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Preoperative Statin use is not Associated with a Reduced Risk of Atrial Fibrillation After Cardiac Surgery

Brian J Barnes, PharmD\textsuperscript{a,b,c}, Scott Solomon, MD\textsuperscript{d}, Patricia A Howard, PharmD\textsuperscript{a,b}, Dhanunjaya Lakkireddy, MD\textsuperscript{c,d}, Jeffrey B Kramer, MD\textsuperscript{b}, Gregory F Muehlebach, MD\textsuperscript{b}, Emmanuel Daon, MD\textsuperscript{b}, George L Trip Zorn III, MD\textsuperscript{b}, James L Vacek, MD, MS\textsuperscript{c,d}

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Abstract

Introduction: Postoperative atrial fibrillation (POAF) is prevalent after cardiac surgery and associated with significant morbidity and costs. Statins are commonly used in this population and may be a preventative strategy for POAF. We wished to examine the effect of preoperative statin use on the risk of POAF after cardiac surgery.

Methods: A retrospective, observational study was conducted using data from 489 adult patients who underwent cardiac surgery at a single institution. Univariate analyses and unconditional logistic regression were used to determine the impact of preoperative statin use on the probability of developing POAF, while controlling for the baseline risk of POAF and the use of amiodarone prophylaxis (AMP). A baseline risk index was calculated for each patient using a previously validated model. Patients with chronic atrial fibrillation or missing data were excluded.

Results: Mean patient age was 63 (SD=13) years, 73% were male, 68% underwent isolated coronary artery bypass grafting, 16% underwent isolated valve surgery, with 13% underwent combined CABG and valve surgeries, and 3% underwent other forms of cardiac surgery. POAF occurred in 27% of patients receiving statins and 24% of those not receiving statins (p=0.3792). After controlling for baseline risk of POAF and the use of AMP, we found that preoperative statins were not associated with reductions in POAF (OR=1.19, 95\%CI=0.782-1.822, p=0.4118).

Conclusions: Multiple factors impact the development of POAF after cardiac surgery including patient demographics, comorbidities, surgical type, and concomitant medications. In this study, after adjustment for these factors the preoperative use of statins did not significantly influence the development of POAF.
Introduction

Postoperative atrial fibrillation (POAF) is the most common complication following open heart surgery including coronary artery bypass surgery (CABG) and/or valve surgery, and is a significant source of morbidity and mortality. 1-3 Each year in the United States, POAF following open heart surgery occurs in approximately 26% of patients with an estimated range of 17-35% and in some reports as high as 50%.1,2 The high incidence of POAF has an impact on the health care system in many ways including patient morbidity, health care costs, and length of hospital stay. 3

Beta blockers and amiodarone have been shown to decrease the incidence of POAF and have been used as prophylaxis based on their ability to suppress arrhythmias. In recent years, several investigators have suggested that statins may be a possible therapeutic alternative to lower the incidence of POAF based on their potential pleiotropic properties. 4-17 Statins have been shown to have anti-inflammatory properties and have demonstrated reductions in chemokines and chemokine receptor expression in endothelial cells and macrophages. 12,14 While the etiology of POAF is likely multifactorial, inflammation has been proposed as a possible contributing factor .14

The findings from prior studies examining the use of statins after cardiac surgery for the prevention of POAF are inconsistent. 5-11 The objective of this study was to evaluate the impact of preoperative statin therapy on the risk of developing POAF following cardiac surgery, while controlling for contemporary prophylactic strategies and subjects’ baseline risk for developing POAF.

Methods

After approval from our institutional review board, a retrospective, observational, cohort study was conducted using data from 489 adult patients who underwent cardiac surgery in 2003. During this time period, our research group had previously collected extensive medication administration and heart rhythm data and also calculated a baseline risk index for postoperative atrial fibrillation (described below) on this cohort. 18 For this investigation we supplemented this existing dataset with additional information regarding preoperative statin use.

Data sources included institution-specific data from the Society of Thoracic Surgeons national database plus medical and medication administration records. All adult patients (≥18 years old) who underwent cardiac surgery in 2003 were eligible for the study. Patients with a preoperative diagnosis of chronic atrial fibrillation or those with incomplete medical records were excluded. Patients were considered to have received statin therapy preoperatively if a statin was listed on their home medication list at hospital admission. All patients were placed on continuous telemetry throughout their hospital stay. POAF was defined as the persistence of atrial fibrillation for > 4 hours following cardiac surgery as documented in the patient’s medical record flow sheet. We elected to use this more ridged criteria for POAF as prolonged POAF is likely to impact outcomes more significantly than paroxysmal atrial fibrillation.

Baseline risk for POAF was calculated for each patient using a validated model consisting of 11 variables. 15 This index stratifies patients into 3 risk groups: low, moderate, and high risk. Model variables that increased the risk of having POAF develop included: advancing age, a history of atrial fibrillation or chronic obstructive pulmonary disease, patients undergoing heart valve surgery, or patients whose beta-blockers or angiotensin converting enzyme inhibitors are withdrawn after surgery. Variables that decrease the risk of having POAF develop include the use of postoperative beta-blocker alone, both preoperative and postoperative beta-blockade or angiotensin converting enzyme inhibition, postoperative nonsteroidal anti-inflammatory drugs, or postoperative potassium supplementation. In this risk index, each of these variables possesses their own contribution weights. When the weights are totaled, patients are classified as low-risk (< 14 points), moderate-risk (14 to 31 points), or high-risk (> 31 points). We combined patients in the moderate-risk and high-risk groups into a single elevated-risk group. The final risk index (as a continuous variable) was included in the multivariate logistic regression model to control for baseline risk of POAF. Medication exposure was collected from medication administration records. Medication administration to the
patient was verified by reviewing Pyxis MedStation 2000 dispensing records. Amiodarone prophylaxis was defined as documented administration of greater than or equal to 1 day of either intravenous or oral amiodarone, or a combination of both routes, between postoperative days 0 to 4, prior to the onset of any POAF. Timing of amiodarone administration was compared with the onset of POAF to verify patients had received amiodarone as prophylactic therapy. To be counted in the risk index calculation, medications (i.e. beta blockers, ACE inhibitors, NSAIDs, potassium) were required to administered for greater than or equal to 1 day of between postoperative days 0 to 4, prior to the onset of any POAF.

Using SAS (version 9.1.4) and an a priori alpha level of 0.05 to indicate statistical significance, univariate analysis (t-tests, Wilcoxon rank sum, and chi square tests) and unconditional, logistic regression, utilizing stepwise selection (model entry and retention were set at 0.15 and 0.05, respectively) were used to determine the impact of preoperative statin use on the probability of developing POAF, while controlling for the baseline risk of POAF and the use of amiodarone prophylaxis (AMP). Successful model convergence was noted during the stepwise selection procedure. Interactions between model variables were assessed by incorporating the product of the various explanatory factors and assessing their impact on the model. Statistically significant variable interactions did not exist. Goodness of fit for the model was assessed by evaluating the Hosmer and Lemeshow test which indicated the predicted responses generated by our model were not statistically different from that which we observed. Model overfitting was checked by determining if each explanatory variable included in the model had at least 10 positive outcomes. Odds ratios and their corresponding 95% confidence intervals were calculated for the explanatory variables by exponentiation of the values of the regression coefficients (see TABLE 2).

