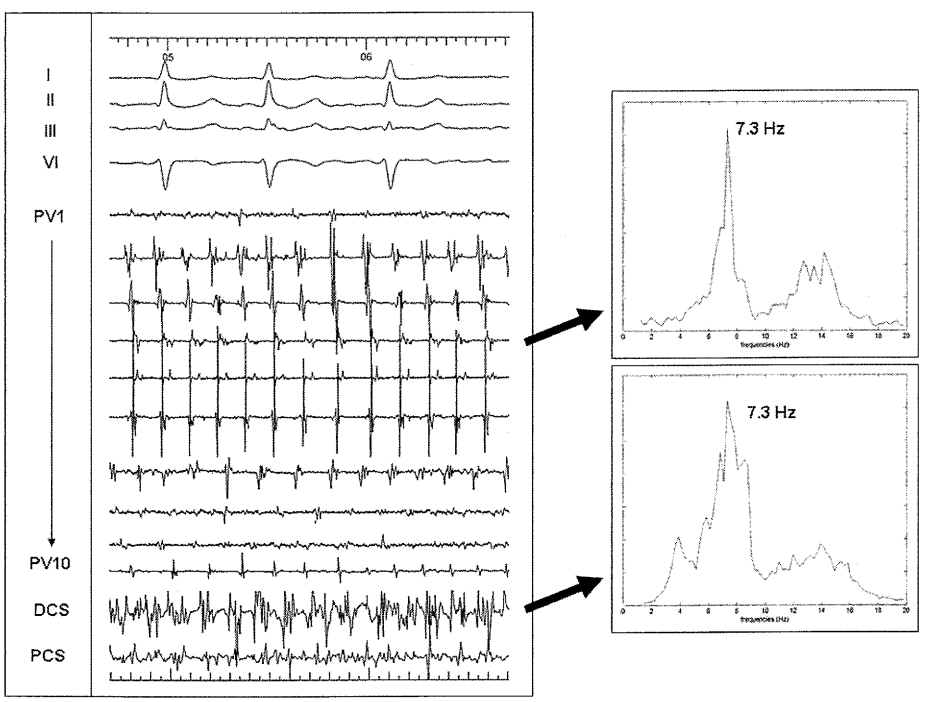

Figure 2. *PV and CS activities in a patient with permanent AF. In this patient, the atrial activity in the CS demonstrates rapid and almost continuous activity compared to the patient in Figure 1. This is reflected in the frequency spectra that demonstrate a higher frequency (7.3 Hz), which is also broader than that of the spectra seen in the patient with paroxysmal AF. In this example, the PV demonstrates a similar frequency of activation with no significant PV to atrial frequency gradient, suggesting that the continuous activity reflected in the CS is probably a result of local fractionation in addition to the rapid frequency of atrial activation.*

