Atrial Fibrillation Ablation Strategies for Paroxysmal Patients: randomized comparison between different techniques.

Running title: Catheter ablation for paroxysmal AF

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Abbreviations

CFAE: complex fragmented and/or rapid atrial electrograms
AF: atrial fibrillation
AT: atrial tachyarrhythmia
PVAI: pulmonary vein antrum isolation
RA: right atrium
CS: coronary sinus
LA: left atrium
AADs: antiarrhythmic drugs
E.F.: Ejection fraction
EP lab: Electrophysiology laboratory.
EP: Electrophysiologist
**ABSTRACT**

**Background:** Whether different ablation strategies affect paroxysmal AF long term freedom from AF/AT is unclear. We sought to compare the effect of 3 different ablation approaches on the long-term success in patients with paroxysmal AF.

**Methods and Results:** One hundred and three (103) consecutive patients with paroxysmal AF scheduled for ablation and presenting in the electrophysiology laboratory (EP lab) in AF were selected for this study. Patients were randomized to pulmonary vein antrum isolation (PVAI) (35 pts) versus bi-atrial ablation of the complex fractionated atrial electrograms (CFAEs) (34 pts) versus PVAI followed by CFAEs (34 pts). Patients were given event recorder(s) and followed up at 3, 6, 9, 12 and 15 months post ablation. There was no statistical significant difference between the groups in term of sex, age, AF duration, LA size and EF. At one year follow up, freedom from AF/AT was documented in 89% of patients in the PVAI group, 91% in the PVAI plus CFAEs group, and 23% in the CFAE group (p< 0.001) after a single procedure and with AADs.

**Conclusion:** No difference in terms of success rate was seen between PVAI alone and PVAI associated with defragmentation. CFAEs ablation alone had the smallest impact on AF recurrences at one-year follow-up. These results suggest that antral isolation is sufficient to treat most patients with paroxysmal AF.

**Key Words:** pulmonary vein antrum isolation, catheter ablation of atrial fibrillation, radiofrequency, paroxysmal atrial fibrillation, randomized study
INTRODUCTION

Catheter ablation has been shown to be a successful and effective therapy for the treatment of atrial fibrillation (AF) (1). Although the pulmonary veins (PVs) have been shown to play a major role in the initiation of AF, different ablation strategies, including isolation of the pulmonary veins and ablation of sites outside the pulmonary veins, have been proposed (2-7). However, the relative benefit and success of each approach alone and in combination has not been evaluated in randomized studies.

We sought to compare the effect of different ablation strategies on the AF termination mode and the long term success of patients with paroxysmal atrial fibrillation presenting to the electrophysiology laboratory (EP lab) in AF.

We compared pulmonary vein antrum isolation (PVAI) alone, ablation of complex fractionated atrial electrograms (CFAEs), and a hybrid strategy that combines PVAI followed by ablation of complex fractionated atrial electrograms.
METHODS

Study population

We enrolled 103 consecutive patients with paroxysmal AF presenting to the EP lab with spontaneous AF. The definition of paroxysmal AF followed the guidelines suggested by the ACC/AHA/ESC society.

Patients included in this study were enrolled for their first AF ablation by 6 different Institutions in the period between November 2004 and January 2007.

Patients were assigned a treatment based on the permuted block strategy. The treatments were balanced within a block size of 3, with the block randomly assigned to each center using a web-based centralized control program.

Patients underwent PVAI only (group I n= 35), ablation of CFAE only (group II n= 34), or a hybrid approach including PVAI plus CFAE (group III n= 34).

Patients were enrolled if: 1) they had a history for at least one year of paroxysmal AF, 2) they were refractory to at least 2 antiarrhythmic drugs (AADs) and 3) they presented to the EP lab in spontaneous AF.

Patients who underwent a prior ablation procedure for AF were excluded from this study.
Before enrolling patients, the EP physicians, performing ablations at the different institutions, assessed sample electrograms showing CFAE to ensure uniformity in CFAE definition and identification.

