Efficacy and Risk of Atrial Fibrillation Ablation Before
45 Years of Age

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Background—Young patients with atrial fibrillation (AF) tend to be more symptomatic and less willing to take long-term medications, yet catheter ablation remains recommended as second-line therapy for AF regardless of age. This study seeks to characterize the effectiveness and risk of AF ablation in the young.

Methods and Results—Consecutive (n=1548) patients who underwent 2038 AF ablation procedures were included. Major procedural complications and efficacy were analyzed on the basis of age at the initial procedure: <45 years (group 1), 45 to 54 years (group 2), 55 to 64 years (group 3), and ≥65 years (group 4). AF control was defined as no or rare AF on or off antiarrhythmic drugs. The primary outcome of AF control was similar in all groups; it was achieved in 87% in group 1, 88% in group 2, 88% in group 3, and 82% in group 4 (P=0.06). However, more group 1 patients demonstrated freedom from AF off antiarrhythmic drugs (76%) compared with group 2 at 68%, group 3 at 65%, and group 4 at 53% (P<0.001). There were no major complications in group 1, 10 (1.7%) in group 2, 14 (1.4%) in group 3, and 10 (2.6%) in group 4 (P=0.01).

Conclusions—In patients younger than 45 years, there is a lower major complication rate and a comparable efficacy rate, with a greater chance of being AF free without antiarrhythmic drugs. These findings suggest that it may be appropriate to consider ablative therapy as first-line therapy in this age group. (Circ Arrhythm Electrophysiol. 2010;3:452-457.)

Key Words: catheter ablation ■ ablation ■ tachycardia ■ arrhythmia ■ complications

The 2006 American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) Atrial Fibrillation (AF) Guidelines indicate that ablation is a second-line therapy for all categories of patients.1 The 2007 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society (HRS/EHRA/ECAS) Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation stated that catheter ablation may be appropriate as first-line therapy only in rare clinical situations.2

Although AF is more common with increasing age,3,4 clinical experience has suggested that younger patients tend to be more symptomatic and less willing to take long-term medications. We have previously reported that in patients undergoing AF ablation ages 75 years and older, there appeared to be no significant increase in risk from the ablation procedure but a greater likelihood to remain on antiarrhythmic drugs.5 Limited data have been reported on the efficacy and risks of catheter ablation of AF in the young patient. We sought to gain a better understanding of the outcomes and complications of the procedure in the young patient with AF.

Methods

Patient Population

We studied 1548 consecutive patients with drug-refractory AF undergoing 2038 AF ablation procedures between November 2000 and September 2008. All patients were referred to the University of Pennsylvania Health System for catheter ablation of AF and signed a written informed consent according to the institutional guidelines of the University of Pennsylvania Health System. Demographic and clinical information was obtained and included age, sex, and presence of comorbid conditions such as hypertension, coronary artery disease, diabetes, structural heart disease, sleep apnea, and history of stroke or transient ischemic...
attack. AF was defined in accordance with published guidelines: paroxysmal if AF episodes were self-terminating in <7 days, persistent if typical AF episodes lasted ≥7 days and/or required intervention for termination, and permanent AF if it continued uninterrupted for >1 year.1

Ablation Procedure
All patients underwent proximal ostial/antral pulmonary vein (PV) isolation guided by intracardiac echocardiogram and circular multipolar electrode catheter recording. The procedural end point was isolation of PVs (arrhythmogenic and/or otherwise) and elimination of all provokable non-PV triggers of AF. An intracardiac echocardiogram (AcusonTM, Acuson Inc, Mountain View, Calif) was used to guide transeptal puncture as well as catheter placement. Maneuvers to elicit PV and non-PV triggers of AF performed before and after PV isolation included (1) cardioversion of spontaneous AF to identify triggers associated with the early recurrence of AF; (2) infusion of up to 20 µg/min isoproterenol in incremental doses of 3, 6, 12, and 20 µg/min; and (3) cardioversion of AF induced with rapid burst atrial pacing AF, during low dose isoproterenol infusion at 2 to 3 µg/min. All 4 PVs were routinely isolated with successful PV isolation defined as loss of PV potentials (entrance block) and failure to capture the left atrium (LA) when pacing each electrode pair (10 mA at 2-ma pulse width) of the 10 pair circular mapping catheter (exit block) placed at the ostium of the PVs just distal to the RF ablation lesions. PVs were revisited with the circular mapping catheter 20 to 60 minutes after initial isolation to reassess for entrance/exit block and veins were reisolated if acutely reconnected. Patients with a clinical history of typical right atrial flutter during the ablation procedure also underwent cavotricuspid isthmus ablation. No LA linear ablation lesions were performed unless there was evidence of macroreentrant LA flutter. The ablation end point was both persistent PV isolation and no AF with the repeat incremental infusion of up to 20 µg/min of isoproterenol. Patients undergoing repeat procedures had all 4 PVs reisolated and underwent the same ablation protocol with respect to provocation of non-PV triggers and end points for ablation as described for the original ablation procedure. Patients with identified macroreentrant atrial tachycardias had the circuit defined using activation and/or entrainment mapping to guide appropriate ablation strategy.