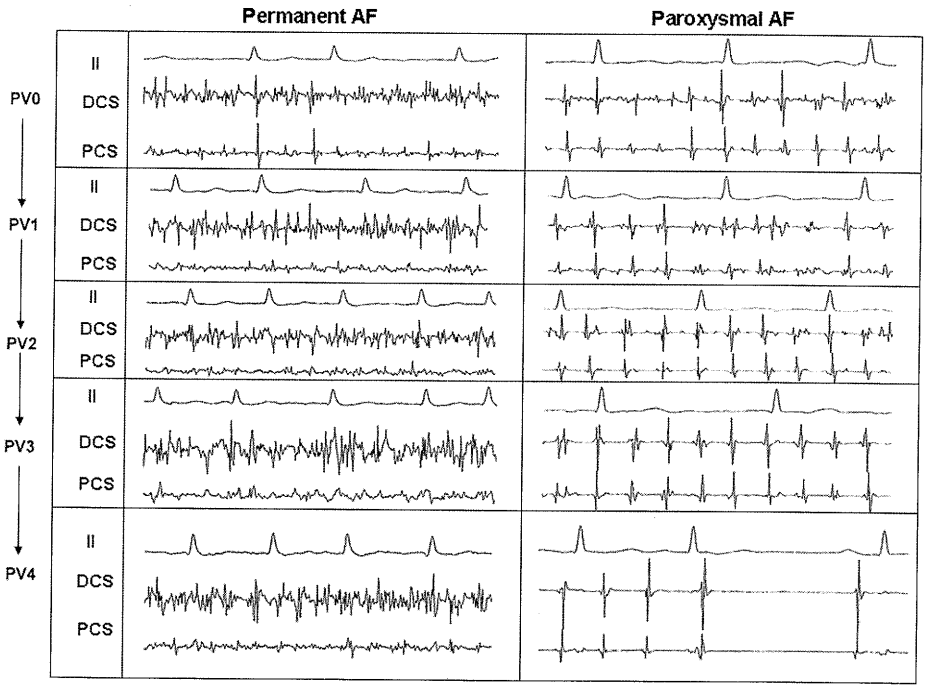

Figure 3. *Effect of ablation on the global fibrillatory process in a patient with permanent AF (left panel) and a patient with paroxysmal AF. Demonstrated are the electrograms in the CS at each stage of the PV ablation strategy. In the patient with paroxysmal AF, the baseline activity is comparatively slower and more organized. With ablation, there is a further prolongation of the AFCL and eventual termination of AF during ablation of the last PV. In contrast, in this patient with permanent AF, atrial activity in the CS is almost uncountable and continuous. PV isolation results in minimal change in the organization and the AFCL of the CS.*

with PV ablation was significantly greater in patients with paroxysmal AF (49 ± 35 msec; median 34 msec, range 12–136 msec) compared to permanent AF (5 ± 6 msec; median 5 msec, range −7 to 13 msec; $P < 0.0001$). Similarly, total change in the atrial frequency of activation with PV ablation was significantly greater in patients with paroxysmal AF (1.0 ± 0.7 Hz; median 0.7 Hz, range 0.2–3.7 Hz) compared to permanent AF (−0.05 ± 0.4 Hz; median 0 Hz, range −1.0 to 0.5 Hz; $P < 0.0001$).

The gradual prolongation of the AFCL and decrease in the atrial frequency of activation was associated with the termination of paroxysmal AF in 11 of 20 patients (55%), during the ablation of the PV. In contrast, termination of AF was not achieved in any patient with permanent AF by PV ablation ($P = 0.0007$).

Discussion

This study presents new information regarding the role of the PVs in the maintenance of paroxysmal AF compared to permanent AF in humans. First, paroxysmal AF is associated with a greater PV frequency of activity and a lesser atrial frequency compared to patients with permanent AF. Second, isolation of the PVs resulted in a significant slowing and termination of paroxysmal AF but with a lesser effect on the fibrillatory process in patients with permanent AF. Finally, the automated monitoring of the atrial frequency within the CS may be an effective mean of monitoring the effect of ablation at each site.

Thus, the present study suggests that high-frequency activity emanating from the PVs have a dominant role in the maintenance of paroxysmal AF. In permanent AF, while these structures have been observed to have a role in the initiation of AF, their independent contribution to the maintenance of permanent AF seems relatively limited.

PVs in the Maintenance of Paroxysmal AF

That localized sources of activity could maintain AF has been observed in several experimental studies.[13,26–30]