Patients were enrolled from: 1) Sutter Pacific Heart Centers, San Francisco, CA, USA (18 pts, 18%); 2) Catholic University, Rome, Italy; (22 pts, 21%); 3) Southlake Regional Health Center, Toronto, Canada; (21 pts, 20%); 4) Casa Sollievo Della Sofferenza, Foggia, Italy (20 pts, 19,5%); 5) Hospital Umberto I Mestre, Italy (20 pts, 19,5%) and 6) Stanford University, Palo Alto (USA) (2 pts, 2%).

All patients signed an informed written consent prior to the procedure.

The Institutional Ethical Committees approved the study.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Ablation procedure.

All patients discontinued AADs at least five half lives before ablation.

Amiodarone therapy was discontinued 6 months before the procedure.

PVAI: The PVAI has been described in detail elsewhere (8, 9). Briefly, we used a circular mapping catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA) and a 3.5 mm irrigated tip catheter (ThermoCool®) to ablate the antrum of the pulmonary veins (PVs) and to achieve abolition of all
electrograms. Intracardiac echocardiogram (ICE) was used to monitor the trans-septal puncture and to define the anatomy of the pulmonary veins. An esophageal probe was used to monitor the temperature in the esophagus during ablation.

Radiofrequency energy output was titrated to a maximum of 45 W while maintaining a catheter tip temperature of < 41°C. At each site energy was delivered for 20 seconds. The maximum power over the esophagus and within the coronary sinus (CS) was limited to 30 Watts and energy delivery was discontinued when the esophageal temperature probe reached 39°C.

A 3-dimensional geometry of the left atrium (LA) was reconstructed with the CARTO system (Biosense Webster, Diamond Bar, CA, USA) or the NavX system (St. Jude Medical, St Paul, MN, USA) (figure 1 A-D).

The procedural end point for this ablation strategy was the local elimination of all the pulmonary vein potentials along the antra or inside the veins (entry and exit block).

The antrum included the entire posterior wall and extended anteriorly to the right PVs along the left septum. Further ablation of the superior vena cava (SVC) along the right atrium/SVC junction was also performed if mapping revealed PV-like potentials around this region and when high output (30 mA) pacing did not capture the phrenic nerve (10).
During ablation, the categories of AF termination (secondary endpoint) considered have been: 1) conversion to SR, 2) organization into a regular atrial tachyarrhythmia (AT), with a similar cycle length in both the atria and CS, or 3) persistence of AF requiring cardioversion.

When AF organized into an AT, the latter arrhythmia was mapped and ablated.

**CFAEs only Group (Group II)**

CFAEs were defined as: (1) atrial electrograms with two deflections or more and/or with fractionated baseline complexes with continuous activity over 10 seconds recording time, (2) atrial electrograms with a cycle length ≤ 120 ms over a 10 seconds recording time. The ablation catheter was required to be in a stable position when recording these electrograms (3, 11).

All operators assessed sample of CFAEs electrograms to ensure uniformity in selecting ablation sites (Figure 2).

The left and right atria (including the CS) were mapped to identify areas with electrical fractionation. These areas were ablated with the open irrigation ablation catheter (same settings parameters as described above for the PVAI group) until the CFAEs were completely eliminated.

The CFAEs were first ablated in the left atrium, then CS and right atrium, respectively.
The procedural endpoint of this ablation strategy was complete elimination of the CFAEs potentials.

If atrial fibrillation terminated before elimination of all CFAEs, induction of AF was attempted with pacing on and off isoproterenol (up to 20 mcg/min).

The categories of AF termination considered have been described above (secondary endpoint).

If AF persisted after elimination of all CFAEs's sites, cardioversion was utilized to restore sinus rhythm.

**Hybrid approach (PVAI followed by Ablation of CFAE), (Group III).**

This ablation strategy was a combination of the two previously described approaches.

PVAI was followed by CFAEs ablation; therefore patients underwent antrum isolation of all pulmonary veins and subsequently the elimination of CFAEs in both atria.