Anticoagulation Management
Heparin anticoagulation was used during the procedure to maintain an activated clotting time >250 seconds until 2004 and >350 seconds after that date because of the recognized risk of spontaneous soft thrombus on sheaths/catheters. All patients were started on warfarin anticoagulation after the procedure, and heparin was restarted and continued for at least 24 hours after the procedure. The patients were routinely discharged once the international normalized ratio was ≥1.8.

Routine Follow-Up
All patients had a standard transthoracic echocardiogram the day after the procedure in sinus rhythm to assess LA diameter and left ventricular ejection fraction (LVEF). Patients were routinely treated with previously ineffective antiarrhythmic medications (usually a class 1C agent or sotalol) before discharge. The patients were evaluated as outpatients at 6 to 12 weeks, 6 months, and 1 year, at which time they were queried for symptoms, a 12-lead ECG was obtained, and an echocardiogram was performed (first 2 visits). Antiarrhythmic medications were typically discontinued at 6 to 12 weeks if patients had paroxysmal AF and at 6 months if they had persistent AF but were continued beyond this point in selected patients, based on physician and/or patient preference even in the absence of an arrhythmia event. The patients were provided with a transtelephonic monitor and instructed to transmit 2 times daily and with symptoms during several time periods: (1) at 6 to 12 weeks; (2) at 6 months; and (3) at 1 year. Patients also made additional transtelephonic monitor transmission if they had any arrhythmia symptoms at any time during follow-up and/or when antiarrhythmic drugs (AADs) were discontinued. Beyond the 1-year period, patients were encouraged to see us every 6 months, failing which, our research personnel continued to follow them with telephone calls every 6 months. Source documentation of arrhythmia recurrence was sought. However, arrhythmia recurrence was assumed on the basis of recurrence of any symptoms and or asymptomatic ECG showing atrial fibrillation/flutter. A computerized tomography angiogram or MRI was routinely obtained at 3 months after the procedure to assess for PV stenosis and obtained on the basis of clinical symptoms and physician discretion.

Procedure Outcome
The first 8 weeks after ablation were censored from follow-up for judging procedure efficacy. Procedural success was defined as AF control, based on patient status ≥1 year after the last ablation procedure (≤300 days after the blanking period) and categorized as (1) no AF episodes off antiarrhythmic therapy; (2) no AF episodes on any antiarrhythmic drug; or (3) rare AF. The latter category was included to highlight good long-term clinical outcome in a small group of patients who have a rare episode of AF. We defined this rare AF as ≤6 AF episodes over the follow-up year that terminated either spontaneously and/or with a single cardioversion and/or a ≥95% reduction in AF burden when monitoring was compared before and after ablation.

Long-Term Anticoagulation
The decision to discontinue warfarin was left up to the individual electrophysiologist performing the procedure in consultation with the patient’s referring physician. As a general guideline, warfarin was stopped with (1) LA size ≤4.5 cm on transthoracic echocardiography; (2) no history of stroke or transient ischemic attack; (3) presence of ≤2 stroke risk factors (hypertension, diabetes mellitus, age ≥75 years, LV dysfunction); and (4) the absence of symptomatic and asymptomatic AF during at least 1 30-day transtelephonic monitoring period ≥6 months after the last ablation procedure. For patients who demonstrated AF control but did not fit into these guidelines, continuing warfarin was recommended. Additional 30-day transtelephonic monitoring and demonstrated absence of irregularity of pulse when assessed twice daily on an ongoing basis but for at least 2 months was also strongly encouraged before warfarin was stopped in patients deemed at higher risk.