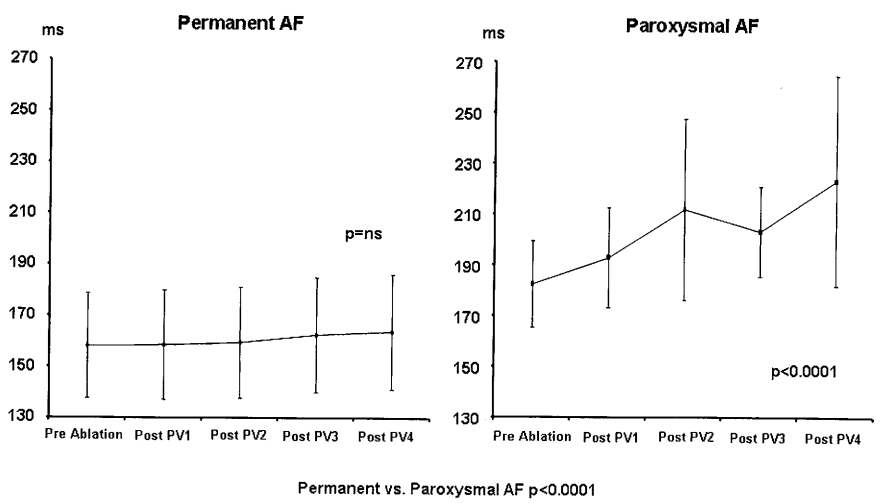

Figure 4. *Effect of PV isolation on the AF process determined by the AFCL in the CS. In patients with paroxysmal AF, there is a progressive prolongation of the AFCL, which culminates in the termination of AF. In contrast, there is a minimal change in the AFCL with PV isolation in patients with permanent AF.*

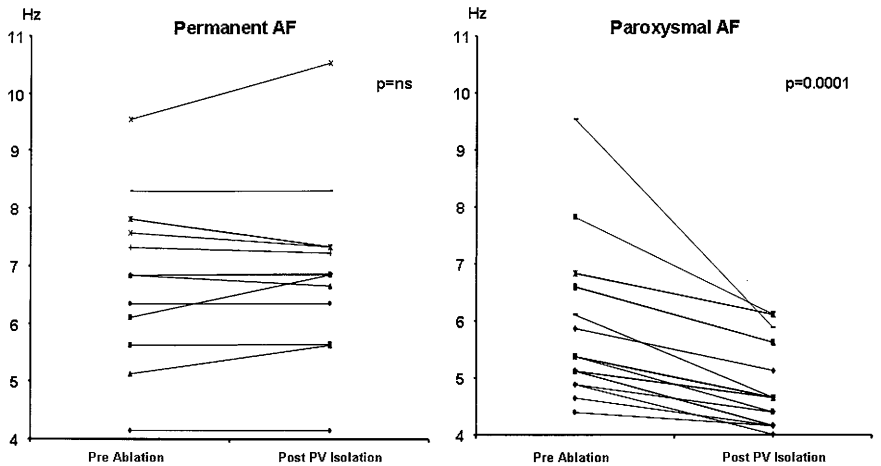

Figure 5. *Effect of PV isolation on the atrial frequency. In patients with paroxysmal AF, there is a significant decrease in the frequency of atrial activation. In contrast, there is no significant change in atrial activation with PV isolation in patients with permanent AF.*

Increasingly, it has been suggested that the PVs may be a site harboring sites of rapid activity. Jais et al. reported a small series of patients with irregular rapid focal discharges, persisting sometimes for hours, days, or even longer, driving sustained AF; this represents the true "focally driven AF."[8] These patients were cured of their arrhythmia by focal application of radiofrequency energy.

More recently, investigators have observed paroxysmal short cycle length activity within the PVs during AF and suggested that this may represent a repetitive contribution from the PV activity to maintain AF.[9-11] Such paroxysmal bursts of activity demonstrate a distal-to-proximal activation sequence, instead of proximal-to-distal activation that would be expected if activation originated from within the atrium. Others have observed a gradient of high-frequency activity from the PVs during ongoing paroxysmal AF and suggested that activity from these structures may maintain AF.[18,20] In addition, PV isolation performed during paroxysmal AF has been observed to produce progressive and cumulative slowing of the AF process[12]; this effect occurred with ablation of PVs harboring high-frequency sites, whereas ablation at sites without DF activity had no impact on the fibrillatory process.[20]

The present study confirms the above findings in patients with paroxysmal AF but demonstrates a significant difference in the contribution of the PVs to the maintenance of AF in permanent AF.