The procedural endpoint for this strategy was the complete elimination of CFAEs areas and electrical isolation of all the PV antra defined by entrance and exit block. If AF terminated before CFAEs ablation or before all CFAEs were ablated, induction of AF was performed with pacing on and off isoproterenol (up to 20 mcg/min).

Modes of AF termination were the same as in Group I and II (secondary
If AF persisted after PVAI plus CFAE, cardioversion was utilized to restore sinus rhythm.

**Primary endpoint**

The primary endpoint of this study for all the ablation strategies was freedom from atrial fibrillation defined as no episodes of AF/AT with or without AADs that lasted more than one minute at the one year follow-up. Episodes that occurred during the first two months (blanking period) after the procedure were not considered as recurrences. AADs were discontinued in all patients 2 months after the ablation when no recurrences were present. In cases of recurrences, patients were given their previously ineffective AADs. Patients with arrhythmia recurrence six months beyond the first procedure and on AADs were offered a repeat ablation.

**Post ablation Management and Follow-Up**

All patients were discharged on warfarin with a target INR of 2 to 3 and on AADs previously ineffective, except for amiodarone. Warfarin was continued for a minimum of 6 months after the ablation procedure.

They were followed in the outpatient clinic at 3 months after the procedure.
and then every 3 months. Patients were also given an event recorder for 5 months. They were asked to record four times a week even if asymptomatic and anytime they experienced symptoms. A 48-hour Holter monitor was obtained at 3, 6, 9, 12 and 15 months post ablation.

**Statistical Analysis**

A permuted block randomization schedule with block size of 3 was generated using a random number generator. Each permuted block was assigned a number and each block was randomly assigned to a center.

Although Nadamanee et al (3) had reported high success with CFAEs, our initial experience did not agree with his published results. We expected a 50% success rate using a CFAEs-only approach and, based on published results from our experience, we expected an 80% success rate with a PVAI-only approach. Under these assumptions, using a 1-tailed alpha of 5% and 80% power, a total of 32 patients would be required.

All continuous data are presented as “Mean +/- SD” and were compared by student t-test or by ANOVA. Tukey-Kramer method for multiple comparisons was used to compare the efficacy of the three procedures.

The analysis used the intention-to-treat principle. Categorical variables comparison used \( \chi^2 \) analysis. A p value < 0.05 was considered statistically significant. (SPSS software version 11.0 Chicago, II, inc.).
RESULTS

Patients Characteristics

Baseline characteristics of the three groups are presented in table 1. No significant difference between groups in term of sex, age, AF duration, left atrium size and ejection fraction (EF) was present. Previously ineffective AADs are also reported in table 1.

Procedural Results

The procedural endpoint was achieved in all patients (100%) in each group.

The total fluoroscopy times of the groups were 65.6 ± 22.6 for group I, 59.9 ± 24.7 for group II and 76.8 ± 21.8 for group III. (P = 0.8).

The duration of radiofrequency applications were 54 ±11 min for group I, 48 ± 9 min for group II and 68 ± 14 min for group III ( P = 0.04).

The total number of patients with CFAEs ablated and the median number of RF applications necessary to abolish CFAEs at each right and left atrial sites are reported in table 2. (Figure 1)

Secondary endpoint: AF termination during ablation:

Organization into atrial tachyarrhythmia was 34% in group I, 16% in group II and 29% in group III (P=0.158) with a mean cycle length 236.8 ± 32.9 ms; conversion to sinus rhythm was seen in 60% (group I), 17% (group II), and 65% (group III) of patients respectively (p<0.001); persistence of AF
requiring cardioversion was observed in 6% of group I, 67% of group II and 6% of group III. (p < 0.001) (Table 3).

When AF organized into AT, an attempt to map and terminate the AT during ablation was performed each time. Conversion from an organized flutter/tachycardia to SR was observed in 7 patients in group I, 2 patients in group II and 6 patients in group III) (p = 0.2).