Results

A total of 489 patients were included in the analyses. Baseline demographics are listed in [TABLE 1]. The mean patient age was 63 (SD=13) years, 73% were male, 68% (n=334) underwent isolated coronary artery bypass grafting, 16% (n=79) underwent isolated valve surgery, with 13% (n=61) underwent combined CAGB and valve surgeries, and 3% underwent other cardiac surgical repair of aortic aneurysms (n=7), atrial septal defects (n=5), and patent foramen ovale (n=4). Beyond inclusion of valve surgery in the risk index, the other surgical procedures did not significantly influence the probability of developing POAF when included in the model, and thus did not remain in the final model. Subjects receiving preoperative statins were more likely to be older and have a history of hypertension, prior MI and prior CAGB. Patients in the statin group were also more likely to be undergoing CAGB rather than valve surgery during the index admission and more likely to be prescribed preoperative and postoperative beta blockers. Left ventricular ejection fraction was not different between the statin and nonstatin groups (46%±14% among statin users, and 47%±14% among non statin users, p=0.5984). Based on the calculated risk index, 51% of patients were consid-

<table>
<thead>
<tr>
<th>Factor</th>
<th>b parameter</th>
<th>Odds ratios (95% Wald CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-1.6808</td>
<td>n/a</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preoperative statin use</td>
<td>0.0886</td>
<td>1.194 (0.782-1.822)</td>
<td>0.4118</td>
</tr>
<tr>
<td>Postoperative amiodarone prophylaxis</td>
<td>-0.2493</td>
<td>0.607 (0.397-0.930)</td>
<td>0.0218</td>
</tr>
<tr>
<td>POAF risk index</td>
<td>0.0474</td>
<td>1.049 (1.030-1.067)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table 1
Demographics of the study population (N=489)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Group, (N = 489)</th>
<th>Statin - (n=263)</th>
<th>Statin + (n=226)</th>
<th>P value, +/- Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean years, (SD)</strong> ‡ £</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30, n (%)</td>
<td>10 (2)</td>
<td>10 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>30-39, n (%)</td>
<td>21 (4)</td>
<td>16 (6)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>40-49, n (%)</td>
<td>39 (8)</td>
<td>27 (10)</td>
<td>12 (5)</td>
<td></td>
</tr>
<tr>
<td>50-59, n (%)</td>
<td>123 (25)</td>
<td>58 (22)</td>
<td>65 (29)</td>
<td>0.0023</td>
</tr>
<tr>
<td>60-69, n (%)</td>
<td>132 (27)</td>
<td>72 (27)</td>
<td>60 (27)</td>
<td></td>
</tr>
<tr>
<td>70-79, n (%)</td>
<td>118 (24)</td>
<td>57 (22)</td>
<td>61 (27)</td>
<td></td>
</tr>
<tr>
<td>80+, n (%)</td>
<td>46 (10)</td>
<td>23 (9)</td>
<td>23 (10)</td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>359 (73)</td>
<td>189 (72)</td>
<td>170 (75)</td>
<td>0.4020</td>
</tr>
<tr>
<td>Weight (mean kilograms ± SD) ‡</td>
<td>87 ± 20</td>
<td>85 (19)</td>
<td>90 (21)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Preoperative history of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation £, n (%)</td>
<td>40 (8)</td>
<td>25 (10)</td>
<td>15 (7)</td>
<td>0.2485</td>
</tr>
<tr>
<td>Lung disease £, n (%)</td>
<td>68 (14)</td>
<td>33 (13)</td>
<td>35 (15)</td>
<td>0.3490</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>75 (15)</td>
<td>47 (18)</td>
<td>28 (12)</td>
<td>0.0935</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>345 (71)</td>
<td>155 (59)</td>
<td>190 (84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>173 (35)</td>
<td>76 (29)</td>
<td>97 (43)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Renal failure, n (%)</td>
<td>24 (5)</td>
<td>16 (6)</td>
<td>8 (4)</td>
<td>0.1942</td>
</tr>
<tr>
<td>Prior coronary artery bypass surgery, n (%)</td>
<td>48 (10)</td>
<td>16 (6)</td>
<td>32 (14)</td>
<td>0.0028</td>
</tr>
<tr>
<td>Prior valve surgery, n (%)</td>
<td>18 (4)</td>
<td>13 (5)</td>
<td>5 (2)</td>
<td>0.1099</td>
</tr>
<tr>
<td>CABG during admission, n (%)</td>
<td>334 (68)</td>
<td>153 (58)</td>
<td>181 (80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Valve surgery during admission £, n (%)</td>
<td>79 (16)</td>
<td>65 (25)</td>
<td>14 (6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Combined CABG and valve surgery, n (%)</td>
<td>61 (13)</td>
<td>34 (13)</td>
<td>27 (12)</td>
<td>0.7430</td>
</tr>
<tr>
<td>Other cardiac surgery, n (%)</td>
<td>15 (3)</td>
<td>11 (4)</td>
<td>4 (2)</td>
<td>0.1230</td>
</tr>
<tr>
<td>Surgery status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective, n (%)</td>
<td>275 (57)</td>
<td>149 (57)</td>
<td>126 (56)</td>
<td>0.1200</td>
</tr>
<tr>
<td>Urgent, n (%)</td>
<td>195 (40)</td>
<td>99 (38)</td>
<td>96 (42)</td>
<td>0.1200</td>
</tr>
<tr>
<td>Emergent, n (%)</td>
<td>17 (3)</td>
<td>13 (5)</td>
<td>4 (2)</td>
<td></td>
</tr>
<tr>
<td>Cross clamp time, median min. (range) †</td>
<td>82 (53-270)</td>
<td>83 (0-270)</td>
<td>80 (0-225)</td>
<td>0.2067</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, median min. (range) †</td>
<td>107(75-403)</td>
<td>111 (0-403)</td>
<td>102 (0-279)</td>
<td>0.0815</td>
</tr>
<tr>
<td>Postoperative atrial fibrillation (POAF) related variables:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients at elevated POAF risk (from risk index £), n(%)</td>
<td>238 (49)</td>
<td>129 (54)</td>
<td>109 (46)</td>
<td>0.8566</td>
</tr>
<tr>
<td>POAF, n (%)</td>
<td>125 (26)</td>
<td>63 (24)</td>
<td>62 (27)</td>
<td>0.3792</td>
</tr>
<tr>
<td>POAF recurrence, n (%)</td>
<td>53/125 (42)</td>
<td>26/63 (41)</td>
<td>27/62 (44)</td>
<td>0.7987</td>
</tr>
<tr>
<td>Duration of POAF, in # of days, median (range) †</td>
<td>2 (1-36)</td>
<td>2 (1-28)</td>
<td>2 (1-36)</td>
<td>0.8269</td>
</tr>
<tr>
<td>Postoperative use of amiodarone prophylaxis, n (%) ¥</td>
<td>294 (60)</td>
<td>155 (59)</td>
<td>139 (62)</td>
<td>0.5630</td>
</tr>
<tr>
<td>Post surgical withdrawal of beta-blockers, n (%) £</td>
<td>96 (20)</td>
<td>46 (17)</td>
<td>50 (22)</td>
<td>0.1984</td>
</tr>
<tr>
<td>Post surgical withdrawal of ACE-inhibitors, n (%) £</td>
<td>132 (27)</td>
<td>62 (24)</td>
<td>70 (31)</td>
<td>0.0699</td>
</tr>
<tr>
<td>Pre and postoperative use of beta-blockers, n (%) ¥ £</td>
<td>228 (46)</td>
<td>105 (40)</td>
<td>123 (54)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Postoperative use of beta-blockers, n (%) ¥ £</td>
<td>327 (67)</td>
<td>165 (63)</td>
<td>162 (72)</td>
<td>0.0362</td>
</tr>
<tr>
<td>Pre and postoperative use of ACE inhibitors, n (%) ¥ £</td>
<td>128 (26)</td>
<td>55 (21)</td>
<td>73 (32)</td>
<td>0.0043</td>
</tr>
<tr>
<td>Postoperative use of NSAIDs, n (%) ¥ £</td>
<td>153 (31)</td>
<td>86 (33)</td>
<td>67 (30)</td>
<td>0.4678</td>
</tr>
<tr>
<td>Postoperative potassium replacement, n (%) ¥ £</td>
<td>489 (100)</td>
<td>263 (100)</td>
<td>226 (100)</td>
<td>1.0000</td>
</tr>
</tbody>
</table>
ere a low-risk for POAF and 49% were considered moderate to high risk. The proportion of subjects at elevated-risk for POAF did not differ between those receiving preoperative statins (46%) and those who did not (54%, p=0.8566)