PVs in the Maintenance of Permanent AF

In persistent and permanent AF evidence implicating the PVs in the maintenance of AF has been varied. Sih et al. have demonstrated differences in the degree of organization in acute and chronic AF in a canine model.[31] Lazar et al. reported no difference in the left and right atrial frequencies of activation in patients with persistent AF.[18] Using sequential point-by-point mapping, we have observed a wide distribution of high-frequency sites in patients with permanent AF.[20] Similarly, Nitta et al. have observed multiple right and left atrial foci during permanent AF in patients with mitral valve disease.[32] In contrast, Wu et al. performed mapping in permanent AF at the time of surgery and observed activity emanating from the PV region with regularity to suggest that these structures may have a role in maintaining AF.[4] In addition, Sahadevan et al. performed epicardial mapping in patients with AF of 1 month to >15 years duration and observed regions of rapid regular activity that could have been drivers of AF located dominantly within the left atrium.[19]

In a previous study, we have demonstrated that the PVs in patients with permanent AF were less likely to harbor sites of high frequency.[20] However, this was based on sequential mapping, with 1–2 sampling points in each PV for a limited duration (5 seconds). It may be expected that in the atria remodeled by permanent AF that the temporal stability of activity and the local differences in frequency may require a greater density of mapping and longer recording intervals to identify a frequency gradient. Thus, in the current study, circumferential PV mapping together with longer analysis time (32 seconds) was utilized. Using the longer and higher density recordings, in the current study, we were able to confirm the temporal stability of activity within the PVs. Patients with permanent AF were observed to have a higher atrial frequency with a smaller PV to atrial frequency gradient compared to patients with paroxysmal AF. In addition, ablation of the PVs in these patients was not associated with a slowing or termination of the fibrillatory process. However, although the frequency gradient between the PV and atria was reduced in patients with permanent AF it persisted; probably reflecting the distinctive remodeling that occurs within the PV due to AF (with ERP as low as 80 msec).[33] Thus, the findings of the current study suggest that in patients with permanent AF, these structures do not have an independent role in the majority of patients. However, they may have a role in interaction with other regions of the atria that was not readily apparent, as recently suggested.[34]

Clinical Implications

These observations suggest that while many patients with paroxysmal AF may be cured by PV isolation alone, patients with permanent AF will require ablation at other sites in addition to PV isolation. Furthermore, while AFCL has been advanced as a means to monitor the effectiveness of ablation, such interval analysis is limited by the laborious counting of intervals, the frequent changes in activation fronts, and the appearance of electrogram fractionation. In this study, an automated power spectra aimed at providing a DF of activation was found to be a useful indicator to monitor the effect of ablation at each site.

Study Limitations

The mapping in this study was limited to the PVs and CS; consequently, no analysis could be performed of other

potential sites that may have contributed to the maintenance of AF. While the CS may be considered suboptimal in some patients due to its variable interconnection with the atria, it was selected as it is routinely used during AF ablation, is remote from the site of ablation (the PVs), and has the major advantage of being anatomically stable to allow reproducible serial measurements, as previously demonstrated.[12] Recent studies have suggested that this site provides the longest cycle length with least fragmentation, allowing the unambiguous measurement of atrial activity.[35] In addition, the temporal stability of frequency within the CS has been demonstrated.[20]

Although this study evaluated the acute effects of PV ablation on the fibrillatory process, it did not study the long-term effects of the PVs on AF recurrence, as the ablation strategy was individualized. Nevertheless, data exist to suggest that PV isolation alone may be less effective in patients with persistent or permanent AF.[36-39]

Conclusion

The PVs have a critical role in the maintenance of paroxysmal AF; however, this study provides evidence, arguing against a dominant independent role of this region in the maintenance of permanent AF.

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