The majority of these ATs were located at the mitral valve level (16 patients), and in the posterior wall (11 patients) as demonstrated by mapping/entrainment around the PVs.

**Chronic follow-up/Primary endpoint**

The primary endpoint of the study is reported in table 4 and 5 as freedom from AF/AT after a single procedure with or without AADs at 1 year of follow up.

In group I and group III freedom from AF/AT after 6 months was observed in 94% of patients (14% requiring AADs), while in group II it was 59% (11% requiring AADs). (p< 0.001).

After one year follow up (13.7±2.2 months), in group I and group III freedom from AF/AT was seen in 89% (15% requiring AADs) and 91% (15% requiring AADs) of patients respectively, while in group II was achieved in 23% (11% requiring AADs) of patients (p< 0.001). (tables 4 and
The timing for a second procedure was at least 6 months after the first procedure.

All 7 patients, belonging to group I and III and with primary endpoint failure, accepted a second procedure after \(7.1 \pm 1.1\) months from the first procedure. Six out of the seven (86%) patients demonstrated no further AF/AT at \(9 \pm 7\) months follow up from the second procedure without any AADs.

Twenty two patients out of the 26 patients of group II failing the primary endpoint accepted a second procedure after \(7.3 \pm 1.1\) months. These procedures were performed using the PVAI-only approach. After a mean follow up of \(9 \pm 7\) months from the second procedure 20 patients (91%), were free from AF/AT without AADs.

**Complications**

No major complications have been observed in these groups of patients during and after the procedures.

**DISCUSSION**

**Main findings**: This is the first prospective multicenter randomized study comparing three ablation techniques in patients with paroxysmal AF.

CFAEs ablation alone had the smallest impact on both acute AF termination
and freedom from AF/AT at one year follow up.

The hybrid strategy, which combines isolation of the PV antra and ablation of CFAEs, was not associated with a better acute success rate (defined as conversion to sinus rhythm) or chronic success rate (defined as event freedom from AF or AT at 6-month and 1-year follow up), when compared to PVAI alone.

**Previous studies**

The pulmonary veins are known for their preponderant role in triggering and maintaining atrial fibrillation (2). Segmental ostial pulmonary vein isolation maintains sinus rhythm in approximately 2/3 of the patients with paroxysmal atrial fibrillation (12, 13). Additional lesions such as mitral isthmus ablation (5) or antrum isolation (14) have been reported to increase this success to approximately 90%. More recently, ablation targeting CFAEs has been shown to result in sinus rhythm maintenance in approximately 80% of patients with paroxysmal and persistent AF (3).

However, these results originated from a single center. To date, CFAEs ablation for paroxysmal AF has only been reported in another publication during the tailored approach described by Oral et al (15), but CFAEs ablation was never performed alone and was not performed in all patients.
Our results are different from the data published by Nadamanee et al (3) who reported a success rate of 82% at 1-year follow up, in paroxysmal patients who underwent CFAEs ablation alone (two of them with amiodarone) and 100% conversion to SR in paroxysmal patients including 8 patients (14%) who required concomitant ibutilide administration during ablation.

The results of this study also indicate that CFAEs ablation alone has a minimal impact on AF termination during ablation of patients with paroxysmal AF and should not be considered as an alternative strategy unless a better identification of critical CFAEs zones becomes widely available and proven effective. In this respect, although we believe that the technique utilized in this series of patients was really similar to the one described by Nadamanee (3), it is possible that a difference exists in the technique and extent of ablation used in our study.

**General comments**

Of note, after a short follow-up (≤ 6 months), CFAEs ablation alone appeared to lead to an improvement in a significant number of patients; however, most of this effect was lost by 12 months (tables 4 and 5).

This suggests that a longer follow up is required to assess the real impact on AF recurrences following any ablation procedures.

The presence of sites other than the PVs which are able to initiate and
maintain AF is probably responsible for the inability to treat all patients with PV isolation alone and has prompted the utilization of different strategies adjunctive to PV isolation.