Complications
Complications were grouped on the basis of seriousness and/or permanence of the event. Major complications were defined as a stroke or transient ischemic attack, significant PV stenosis (≥70%), pericardial effusion resulting in tamponade and/or requiring pericardiocentesis, atrioesophageal fistula, phrenic nerve injury, retroperitoneal bleeding, or severe anaphylaxis. Other complications included large hematomas (>10 cm or requiring transfusion), femoral arteriovenous fistula or pseudoaneurysm, asymptomatic PV stenosis (≥70%), fluid overload prolonging hospitalization, superficial x-ray–induced skin change, and deep venous thrombosis.

Statistical Analysis
The patients were divided into 4 groups on the basis of age at the time of first procedure: group 1, <45 years; group 2, 45 to 54 years; group 3, 55 to 64 years; and group 4, ≥65 years. Results are expressed as mean±2 SD. Success rates, complication rates, and aspects of clinical history (sex, presentation, presence of structural heart disease, number with LVEF <50%) were compared using a 4×2 contingency table and a χ² analysis for linear trend. CHADS risk was analyzed using the Kruskal-Wallis nonparametric comparison. LVEF, LA size, and follow-up duration were compared among the groups, using ANOVA for linear
Comparison of clinical characteristics were performed at the patient level rather than per procedure. Procedure of temporal was performed at the procedural level. For the primary outcome of AF, control off of AADs, a multivariate logistic regression model was used following univariate regression of covariates and analysis for clinically relevant interactions using SPSS 17.0.1 software (SPSS Inc., 2008). The regression was performed on the basis of characteristics from the index procedure only. A probability value ≤0.05 was considered significant.

### Results

Between November 2000 and September 2008, 1548 consecutive patients with drug-refractory AF underwent 2038 AF ablation procedures (Table 1). The mean age of all patients was 55.6 ± 22 years, with 1188 (69.7%) male. One thousand procedures (69.7%) male. One thousand/H11006 was 55.6

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Age &lt; 45 y</th>
<th>Group 2 Age 45 to 54 y</th>
<th>Group 3 Age 55 to 64 y</th>
<th>Group 4 Age ≥65 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>179 (77%)</td>
<td>372 (85%)</td>
<td>439 (77%)</td>
<td>199 (65%)</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation, n (%)</td>
<td>165 (71%)</td>
<td>271 (62%)</td>
<td>374 (66%)</td>
<td>193 (63%)</td>
</tr>
<tr>
<td>LVEF, %, SD</td>
<td>58 ± 10</td>
<td>58 ± 9</td>
<td>58 ± 10</td>
<td>60 ± 10</td>
</tr>
<tr>
<td>LA size, cm, SD</td>
<td>4.2 ± 0.7</td>
<td>4.4 ± 0.7</td>
<td>4.4 ± 0.7</td>
<td>4.5 ± 0.8</td>
</tr>
<tr>
<td>CHADS2 score, median (IQR)</td>
<td>0 (0, 1)</td>
<td>1 (0, 1)</td>
<td>1 (0, 1)</td>
<td>1 (0, 2)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>7 (3.0%)</td>
<td>25 (5.7%)</td>
<td>60 (11%)</td>
<td>22 (7.1%)</td>
</tr>
</tbody>
</table>
| Diabetes, n (%) | 454 Circ Arrhythm Electrophysiol October 2010

Clinical Outcomes

Outcome is described for all patients who have completed the minimum 1-year follow-up after the last ablation (more than 300 days after the blanking period). Figure 1 demonstrates that AF control was comparable in all groups, with no significant difference for the duration of the follow-up. In an unadjusted analysis, AF control in group 1 was 87%; group 2, 88%; group 3, 88%; and group 4, 82% (P = 0.06). Those with rare AF accounted for 4% of group 1, 9% of group 2, 6% of group 3, and 6% of group 4. Of those with rare AF, the median number of episodes was 2 (interquartile range, 1 to 2). To achieve this level of AF control, the proportion of patients with repeat procedures was 25% in group 1, 21% in group 2, 30% in group 3, and 19% in group 4 (P < 0.01).

The proportion of patients who were free from AF off of AADs was higher in the younger patients. Over the follow-up period, 76% of patients in group 1 were free from AF off of antiarrhythmic medications compared with 68% in group 2, 65% in group 3, and 53% in group 4 (P < 0.001). Some of the patients on antiarrhythmic medications were stopped at 6 weeks and restarted due to clinical recurrence of AF, whereas others were not stopped at 6 weeks, as recommended by study protocol. Those who were not stopped at 6 weeks accounted for 87% of group 4, 88% of group 3, 88% of group 2, and 82% of group 1. The stroke risk score in younger patients. Procedural length using pulsed fluoroscopy time as a surrogate was shorter in group 1 patients, at 89 ± 36 minutes, compared with group 2, at 91 ± 36 minutes, group 3 at 90 ± 36 minutes, and the longest in group 4 at 97 ± 39 minutes (P < 0.001).