POAF occurred in 27% of patients who received preoperative statins compared to 24% of those not receiving statins (p=0.3792). After controlling for the baseline risk of POAF and the use of AMP, we found that statins continued to not be associated with reductions in POAF (See TABLE 2, OR=1.19, 95%CI=0.782-1.822, p=0.4118). The frequency of use for specific statins is described in [TABLE 3]. The most commonly prescribed statins were atorvastatin and simvastatin (37.6% and 49.6%, respectively). Statin dosing was variable, consistent with the typical low and high dose ranges used in clinical practice. There was no significant difference in the use of preoperative statins in the patients who developed atrial fibrillation (50%, 62/125) vs. those who did not develop atrial fibrillation (45%, 164/364), p=0.3792. Likewise there was no significant difference in the use of lipid lowering therapy at hospital discharge in those subjects who did develop atrial fibrillation (66%, 83/125) vs. those who did not (67%, 243/364), p=0.9203. There was no significant difference in the performance of atrial fibrillation preventative surgery at the time of their procedure between those patients who did or did not develop postoperative atrial fibrillation (p=0.1603).

Discussion

Previous observational studies have found that statin therapy prior to and following cardiac surgery reduces the risk of developing POAF. In a nested cohort trial, Lertsburapa et al. evaluated the impact of statins in 555 patients undergoing cardiac surgery. Among the 331 patients who received statins, rates of POAF were reduced by 40%.

A study of 362 patients, also found that preoperative statins were associated with a lower risk of POAF (8.2% vs 16.8%, p=0.03)

In a well designed, prospective observational study, Mariscalco et al. studied 405 patients undergoing CABG surgery. The effect of statin therapy was evaluated using logistic regression modeling, stratification and propensity scoring. Preoperative statin use was associated with a 42% reduction in POAF (p=0.017).

It should be noted that this study included patients with a prior history of AF and those undergoing emergent surgery, thus suggesting a population at higher risk.

In addition to the observational data, one randomized, double-blind, placebo-controlled study has evaluated the impact of preoperative statins on POAF risk. The Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery (ARMYDA-3) compared atorvastatin 40 mg, started seven days prior to surgery, to placebo in 200 patients undergoing elective open heart surgery. This study found that atorvastatin significantly reduced the risk of POAF (OR 0.39, 95%CI 0.18-0.85, p=0.017) and statistically resulted in a shorter length of hospital stay (6.3 vs 6.9 days, p=0.001).

While this was the most rigorous study to date, it did not examine the influence of baseline risk for POAF, which is likely an important determinant of the effectiveness of prophylactic regimens.

In contrast to these positive studies, other studies have failed to support the theory that statins reduce the risk of POAF. Virani et al performed a retrospective cohort analysis with a large patient population (n=4044) and found that statin use prior to and following cardiac surgery did not reduce the incidence of POAF.

Recently, Miceli et al. reported a significantly higher incidence of POAF in patients undergoing CABG who had taken statins.

Table 3

<table>
<thead>
<tr>
<th>Statin</th>
<th># (%) subjects receiving drug</th>
<th>Mean dose (mg) ± SD</th>
<th>Dose range (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin</td>
<td>85 (37.6)</td>
<td>22±16</td>
<td>5-80</td>
</tr>
<tr>
<td>fluvastatin</td>
<td>3 (1.3)</td>
<td>80±0</td>
<td>80-80</td>
</tr>
<tr>
<td>lovastatin</td>
<td>6 (2.7)</td>
<td>22±10</td>
<td>10-40</td>
</tr>
<tr>
<td>pravastatin</td>
<td>17 (7.5)</td>
<td>34±24</td>
<td>10-80</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>3 (1.3)</td>
<td>20±17</td>
<td>10-40</td>
</tr>
<tr>
<td>simvastatin</td>
<td>112 (49.6)</td>
<td>35±24</td>
<td>5-80</td>
</tr>
</tbody>
</table>

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as compared to those patient who had not re-
ceived statin therapy (n=411, 19.5%, versus
336; 15.8%, p = 0.002). 9

Similarly, our retrospective observational
analysis concluded that preoperative statin
use did not significantly reduce the incidence
of POAF following cardiac surgery. One limi-
tation of the retrospective study design was
the inability to control for statin dosing. Pre-
viously, it has been found that higher statin
doses may produce more significant reduc-
tions in POAF. 5 Likewise, Kourliouros et al
provided support for a dose-dependant re-
duction in POAF with simvastatin and atorv-
astatin, concluding that low dose statin ther-
apy is not effective for preventing POAF. 10 The
majority of our patient population received
low to moderate statin doses (TABLE 3). Fur-
ther, the potency of the various statins used
is highly variable. Because inflammation may
contribute to a higher incidence of POAF and
the anti-inflammatory benefit of statins is like-
ely achieved at higher doses, this may explain
the lack of benefit seen in this study cohort.
Additionally, we were unable to control for
LDL levels or other inflammatory markers to
determine whether patients in our study were
achieving optimal cardioprotective or anti-
flammatory benefit of statins. For example,
it has been shown that lower CRP levels fol-
lowing the administration of statins are asso-
ciated with improved event free survival fol-
lowing an acute coronary syndrome 12 Future
studies could include a more specific analysis
of the dose-dependent effects of statins on in-
flammation and the subsequent influence on
POAF.

Baseline risk is a major determinant of the risk
for POAF. In particular, it has been shown
that valve surgery significantly increases the
risk. In a study by Creswell et al., the inci-
dence of atrial arrhythmias was higher in pa-
tients undergoing mitral valve replacement
and aortic valve replacement versus CABG
alone (42.4% versus 48.8% versus 31.9%). 13
Our patient population included a significant
number of patients undergoing valve surgery
or combined valve and CABG surgery (TA-
BLE 1). The higher incidence of POAF when
valve surgery occurs could explain why our
analysis did not support statin use as prophyl-
axis for POAF. Virani et al found similar re-
results with no reduction in POAF with statin
therapy for a study population that included
a higher proportion of patients undergoing
valve surgery. 6 Our study has several addi-
tional limitations. Ours study indicated that
patients with more co morbidities and thus
at increased likelihood to develop POAF,
were more likely to be on a statin prior to sur-
gery. However, the calculated risk index for
baseline risk for POAF was not different be-
tween the groups and was controlled for in
the regression model. With the retrospective
design of our study, it is difficult to control
for events that may or may not have occurred
in the perioperative and postoperative time
period. Examples include administration or
discontinuation of medications that may pro-
vide cardio protection or influence the devel-
opment of POAF, such as steroids and aspirin
which were not assessed in this study. We did
however verify the administration and timing
of drugs used specifically to prevent POAF.
The high use of amiodarone and beta blockers
may have clouded the results as these agents
may reduce POAF, however as they are fre-
quently used in clinical practice, it would not
be practical to perform a study in the present
era which excluded their prescription.