These strategies include: creation of various ablation lines such as the mitral isthmus (5), roof line (4), posterior LA wall lines (16), antrum isolation (14) and cardiac autonomic denervation (6, 7).

Our results demonstrate a reduced efficacy of the CFAE ablation alone when compared to PVAI alone and PVAI plus CFAE in the treatment of the paroxysmal AF. In fact, the success rate of the PVAI approached 90% at 13.7±2.2 months of follow up with a single procedure with AADs, while the success rate of CFAE ablation alone was 23%.

In our study, all patients had paroxysmal AF, which was present for at least one year prior to ablation.

The lack of differences between PVAI and PVAI plus CFAEs, and the small impact on success rate reached by CFAEs alone suggest that electrical isolation of the PVs remains a cornerstone for catheter ablation of paroxysmal AF.

Our results are consistent with the revised strategy reported by Morady et al in a recent viewpoint (17). The authors state that they do not limit the ablation to the arrhythmogenic veins as in their previous tailored approach
(15), but they perform an antral ablation of all the pulmonary veins.

CFAEs ablation did not have a statistically significant additive effect when combined with PVAI on AF termination mode (CFAE terminated AF during ablation in 17% of cases, PVAI in 60%, and the combination of both in 65% of cases).

This suggests that extra-antral CFAEs areas may be less relevant in maintaining AF and that isolation of the antrum is necessary in nearly all cases of paroxysmal atrial fibrillation to achieve long term success.

Of note, it is important to recognize that isolation of the antrum eliminates many areas associated with fragmented electrograms. However, the poor chronic success obtained with defragmentation alone reinforces the importance of PVs isolation.

In agreement with our results, Morady et al (17) found that many of CFAEs, which appeared critical for the maintenance of the AF, were in the antral region, suggesting that CFAEs present in other areas (coronary sinus, left atrial roof, and mitral annulus) should be considered as “innocent bystanders” at least in the paroxysmal AF patients.

Based on our findings, additional sites of ablation should be reserved for selected patients, and probably should not be driven by empirical targeting of fragmented electrograms but by mapping triggers disclosed with
administration of isoproterenol and/or adenosine.

Several other groups have shown that ablation strategies encompassing the areas equivalent to the antrum achieve similar results and are better than more limited approaches (18-20).

**Study limitations:**

Methods to identify CFAEs, although similar to the ones described by Nademanee, (3) may be operator-dependent because they are based on visual evaluation.

Software analysis tools to identify CFAEs were not used in our study. However Scherr et al (21) demonstrated a high correlation between software and visual identification of the CFAEs areas. In addition, the initial description of defragmentation relied on visual identification of fragmented electrograms.

Using a fixed block size of 3, it is possible to determine the assignment of the third patient in the block before randomization. However, in a study such as this, the operators cannot be blinded to the procedural endpoints, since they had to know the type of procedure to perform. In addition, the physicians performing the procedures were not involved in patient’s recruitment and the outcome at follow-up was based on the objective documentation of freedom from AF/AT.
Finally the study was underpowered to detect a difference between PVAI alone vs CFAEs plus PVAI; taking into account the adjustment for multiple comparisons with a Family Wise Error Rate (FWER) <= 0.05, the sample size required to provide 80% power to detect a difference of 5% (comparing 85% to 90%) between any two groups is 353 patients per group. While acknowledging the statistical limitations, we deem that the data presented in this study would serve as an important reference point for future studies comparing the efficacy of PVAI+CFAEs procedures.

CONCLUSIONS

Ablation of the CFAEs alone had the smallest impact on both acute AF termination and 1-year follow up success rate in patients with paroxysmal AF. No difference in terms of acute and chronic success rates was observed between PVAI alone and PVAI associated with defragmentation (CFAEs) ablation. These results suggest that antral isolation and/or equivalent strategies are sufficient to treat most patients with paroxysmal AF.