Figure 1. Control of AF after AF ablation on the basis of age with and without adjuvant drug therapy. Mean follow-up in months is noted. Control of AF with or without AADs was similar in all groups (P = 0.06). However, the absence of AF without AAD use was higher in young patients compared with the other groups (P < 0.001).
for 6% of patients in group 1, 12% of group 2, 12% of group 3, and 16% of group 4. The main documented reason for failure to stop an AAD was physician preference, followed by patient preference.

In a univariate analysis, age was not a predictor of recurrence of AF, with an odds ratio (OR) of 1.04 (95% confidence interval [CI], 0.94 to 1.15; \( P = 0.51 \)) for every 10-year increase in age. There was no significant interaction between age and sex, age and type of AF, diabetes and hypertension, or LA enlargement and LV function. In a multivariate model, only the type of AF was a significant predictor of AF recurrence with persistent AF having an OR of 1.64 (95% CI, 1.27 to 2.12; \( P < 0.001 \)) compared with paroxysmal AF. The presence of LA enlargement (OR, 1.29; 95% CI, 0.98 to 1.69; \( P = 0.07 \)) and diabetes (OR, 1.55; 95% CI, 0.95 to 2.53; \( P = 0.08 \)) approached significance after controlling for all other factors.

Complications

Of a total of 2038 procedures, there were 35 major complications (1.7%) and 52 (2.6%) other complications. Table 2 lists the complications by age group. Of 309 procedures performed on group 1 patients, there were no major complications. This complication rate was statistically less than the major complications in the other groups: 10 major complications during 583 procedures in group 2 (1.7%), 15 major complications during 768 procedures in group 3 (2.0%), and 10 major complications during 378 procedures in group 4 (2.6%) (\( P = 0.01 \)) (Figure 2). The most common major complication among all groups was pericardial effusion or tamponade requiring drainage, which occurred 17 times (0.8%), followed by stroke or transient ischemic attack, which occurred 9 times (0.4%). Three patients had phrenic nerve injury during ablation, but all 3 recovered diaphragmatic motion after the procedure. Nine patients had PV stenosis (0.4%), but only 2 were symptomatic and required intervention with PV stenting. There was 1 death associated with an atrioesophageal fistula in a group 2 patient (0.05%).

With respect to nonmajor complications, group 1 patients once again had the lowest rate, with 2 (0.6%) compared with group 2 with 13 (2.3%), group 3 with 22 (2.9%), and group 4 with 15 (4.5%). The majority of these complications in the entire series were vascular with 13 pseudoaneurysms (0.6%), 15 arteriovenous fistulas (0.7%), and 11 large groin hematomas (0.5%). In group 1, the only complications seen were 1 arteriovenous fistula and 1 large groin hematoma. One patient each in group 3 and group 4 had transient ST elevation consistent with an air embolism with full recovery and no detectable new wall motion abnormality on intracardiac echocardiogram.

### Table 2. Major and Minor Complications

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Age &lt;45 y (n=309 Procedures)</th>
<th>Group 2 Age 45 to 54 y (n=583 Procedures)</th>
<th>Group 3 Age 55 to 64 y (n=768 Procedures)</th>
<th>Group 4 Age ≥65 y (n=378 Procedures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major complications</td>
<td>0</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Tamponade/effusion requiring drainage</td>
<td>0</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Atrioesophageal fistula</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PV stenosis requiring intervention</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Phrenic nerve injury resolved</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Retroperitoneal bleed</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Major complication totals</td>
<td>0</td>
<td>10 (1.7%)</td>
<td>15 (2.0%)</td>
<td>10 (2.6%)</td>
</tr>
<tr>
<td>Other complications</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PV stenosis, asymptomatic</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pseudoaneurysm</td>
<td>0</td>
<td>2</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Large groin hematoma</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fluid overload prolonging hospitalization</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Radiation burn</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Air embolism with transient ST changes</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other complication totals</td>
<td>2 (0.6%)</td>
<td>13 (2.3%)</td>
<td>22 (2.9%)</td>
<td>15 (4.5%)</td>
</tr>
</tbody>
</table>

Figure 2. Rate of major complications after AF ablation procedures. No major complications were seen in patients younger than 45 years.
Discussion

The most recent ACC/AHA/ESC guidelines from 2006 suggest that ablation therapy for AF is second-line for all categories of patients. The HRS/EHRA/ECAS Expert Consensus Statement from 2007 states that ablation should only be considered as a first-line therapy in rare clinical situations. This data detailing the efficacy and complication rates from 2038 procedures challenge those guidelines. When separating the patients into a group including only the young (<45 years of age), we have found that there is a very small complication rate and a comparable efficacy rate. Additionally, there is a greater chance of being able to achieve AF control without the use of antiarrhythmic medications, which is an important factor in young patients.