As previously discussed, we were unable to
control for the statin used, dose of statin or
duration of therapy. In addition post opera-
tive statin use was not available for the analy-
sis. However, our hypothesis was that preop-
erative statin use would have a greater impact
on the occurrence of POAF than would post-
operative use where initiation and cellular in-
fluence may be delayed and variable. A future
carefully controlled double blind prospective
study may reduce the impact of these rec-
ognized as well as other unrecognized con-
 founding factors.
It is of interest that certain randomized studies have suggested a benefit of statins for POAF while some observational studies present have not. This suggests the possibility that over-selection in the randomized trials may have reduced the applicability to general clinical practice, or that the inclusion of unrecognized confounders in the observational studies may have reduced the potential benefit of statin therapy. It is also possible that varying criteria for the diagnosis of POAF has led to some of the differences in prior study outcomes. For example the ARMYDA-3 study which demonstrated benefit with statins used a very sensitive definition of POAF (duration of > 5 minutes) as compared to our more stringent definition of duration > 4 hours. Our study is unique in that we included all patients undergoing cardiac surgery and did not limit our research to a homogenous population. Additionally, unlike previous studies we controlled for the use of prophylactic strategies such as amiodarone and beta blockers. It is possible that the use of such agents render the impact of statins on POAF imperceptible unless studied in a very large sample.

Conclusions

In conclusion, this retrospective study did not demonstrate an association between preoperative statin use and the risk of POAF following cardiac surgery. Taken as a whole, the body of evidence examining the relationship between statin use and POAF remains inconclusive and therefore cannot be used to justify the use of statins as a primary prophylactic strategy. However, due to the routine use of statins in the cardiac surgery population for other indications, additional research appears warranted. Future studies focusing more specifically on individual statins and the dose and timing of administration relative to the perioperative period may provide more definitive answers. Likewise, additional studies more fully exploring the potential mechanisms through which statins might impact arrhythmia development may help to further clarify this issue.

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13. Creswell LL, Schuessler RB, Rosenblum M, Cox JL. Hazards
Introduction

Atrial fibrillation ablation is an effective and recognized therapy. However this technique is associated with a high rate of arrhythmia recurrences. Indeed the estimated rate of recurrence following paroxysmal AF ablation is up to 30% and up to 50% for persistent AF after one procedure. Arrhythmia recurrences following AF ablation are characterized according to the timing of recurrence and the type of arrhythmia recurrences.

Early arrhythmia recurrences occur within 1 to 3 months following the index procedure where as late recurrences occur after.

Arrhythmia recurrences can be atrial fibrillation or organized atrial tachycardia such as left macro-reentrant or focal tachycardia.

The rate of early arrhythmia recurrences varies from 20-50% following AF ablation.

Numerous studies have demonstrated that patients experiencing early arrhythmia recurrences are at high risk of developing late arrhythmia recurrences. However some patients with early recurrences will not develop late recurrences justifying a “blanking period” before considering redo ablation.

Choi et al specifically focused on the predictive value of early organized atrial tachycardia following AF ablation on late arrhythmia recurrences.

Interestingly patients with early atrial tachycardia recurrences had a significant higher risk of developing late recurrences compared to patients without early atrial tachycardia occurrence.

This study confirms previous studies results including AF and atrial tachycardia in the definition of early arrhythmia recurrences.

However organized atrial tachycardias are usually seen following persistent AF ablation. This rate is estimated to 3-10% following paroxysmal AF ablation and 10-30% after persistent AF ablation. In the present study only 30% of patients experienced persistent AF ablation explaining the rate of 15% of early atrial tachycardia. However it is unclear why the authors included such a low rate of persistent AF patients.

A lot of questions remain to be elucidated about early arrhythmia recurrences following AF ablation:

1) How can we prevent early arrhythmia recurrences?
2) As early recurrence is associated with late ar-
rhythmia recurrence, is a reduction of early arrhythmia recurrences will decrease late arrhythmia recurrences?

3) When is the best timing for reablation?

The mechanisms underlying early arrhythmia recurrences are unclear. Two main hypotheses can be advanced: local tissue inflammation and persistence of arrhythmogenic atrial tissue. One could then hypothesize that pro-arrhythmogenicity due purely to inflammation could decrease with time and would explain patients with early arrhythmia recurrences but not late. Conversely patients with persisting arrhythmogenic tissue will experience both early and late arrhythmia recurrences. However very few studies have been published about inflammation and arrhythmia recurrences and are contradictory. The main limitation of these studies is the absence of local inflammation tissue data to correlate with clinical recurrences. However recently Koyama et al. have demonstrated that corticosteroids administered 3 days following paroxysmal AF ablation could reduce very early (3 days after AF ablation) and late arrhythmia recurrences (>1month post-ablation). These results need to be confirmed by other groups and extended to persistent AF ablation.

We also have demonstrated (unpublished personal data) that the prevalence of acute, small and asymptomatic pericardial effusion were frequent following AF ablation (22%) particularly following persistent AF ablation (35%). Moreover these effusions were independently associated with early arrhythmia recurrences but not late recurrences. Non steroids anti-inflammatory could then be proposed in this specific population following AF ablation to reduce early and/or late recurrences.

Additionally Baman et al. have recently demonstrated that 50% of patients with early recurrences and experiencing a cardioversion within the first month following AF ablation were in sinus rhythm after one year of follow-up. Randomized studies evaluating the effect of an aggressive strategy for sinus rhythm maintenance immediately after AF ablation are required.

Finally the best timing for re-ablation is not established. International guidelines recommend waiting at least 3 months, during the “blanking period”, before performing a redo ablation. However recently Wang et al. proposed that the proper timing for re-ablation could be one month. Indeed no difference in late arrhythmia recurrences was found during the mid-term follow-up in patients re-ablated 1 month or 3 months after the index procedure. Conversely Lellouche et al. demonstrated that an early re-ablation within the first month post-ablation was associated with a higher number of AF ablation procedures.

More studies need to be performed to elucidate the precise mechanisms and the appropriate treatment for early arrhythmia recurrences following AF ablation.

References

Introduction

The most common sustained supraventricular arrhythmia in adults is atrial fibrillation (AF). The overall prevalence of AF is reported as 0.4% with prevalence increasing with age: 16-20% of those aged >85 years have AF. In most patients, AF is treated with the goal to reduce symptoms and decrease risk of stroke. Left atrial appendage (LAA) thrombi have been documented in approximately 10% of patients with AF in the absence of anticoagulation and lends to a risk of stroke several times higher than the general population.

Catheter ablation has increasingly become the therapy of choice for symptomatic, recurrent, drug refractory AF. Since the discovery of the pivotal role of the pulmonary veins (PV) in the genesis of atrial fibrillation by Haissaguerre et al. in 1998, electric isolation of the PVs has formed the cornerstone of current ablation techniques. This can be accomplished by surgical methods, or via catheter-based radio frequency ablation (RFCA). RFCA procedures typically involve the use of a variety of ablation catheters under fluoroscopic guidance to electrically isolate the PVs from the left atrium (LA), with or without the guidance of a three-dimensional (3D) electroanatomic mapping system.

Despite advances in ablation techniques, RFCA continues to be a challenge in part due to the high degree of variability in individual anatomy. It is known that anatomic imaging by fluoroscopy is limited by poor soft tissue resolution and exposure to ionizing radiation. Additionally, the catheter-based electroanatomic map often cannot replicate complex and highly variable PV and LA anatomy. The reported success rate of RFCA procedures at midterm follow up is 70-80% and major com-
plication rate including PV stenosis, tamponade, and stroke is about 5%. The limited success rate and occurrence of major complications is in part due to the complexity and variability in PV and LA anatomy.