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Author Disclosures

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Dr. D.J. Burkhardt reports serving as Consultant/Advisory Board to Stereataxis

All other authors have nothing to declare
REFERENCES


<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>PVAI only (n=35)</th>
<th>CFAE only (n=34)</th>
<th>PVAI + CFAE (n=34)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>57 ± 8.1</td>
<td>59.9 ± 8.6</td>
<td>58.4 ± 7.5</td>
<td>P = 0.43</td>
</tr>
<tr>
<td>Male (%)</td>
<td>83</td>
<td>76</td>
<td>88</td>
<td>P = 0.44</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>34</td>
<td>38</td>
<td>35</td>
<td>P = 0.51</td>
</tr>
<tr>
<td>AF duration (years)</td>
<td>5.3 ± 5.7</td>
<td>5.1 ± 4.1</td>
<td>5.3 ± 5</td>
<td>P = 0.61</td>
</tr>
<tr>
<td>LA size (cm)</td>
<td>4.3 ± 0.6</td>
<td>4.1 ± 0.5</td>
<td>4.4 ± 0.6</td>
<td>P = 0.38</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55 ± 8</td>
<td>55.5 ± 6</td>
<td>54.6 ± 6</td>
<td>P = 0.89</td>
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<tr>
<td>Previously ineffective AA drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>2 (0.5 %)</td>
<td>2 (0.5%)</td>
<td>2 (0.5%)</td>
<td>P = 1.0</td>
</tr>
<tr>
<td>Sotalol</td>
<td>14 (40%)</td>
<td>14 (41%)</td>
<td>13 (38%)</td>
<td>P = 0.9</td>
</tr>
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<td>≥ 1 class I AA drugs</td>
<td>21 (60%)</td>
<td>20 (58%)</td>
<td>21 (61%)</td>
<td>P = 0.9</td>
</tr>
</tbody>
</table>

Table 1. Baseline Characteristics and previous ineffective AADs.
Table 2: Table 2: Total number of patients with CFAEs and median number of RF applications necessary to abolish CFAEs at each right and left atrial sites.

<table>
<thead>
<tr>
<th>CFAE Sites</th>
<th>GROUP II (CFAEs only)</th>
<th>GROUP III (PVAI plus CFAEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LA (11)</td>
<td>LA (8)</td>
</tr>
<tr>
<td>Anterior Wall</td>
<td>33/11</td>
<td>28/8</td>
</tr>
<tr>
<td>Posterior Wall</td>
<td>34/14</td>
<td>21/7</td>
</tr>
<tr>
<td>Mitral Isthmus</td>
<td>9/6</td>
<td>8/5</td>
</tr>
<tr>
<td>Posterior Annulus</td>
<td>10/7</td>
<td>5/6</td>
</tr>
<tr>
<td>Appendage</td>
<td>8/6</td>
<td>9/5</td>
</tr>
<tr>
<td>Roof</td>
<td>34/12</td>
<td>20/11</td>
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<tr>
<td>Septum</td>
<td>32/9</td>
<td>24/7</td>
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<tr>
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<td>22/11</td>
<td>18/10</td>
</tr>
<tr>
<td>Crista Terminalis</td>
<td>/</td>
<td>27/19</td>
</tr>
<tr>
<td>Cavo tricuspid isthums</td>
<td>/</td>
<td>2/7</td>
</tr>
<tr>
<td>Superior Vena Cava</td>
<td>/</td>
<td>11/3</td>
</tr>
</tbody>
</table>

LA = left atrium; RA = right atrium. Note that right coronary sinus refers to the ostium of the coronary sinus.