There are many possible reasons that younger patients may have a better outcome than older patients. Our data showed that younger patients had smaller atria, which may be a contributing factor. Additionally, there was a trend toward a larger portion of patients with paroxysmal AF versus persistent AF in younger patients. With respect to the primary efficacy end point of freedom from AF off of antiarrhythmic medications, the threshold to stop or decision to continue antiarrhythmic medications probably is influenced by patient age. This phenomenon was demonstrated in our previous study demonstrating that in patients younger than 65 years, 5% of patients did not have AF recurrence but remained on antiarrhythmic medications versus 13% to 14% of patients 65 years of age or older who remained on antiarrhythmic medications despite the absence of recurrent AF after ablation.

With respect to complications, the finding of no major complications among 309 procedures in those younger than 45 years was of particular interest. Further, only 2 patients had vascular complications, for a complication rate of 0.6%. There are several reasons contributing to the lower complication rate in the very young: shorter procedure times (as demonstrated by a decreased fluoroscopy time), a more predictable vascular and cardiac anatomy, and fewer comorbidities. Spragg et al described age >70 years and female sex as the only shown predictors of major complications. In our cohort of patients, there was a larger proportion of women in the older age groups, which may also have contributed to the higher complication rates, although specific reasons for this finding are not clear.

Cappato et al recently described the risk of fatal complications during AF ablation with an observed incidence of 0.98 deaths per 1000 patients after studying >45 000 procedures. The risk according to patient age was not detailed. However, this study would suggest that the risk in the patient under the age of 45 years may be even smaller. When making decisions in the young patient regarding antiarrhythmic medications versus ablative therapy, factors such as the potential length of time of antiarrhythmic exposure should be considered. It is well described that with certain antiarrhythmic medications, most notably amiodarone, that the duration of time on the medication is associated with the complications.

Further, the strategy for long-term medical treatment in a patient with AF seems less palatable when the patient is under the age of 45 years and is being destined for decades of exposure to the drug.

Study Limitations

The major limitation to our study is the fact that the data are observational, which may be subject to selection bias. Although we observed a very low complication rate in those younger than 45 years with a relatively high success rate off of antiarrhythmic drugs, a direct comparison between ablation and antiarrhythmic drugs was not made. Although this study cannot demonstrate an absolute benefit of first-line ablation over antiarrhythmic drugs in the young patient, it does show the feasibility of such a strategy. We believe that these data are strongly suggestive that ablation should be considered as a first-line strategy in young patients and reinforces the need for a randomized, controlled trial of first-line ablation versus antiarrhythmic medication in this young age group.

Conclusion

In patients younger than 45 years, there is a lower complication rate, while having a comparable overall efficacy rate with a greater chance of being AF free without the use of antiarrhythmic medications. These findings suggest that it may be appropriate to consider ablative therapy as first-line therapy in patients younger than 45 years. Certainly the results support a randomized, controlled trial of ablation versus AADs as first-line therapy.

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

In patients with persistent or paroxysmal atrial fibrillation younger than 45 years, clinical experience has suggested that symptoms tend to be greater and willingness to take long-term medications tends to be lower. This study demonstrates that pulmonary vein isolation in this cohort is associated with a lower major complication rates, with no major complications found in our cohort of 232 patients undergoing 309 procedures. Furthermore, efficacy is comparable to other age groups, with a greater chance of being free of atrial fibrillation without the use of antiarrhythmic medications. These findings are supportive of a first-line invasive strategy for young symptomatic patients with atrial fibrillation given the favorable risk-benefit ratio. The study findings do not diminish the role of antiarrhythmic medications as a viable option in young patients but emphasizes the role of ablation as a reasonable alternative as a first-line strategy. The clinical impact of a lower threshold for atrial fibrillation ablation in the young may translate into fewer failed drug trials and potentially fewer hospital visits or admissions for drug monitoring or breakthrough episodes of atrial fibrillation.
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