The purpose of this article is to provide a comprehensive review of the utility of computed tomography (CT) in image-guided RFCA, the additional radiographic and functional anatomic data provided by this imaging modality, and a comparison between CT and alternative radiologic modalities in RFCA.

CT for Left Atrium and Pulmonary Vein Mapping

Conventional pulmonary venous anatomy is defined as the presence of single right and left superior and inferior pulmonary veins that drain into the left atrium without any accessory veins (Figure 1). In a series of 201 patients who underwent evaluation of left atrium and pulmonary vein anatomy with thin-section (2.5mm) contrast enhanced CT scans, 71% of patients were found to have two ostia on the right side for upper and lower lobe veins, 28% had three to five ostia on the right side, due to one or two separate middle lobe vein ostia in 26% of patients. The majority of patients (86%) had two ostia on the left side for the upper and lower lobe veins; 14% were found to have a single ostium. In a smaller series of 34 patients, CT detected pulmonary venous variants in 6% of patients and identified other cardiac abnormalities, including suspicious pulmonary malignancy, mediastinal adenopathy, and coronary stenosis in 44% of patients.

While there is considerable variation in the approach to RFCA for AF, at most centers the predominant approach to RFCA for AF focuses on PV isolation at the junction of their entry into the left atrium, or the ostium. In addition to providing important anatomic landmark information, preoperative evaluation of the left atrium and the PVs has been shown to reduce fluoroscopic and procedural time. Preprocedural imaging for RFCA should include the following major features: (i) precise anatomy of the LA and PVs,
(ii) precise measurement of each ostial diameter and the distance to the first branch, (iii) presence of accessory or supernumerary PVs, (iv) the LA dimension and the presence of LAA thrombus, and (v) major anomalies like common PV ostia, persistent left superior vena cava, anomalous pulmonary venous return, vein of Marshall, or hypoplasia or occlusion of PV.

**CT Imaging Protocol**

CT imaging protocols vary by device manufacturer, model, detector number and institution-specific protocols with regards to radiation exposure. Multi-detector CT imaging at our institution is performed with the 320-detector row Aquilion One scanner (Toshiba Medical Systems, Japan). The cardiac CT protocol for all studies is a gated dynamic volume acquisition using slice thickness of 1.0mm, with 0.5mm reconstruction thickness. Image acquisition is gated to 40% of the R-R interval. For patients in atrial fibrillation, rate control is optimized to less than 80 bpm prior to the CT study. The tri-phase contrast protocol includes a total volume of 60mL (70mL if BMI > 29) of the noniodinated contrast material iopamidol (Isovue 370; Bracco Diagnostics, Princeton, NJ) administered at a rate of 4mL/sec in the following sequence: 20mL saline test injection, 40mL (100% contrast), 20mL (50% saline, 50% contrast), 65mL (30% saline, 70% contrast), followed by 30mL saline.

**CT versus Other Imaging Modalities for Pre-Procedural Assessment**

There are a number of imaging modalities for pre- or intra-procedural assessment for AF ablation including fluoroscopy, transesophageal echocardiography (TEE), intracardiac echocardiography (ICE), magnetic resonance imaging (MRI), and CT angiography. Several studies have demonstrated the utility of cardiac multi-detector CT angiography to show the anatomy of the LA and PVs prior to RFCA. In comparison to other imaging modalities, CT has been shown to be superior to fluoroscopy, TEE, and ICE to depict the numbers of PV ostia. In addition, CT angiography showed equivalent diagnostic value to ICE in depicting supernumary PVs, without the user-dependent challenges with ICE. CT can also obtain detailed volumetric data with 0.5mm resolution.
spatial resolution, allowing for better depiction of LA and PV structure compared to ICE and TEE. Perhaps most importantly, CT allows for images to be imported for procedure guidance into the real-time navigation system.

**CT for Left Atrial Thrombus Detection**

The current practice for detection of LA and LAA thrombus usually consists of performing a TEE prior to RFCA. With the increasing use of CT prior to RFCA for anatomic guidance of RFCA, the efficacy of CT for detection of LA thrombus has been studied, although data is limited. LA thrombus is identified by CT as an intracavitary contrast filling defect, with attenuation characteristics similar to nonenhanced tissues and differing from surrounding normal pectinate muscle and fat by the reader [Figure 3]. Anecdotally, CT can provide excellent imaging of LA thrombus, but its systematic use has not been consistently validated.

Our group sought to determine the accuracy and interobserver variability of CT in the evaluation of LA thrombus prior to RFCA in 50 patients who underwent 64-slice multidetector CT scan and TEE prior to ablation [figure 2]. We demonstrated that interobserver variability between the three CT readers was poor (highest kappa statistic 0.43, p=0.0001). Diagnostic accuracy was highly variable, with sensitivities ranging from 100% to 50% and specificities ranging from 85% to 44%. TEE reader agreement, in comparison, was 98%. Based on these findings, even amongst experienced observers, CT cannot reliably diagnose LA thrombus, as the interobserver variability is substantial compared to TEE. Potential factors affecting the accuracy of CT include image quality and the difficulty differentiating clot from pectinate muscle.

Jaber, et al. evaluated CT’s ability to detect LA thrombus, finding perfect CT accuracy (sensitivity and specificity of 100%) in detecting LA thrombus, however used an older generation CT scanner with 4-detector row and 500-ms gantry time. While the reason for this discrepancy is not entirely clear, this latter study did not provide interobserver variability, heart rate at the time of study acquisition, or x-ray tube current during scanning. Another study comparing 64-slice CT to TEE for detection of LA thrombus in 51 patients reported similar efficacy. Limitations of...
this study, however, included small population size, and lack of data on interobserver variability. These studies suggest that the use of CT for the detection of LA thrombus is limited by high interobserver variability, modest diagnostic accuracy, and radiation exposure. At this time it does not appear that CT is an adequate substitute for the gold standard of TEE in the detection of LA thrombus prior to RFCA. Additional research directed at different image acquisition techniques, lowering heart rate, and the evaluation of newly evolving technological developments in CT should be pursued.

CT Image Integration-Guided Ablation versus Conventional Methods

Early case series evaluating image integration-guided RFCA (CartoMerge, Biosense Webster, Inc., Diamond Bar, CA, USA) found this method to be feasible, accurate, reproducible, and independent of breathing artifact. Initial experiences in our group with this method suggested that (i) CT and MR images can be successfully used for the anatomically correct extraction and reconstruction of the LA and PV anatomies; (ii) 3D MR/CT reconstructions can be accurately registered with a real-time mapping system using a combination of two registration strategies; (iii) 3D image integration allows for tailored RFCA to individual PV and LA anatomy during AF ablation (Figure 3).

While limited, randomized control studies to evaluate the efficacy of image integration-guided RFCA suggest this method improves the success of RFCA. Martinek et al. evaluated clinical outcome data in 100 patients undergoing RFCA by either conventional method or image integration-guided method at 6 months. Overall success was reported to be 67.9% in the conventional group compared to 85.1% in the image-integrated RFCA group (p=0.018). Additionally, the group reported over 50% risk of PV stenosis in the conventional method group compared to 5.7% risk in the image integration-guided group. In a prospective, randomized trial of 290 patients, the atrial fibrillation-free survival rate was significantly higher in the image integration-guided RFCA group compared to the conventional method group (88% versus 69%, p=0.017) at a mean follow-up of 14 ± 12 months. While the majority of randomized control data evaluating image integration-guided RFCA demonstrates increased efficacy compared to conventional methods, Kistler et al. found that image integration-guided RFCA did not significantly improve clinical outcomes (acute outcomes or long-term outcomes at 6 months) in 80 patients who were randomized to conventional methods versus image integration-guided RFCA.