Table 3: AF termination mode during ablation

<table>
<thead>
<tr>
<th></th>
<th>PVAI only N=35</th>
<th>CFAE only N=34</th>
<th>PVAI + CFAE N=34</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR</td>
<td>21 (60%)</td>
<td>6 (17%)</td>
<td>22 (65%)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>AT</td>
<td>12 (34%)</td>
<td>5 (16%)</td>
<td>10 (29%)</td>
<td>P = 0.158</td>
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<tr>
<td>No AF Termination</td>
<td>2 (6%)</td>
<td>23 (67%)</td>
<td>2 (6%)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>PVAI only N=35</td>
<td>CFAE only N=34</td>
<td>PVAI + CFAE N=34</td>
<td>P value</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>------------------</td>
<td>---------</td>
</tr>
<tr>
<td>*Freedom from AF/AT after 6 months</td>
<td>33 pts (94%)</td>
<td>20 pts (59%)</td>
<td>32 pts (94%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Freedom from AF/AT after one year</td>
<td>31 pts (89%)</td>
<td>8 pts (23%)</td>
<td>31 pts (91%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freedom from AF/AT after one year</td>
<td>26 pts (74%)</td>
<td>4 pts (12%)</td>
<td>26 pts (76%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>follow up without AADs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Freedom from AF/AT at 6-months and 1-year follow up (13.7±2.2 months).

* With or without AADs
A) Freedom from AF/AT after 6 months follow-up:

<table>
<thead>
<tr>
<th>Compare Procedure</th>
<th>Difference between two compared proportions</th>
<th>Standard Error (SEs)</th>
<th>The “q” statistic</th>
<th>Critical q values for α = 0.05</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 vs 2</td>
<td>24.86</td>
<td>4.84</td>
<td>5.14</td>
<td>3.314</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>1 vs 3</td>
<td>0.22</td>
<td>4.84</td>
<td>0.05</td>
<td>3.314</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>3 vs 2</td>
<td>24.64</td>
<td>4.88</td>
<td>5.05</td>
<td>3.314</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

B) Freedom from AF/AT after one year follow-up

<table>
<thead>
<tr>
<th>Compare Procedure</th>
<th>Difference between two compared proportions</th>
<th>Standard Error (SEs)</th>
<th>The “q” statistic</th>
<th>Critical q values for α = 0.05</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 vs 2</td>
<td>42.1</td>
<td>4.88</td>
<td>8.63</td>
<td>3.314</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>3 vs 1</td>
<td>2.29</td>
<td>4.84</td>
<td>0.47</td>
<td>3.314</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>1 vs 2</td>
<td>39.82</td>
<td>4.84</td>
<td>8.23</td>
<td>3.314</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

C) Freedom from AF/AT after one year follow up without AADs

<table>
<thead>
<tr>
<th>Compare Procedure</th>
<th>Difference between two compared proportions</th>
<th>Standard Error (SEs)</th>
<th>The “q” statistic</th>
<th>Critical q values for α = 0.05</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 vs 2</td>
<td>39.51</td>
<td>4.88</td>
<td>8.1</td>
<td>3.314</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>3 vs 1</td>
<td>1.39</td>
<td>4.84</td>
<td>0.29</td>
<td>3.314</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>1 vs 2</td>
<td>38.12</td>
<td>4.84</td>
<td>7.88</td>
<td>3.314</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Table 5: The Tukey-Kramer method for multiple comparisons was used to compare the efficacy of the three procedures: PVAI only (procedure 1), CFAE only (procedure 2), and PVAI + CFAE (procedure 3).
FIGURE LEGENDS

**Figure 1**: Tridimensional map of the left atrium in the PA and AP views (Figures A, Fig B) and of the right atrium and CS in PA and AP views (Figures C and D) using Navx mapping system. The yellow dots indicate areas where CFAEs have been ablated in a patient belonging to the PVAI plus CFAEs group. Blue dots indicate lesions around the pulmonary vein antrum.

**Figure 2**: Example of CFAEs (Complex fractionated atrial electrograms) on the ablation catheter proxysmal (abl 3-4) and distal (abl 1-2) that were targeted during the hybrid strategy. V1= precordial lead. CS 1-2= Coronary sinus distal lead.
Figure 2
Atrial Fibrillation Ablation Strategies for Paroxysmal Patients: randomized comparison between different techniques.

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