The majority of randomized controlled trials evaluating the efficacy of image integration-guided RFCA have been performed using CartoMerge technology (CartoMerge, Biosense Webster, Inc., Diamond Bar, CA, USA). Initial case series reports using alternative technologies, however, have also suggested feasibility and success for image integration-guided RFCA.

CT Imaging Prior to Balloon-based PVI

The limitations of RFCA including point-by-point creation of ablation lesions, complex navigation, and small but definite risk of complications (PV stenosis, stroke, atrial-esophageal fistula) has led great interest in developing balloon catheter-based ablation technology. Balloon catheters using various ablative energy sources including cryothermal energy (CRYO; CryoCath Technologies, Inc, Canada) and “hot” balloon ablation catheters which are elastic balloon ablation catheters composed of an antithrombotic, heat-resistant resin (Toray Industries, Inc., Houston, Texas), have and continue to be developed to allow for single or few energy applications to achieve PVI, rather than long, contiguous circumferential ablation lines formed in RFCA.

With the use of these techniques, CT is likely to be beneficial in providing individualized imaging of the LA chamber both for size and PV anatomy, as well as to help facilitate selection of the appropriate balloon catheter size and whether more than one balloon size may be required. As further technologies for pulmonary vein isolation are developed in the future, these are likely to be anatomi-
CT Evaluation of Post-Ablation Complications

There are a number of recognized major complications of RFCA, including stroke, tamponade, vascular injury, atrio-esophageal fistula, pulmonary vein stenosis/occlusion, hemothorax, heart block, acute lung injury, and mitral valve injury. The complication rates reported vary considerably; our group found an overall complication rate of 5% in a retrospective study of 641 patients post RFCA. \(^4\) With regards to the cardiac and vascular complications, CT is a relatively low-risk, fast, and readily available imaging modality to assess for the majority of such complications.

A significant risk associated with balloon catheter-based technology is phrenic nerve palsy, with reported complication rates of 7.1% with the high-intensity focused ultrasound (HIFU) technique and 7.5% with the cryoballoon technique. \(^4\) In one study, CT imaging of the right pericardiophrenic artery could reliably locate the right phrenic nerve and, if located within 10mm of the right superior pulmonary vein, poses a higher risk of phrenic nerve injury using balloon ablation devices. \(^5\) In this regard, pre-procedural CT may provide critical information regarding phrenic nerve anatomy and location, thereby identifying patients at higher risk for phrenic nerve injury, although this is not yet routinely examined.

Pulmonary vein (PV) stenosis is a well known complication of PVI for atrial fibrillation management and while the majority of patients who develop PV stenosis are asymptomatic, it can be associated with significant morbidity. In a series of 608 patients undergoing PVI, Robbins et al reported the incidence of pulmonary vein stenosis following catheter ablation. \(^6\) All patients in the series underwent spiral CT at 1, 3, 6 and 12 months post-procedure. The study demonstrated that severe (≥70%) narrowing was detected in 3.4%, moderate (50% to 69%) narrowing in 4.4% and mild (<50%) narrowing in 7.7% of patients. From a total of 15 pulmonary veins considered to be totally occluded by spiral CT, 7 were confirmed by pulmonary vein angiography. Packer et al reported on the clinical presentation, diagnosis, and management of PV stenosis in 23 patients post PVI who underwent CT pre- and post-PVI to assess for PV anatomy and subsequent stenoses. \(^7\) The study found that CT was helpful in identifying the location and extent of stenoses, with limited yet significant correlation between the extent of stenoses seen on CT images and that seen at the time of angiography.

Other Aspects of CT

CT provides the additional advantage that it is operator-independent unlike other imaging modalities such as TEE and ICE. By delineating complex LA and PV anatomy, CT enables the RFCA operator to take a more individualized approach to RFCA for each patient. This preprocedural knowledge may allow for less use of radiation and overall decrease in procedure time during the RFCA. In addition, CT is safe for patients with implanted devices, a known limitation in MRI. Regarding the limitations of CT, of primary concern is the radiation exposure associated with CT compared to other imaging modalities. Increasing data from large patient studies indicate that cumulative effective doses of radiation increase with advancing age, with CT imaging accounting for up to 38% of the total effective radiation dose. \(^4\) While the individual radiation dose from CT is far less than the radiation exposure incurred during a RFCA procedure itself, these findings have prompted a more individualized approach and critical evaluation of the necessity of CT imaging with respect to RFCA. Given the concerns for cumulative radiation exposure over a lifetime, one might consider MRI as the imaging study of choice prior to RFCA, especially in those with a known history of substantial lifetime radiation exposure and otherwise uncomplicated anatomy. Additionally, patients who are relatively young being considered for RFCA may be appropriate candidates for MRI rather than CT prior to RFCA to help minimize their lifetime cumulative radiation exposure. Children and young adults are inherently more radiosensitive and have more remaining years of life during which a radiation-induced cancer may develop. \(^4\)

After evaluation of the benefits and limitations, if CT is still felt to be the most appropriate imaging
study for a particular patient, several studies have reported effective methods to reduce the radiation dose including: (i) lowering kilovoltage setting, (ii) automatic ECG-pulsed tube current modulation, (iii) dose modulation with mid-diastole, (iv) prospective gating, (v) non-ECG gating, and (vi) special filtering. Most importantly, there is always going to be a balance between radiation dose and image quality. RFCA operators should strive to reduce the radiation dose of the pre-procedure CT as much as possible while still obtaining an image quality adequate to help guide the procedure.

Conclusions

Computed tomography has many well-established uses in cardiovascular medicine. Review of both case series reports and randomized control studies demonstrates that CT is a suitable, if not preferred, modality for preprocedural assessment of LA and PV structure, size, and volume prior to RFCA, in addition to its use in the procedure to help guide ablation. CT has also been shown to be potentially beneficial prior to balloon catheter-based procedures, particularly by identifying patients at high risk for phrenic nerve injury complication. Regarding identification of LA thrombus, at this time CT does not appear sufficient to replace TEE prior to RFCA. Overall, as with any imaging technology, the benefits of CT must be weighed against limitations, particularly radiation exposure to the patient.

References


Atrial Fibrillation in the Wolff-Parkinson-White Syndrome

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Abstract
Since the advent of catheter ablation for atrial fibrillation (AF) aiming the pulmonary veins a few years ago, there has been an overwhelming interest and a dramatic increase in AF investigation. AF has a different dimension in the context of the Wolff-Parkinson-White (WPW) syndrome. Indeed, AF may be a nightmare in a young person that has an accessory pathway (AP) with fast anterograde conduction. It may be life-threatening if an extremely rapid ventricular response develops degenerating into ventricular fibrillation. Therefore, it is very important to know the mechanisms involved in the development of AF in the WPW syndrome. There are several possible mechanisms that may be involved in the development of AF in the WPW syndrome, namely, spontaneous degeneration of atrioventricular reciprocating tachycardia into AF, the electrophysiological properties of the AP, the effects of AP on atrial architecture, and intrinsic atrial muscle vulnerability. Focal activity, multiple reentrant wavelets, and macroreentry have all been implicated in AF, perhaps under the further influence of the autonomic nervous system. AF can also be initiated by ectopic beats originating from the pulmonary veins, and elsewhere. Several studies demonstrated a decrease incidence of AF after successful elimination of the AP, suggesting that the AP itself may play an important role in the initiation of AF. However, since AF still occurs in some patients with the WPW syndrome even after successful ablation of the AP, there should be other mechanisms responsible for the development of AF in the WPW syndrome. There is a clear evidence of an underlying atrial muscle disease in patients with the WPW syndrome. Atrial myocardial vulnerability has been studied performing an atrial endocardial catheter mapping during sinus rhythm, and analyzing the recorded abnormal atrial electrograms. This review analyzes the available data on this singular setting since AF has a reserved prognostic significance in patients with the WPW syndrome, and has an unusually high incidence in the absence of any clinical evidence of organic heart disease.

Introduction
Atrial fibrillation (AF) is a common arrhythmia with multiple possible complications that reaches a different dimension in the context of the Wolff-Parkinson-White (WPW) syndrome. Since the advent of catheter ablation for AF aiming the pulmonary veins a few years ago, there has been an overwhelming interest and a dramatic increase in AF investigation. Although, for most WPW patients the AP ablation is a curative solution, sustained episodes of AF still occur in certain patients despite the disappearance of the AP.
al 11 by surgical means, and Haissaguerre et al 12 by catheter ablation, have documented a reduction in AF inducibility following elimination of the AP in patients with WPW syndrome. Indeed, ablation of the AP is very effective in the abolition of conduction through the AP, and of clinical episodes of atrioventricular reciprocating tachycardia (AVRT) and AF; however, it does not prevent recurrences of AF in certain patients. Therefore, it is very important to determine all possible mechanisms for the development of AF in the WPW syndrome. It is paramount to understand that AF may be life-threatening in the setting of WPW syndrome with fast anterograde AP conduction, because a rapid ventricular response may develop degenerating into ventricular fibrillation. 13 Several mechanisms responsible for the development of AF in the WPW syndrome were investigated in detail, namely, the spontaneous degeneration of AVRT into AF, the electrical properties of the AP, the effects of AP on atrial architecture, and the intrinsic atrial muscle vulnerability. 14-22 Considering all the mechanisms proposed to explain the development of atrial fibrillation in the WPW syndrome, this review analyzes the available data on this singular and interesting topic since AF has a reserved prognostic significance in patients with the WPW syndrome, and has an unusually high incidence in the absence of any clinical evidence of organic heart disease.

Electrophysiological properties of the accessory pathway in the WPW syndrome

Anterograde and retrograde electrophysiologic properties of the AP have been well investigated. The coexistence of a functional retrograde AP and sustained episodes of AVRT has been found to play an important role in triggering AF in patients with the WPW syndrome. 13, 23 In the electrophysiological laboratory, it is relatively common to observe spontaneous degeneration of induced AVRT into AF in WPW patients. AF has a different dimension in the context of the WPW syndrome [Figure 1]. It may be a nightmare in a young person that has an AP with fast anterograde conduction. AF may be life-threatening if an extremely rapid ventricular response develops degenerating into ventricular fibrillation. There is clear data to support that retrograde conduction to the atrium through multiple AP, or multifiber AP during AVRT can initiate AF. The incidence of spontaneous degeneration of induced AVRT into AF has been reported to be in the range of 16% to 26%, 13 and it was found to occur in a similar proportion in patients with con-

Figure 1: Atrial fibrillation in the Wolff-Parkinson-White syndrome

cealed WPW, and manifest WPW syndrome.\textsuperscript{24} Frequent tachycardias seem to promote an electrical remodeling and an increased atrial vulnerability to AF. For example, AVRT can increase atrial vulnerability as a result of a shortened atrial cycle length, increased sympathetic tone and atrial stretch due to hemodynamic changes that occur during AVRT. In this regard, Chen et al\textsuperscript{23} observed that the cycle length of reciprocating tachycardia at the time of electrophysiologic study was significantly shorter in WPW patients with than without AF. This finding suggests that it is easier to develop AF in a rapid episode of sustained AVRT.

Successful surgical or transcatheter ablation of the AP in patients without organic heart disease has been demonstrated to prevent future occurrence of AF in the majority of patients.\textsuperscript{11, 13} This fact is well documented by long-term follow-up studies after successful AP ablation that demonstrated significantly reduced incidences of spontaneous AF. The recurrence rate of spontaneous AF after successful ablation of the AP is reported to be in the range of 6\% to 10\%.\textsuperscript{11-13} However, Hamada et al. made a very interesting observation in this respect. They observed that clinical episodes of AF recurred in 71\% of their patients whose AF remained inducible immediately postablation, however, in none of the patients who remained uninducible postablation.\textsuperscript{26} Therefore, there is a high incidence of AF recurrence in a subgroup of patients whose AF remained inducible despite successful ablation of the AP. A detailed examination of this subgroup of patients prone to develop AF could shed more light in the understanding of the mechanisms for the genesis of AF in WPW patients despite successful AP ablation.

Atrial double potentials and retrograde AP conduction.

NHsieh et al\textsuperscript{17} investigated the influence of atrial double potentials in the genesis of AF in patients with WPW syndrome. Double atrial potentials recorded in the coronary sinus are not an unusual phenomenon in patients with supraventricular tachyarrhythmias, and they have shown to potentiate the occurrence of atrial tachycardias. They demonstrated that patients with the WPW syndrome, especially with a left lateral bypass tract, had a higher incidence of double atrial potentials and induced AF than patients with AVNRT. Furthermore, WPW patients with double atrial potentials had a higher incidence of induced AF than those WPW patients without double atrial potentials. Campbell et al\textsuperscript{23} demonstrated a high incidence rate of AF that was initiated with incremental right ventricular pacing and premature ventricular contraction (PVC). They described in detail the role of retrograde multiple AP as a mechanism of premature atrial contraction that initiates atrial repetitive firing or intratrial reentry in the vulnerable period of the atrium during AVRT.\textsuperscript{23} They stated that intermittent retrograde conduction over a second AP with faster conduction caused early atrial depolarization in a critical and vulnerable period of the atrium, setting the scenario for reentry to occur.

Spontaneous occurrence of PVC depolarizes the atrium in a retrograde manner that can cause AF to develop. Iesaka et al\textsuperscript{27} hypothesized that during AVRT, the complex excitation inputs into the atrium over the retrograde multiple or multifiber AP could trigger AF. They identified retrograde multiple and multifiber AP based on the results of electrophysiologic studies and radiofrequency catheter ablation. The incidence of clinical PAF, as well as, induced AF was significantly greater in the multiple AP patients. However, the incidence of clinical AVRT was similar between multiple and single AP.
patients. The incidence of AF initiated during ventricular pacing and AVRT was significantly greater in the multiple AP patients. A very interesting finding in this study was that AF inducibility during AVRT and ventricular pacing was eliminated by partial ablation of multiple or multifiber AP. However, AVRT inducibility remained in most patients with partial ablation of the multiple or multifiber AP. The incidence of induced AF after total ablation was similar between patients with multiple or single AP. The authors based on their findings indicate that the existence of a retrograde multiple or multifiber AP is strongly related to AF inducibility. In addition, the complex excitation inputs into the atrium over the retrograde multiple or multifiber AP is necessary to trigger AF. Retrograde conduction of PVCs to the atrium in the WPW syndrome caused multiple episodes of PAF in a patient without previous arrhythmias after having a myocardial infarction. During the electrophysiological study the patient presented two spontaneous episodes of AF initiated by PVC conducted to the atria through the AP. After successful catheter ablation of the AP the patient did not present arrhythmia recurrences, although he had multiple PVCs recorded in a 24 Hs Holter monitoring. It may be argued that atrial vulnerability could be a predisposing factor in this kind of patients with a previous myocardial infarction. The impairment of the diastolic left ventricular function could modify the electrophysiological properties of the atria because of an increase in atrial pressure and atrial stretch. However, the fact that the patient did not have AF episodes after catheter ablation of the AP is against this mechanism being the only element responsible for the arrhythmia episodes. This interesting single case clearly demonstrates how complex is the mechanism to develop AF in the WPW syndrome. The authors hypothesize that PVCs with a short coupling interval resulted in VA conduction to the atria and activated the left atrium during the atrial vulnerable phase, thereby precipitating the onset of AF. This hypothesis is supported by two facts: first, AF episodes were experienced only after myocardial infarction in the presence of an AP. This could be related to a possible increase in the appearance of PVCs with different origins and coupling intervals. Second, new AF episodes were not experienced after successful AP ablation despite the fact that Holter monitoring performed after ablation demonstrated the presence of frequent polymorphic PVCs. In this regard, Jackman et al. observed multiple retrograde conductions over separate AP branches during AVRT and re-entry originating from the branching networks. They indicated that microreentry mimicking atrial flutter or fibrillation could originate within the branching networks of the AP strands and that this may account for the unusually high incidence of AF in the WPW syndrome. In their study, they utilized closely spaced orthogonal catheter electrodes in the coronary sinus and found electrophysiologic evidence for a branching or multifiber structure of the left free wall AP. However, this finding has not been confirmed in a large population. Moreover, this finding was indirectly contradicted by other mapping studies of AF initiation in patients with the WPW syndrome. These two studies demonstrated that the onset of AF was more frequently initiated near the high right atrium regardless of the AP location. Fujimura et al. showed that most episodes of AF started at a high right atrial site regardless of AP location, with only 19% of AF episodes starting at the electrode site in the coronary sinus closest to the AP.

Intraatrial wavefront collision and antegrade AP conduction

There are several studies that stressed the relation between antegrade conduction properties of the AP and AF in the WPW syndrome. Ong et al. performed an atrial mapping study using a multiple electrode array during surgery and suggested a possible mechanism of sustaining atrial fibrillation in patients with WPW syndrome. They demonstrated that wavefront collisions between incoming atrial wavefronts via an AP during non-preexcited beats generated new wavefronts to help perpetuate AF. This concept of intraatrial wavefront collision possibly explains susceptibility to AF in patients with multiple AP. Multiple and asynchronous wavefronts could be generated by conduction over multiple AP or widely separated strands forming multifiber AP during AVRT. The wavefronts collision in the atrium could be a mechanism for induction and perpetuation of AF. Although, it seems a plausible conception the exact electrophysiologic mechanism remains to be clarified in detail.

Fujimura et al. observed that the antegrade AP effective refractory period (ERP) was shorter in
the group with AF than in the control group, and that there were no significant differences in retrograde properties. Della Bella et al. also reported similar findings. They found that the anterograde ERP of the AP was significantly shorter in WPW patients with spontaneous AF than in those WPW patients without spontaneous AF. They also found that AF was more frequent in patients with manifest WPW than in those with concealed WPW syndrome. These findings suggest that the retrograde conduction properties of a single AP are not the critical determinants of AF. The study by Asano et al. is in accord with this concept. Although they studied symptomatic and asymptomatic patients, they found that the incidence of spontaneous AF in the manifest WPW group was higher than in the concealed WPW group. However, this was not the same for the induction of AVRT in these two groups. The induction of AVRT was 75% in the manifest WPW group compared to 100% in the concealed WPW group. The mean AVRT cycle length was shorter in patients with concealed WPW than in the manifest WPW patients. This fact does not explain the lower incidence of AF in the concealed WPW group, since shortening of the cycle length is known to increase atrial vulnerability. Therefore, the genesis of AF in the WPW syndrome can not be solely attributed to the occurrence of AVRT. Intra-atrial or inter-atrial conduction disturbances may be a possible explanation for the longer cycle length of AVRT in patients with manifest WPW syndrome. The anterograde AP conduction properties distinguished patients with and without AF. It is known that a shorter anterograde AP ERP allows faster ventricular rates during AF, therefore, the associated atrial stretch and hypoxia may contribute to sustaining the arrhythmia.

Atrial structural heterogeneities at the AP insertion. There is no detailed data on the structure of atrial tissue around the AP available currently. Most of the histopathological studies in patients with WPW syndrome have dealt with the AP itself with no special description of the atrial tissue at the insertion of the AP. It is well known that structural heterogeneities play an important role in atrial reentry due to the influence of unidirectional block and conduction delay. Thus, it is possible that in patients with WPW syndrome, the increased structural heterogeneity created by the presence of the AP may play a role in the generation and maintenance of atrial reentry. In experimental studies of the canine heart model of WPW syndrome, structural differences in the AP apparently affect refractoriness and conduction properties of the AP. It was postulated that the AP is the result of an embryologic fault in the formation of fibrous tissue separating the atria and the ventricles. Therefore, developmental abnormalities may also be present in the atrial tissue adjacent to the AP, which may affect the functional electrical properties of the atrium close to the AP insertion. Dispersion of the refractory periods and conduction disturbances apparently occur around the interconnection between different tissues such as the atrium and the AP. Either anatomical or functional properties of the atrial tissue near the AP may play a role in the genesis of AF and may contribute to the
different incidence of atrial vulnerability and AF in the WPW syndrome.

The anatomy, direction and location of the AP may play a role in the genesis of AF in the WPW syndrome. The AP may run in an oblique course rather than perpendicular to the transverse plane of the atrioventricular groove. As a result, the fibers may have an atrial insertion point that is transversely several centimeters removed from the point of ventricular attachment. The AP may occasionally exist as broad bands of tissue rather than discrete hair-like structures. Other than the anatomy of the AP, the location of the AP is better related to induction of AF. Several studies found different induction rates of AF depending on the exact location of the AP [23-26]. It was shown that patients with an anteroseptal AP had a high rate of inducible arrhythmia (62%). Patients with a right free wall AP had a rather low rate of inducible arrhythmia (21%). Patients with left free wall and posteroseptal AP had a 44% and 36% rate of induction, respectively. Patients with a right-sided AP had a lower inducibility of AVRT and a relatively long retrograde ERP over the AP. This allowed only relatively late PVCs to be conducted retrogradely over the AP to the atrium, which might explain the lower rate of inducibility of AF in these patients.

Intrinsic atrial muscle vulnerability in the WPW syndrome

The persistence of AF in certain patients with WPW syndrome despite the successful abolition of the AP may be explained by the presence of an underlying atrial disease considering the AP as an innocent bystander. 

**Figure 2:** Atrial endocardial mapping sites

The upper part of the figure shows 12 endocardial mapping sites in the right atrium. The atrial endocardial electrograms were recorded in each patient from the anterior, lateral, posterior and medial aspects of the high right atrium (a,b,c,d), mid right atrium (e,f,g,h) and low right atrium (i,j,k,l). SVC= superior vena cava; IVC= inferior vena cava; Ao= aorta; PA= pulmonary artery; LA= left atrium; RV= right ventricle; LV= left ventricle.

The lower part of the figure show 2 atrial endocardial electrograms to distinguish an abnormal atrial electrogram (A) with 10 fragmented deflections and 130 ms in duration, from a normal atrial electrogram (B) with 2 deflections and 80 ms in duration. Reprinted with permission from Centurion OA et al. Influence of advancing age on fractionated right atrial endocardial electrograms. Am J Cardiol 2005;96:239-242.
Patients with the WPW syndrome associated with AF were found to have a high incidence of electrophysiological abnormalities of the atrial muscle. This intrinsic atrial muscle vulnerability certainly plays an important role in the occurrence of AF in these patients. AF has a particular prognostic significance in patients with the WPW syndrome, and its incidence is unusually high in the absence of any clinical evidence of organic heart disease. Ablation of the AP is very effective in the abolition of conduction through the AP, and it has been shown that recurrences of AF after successful AP ablation occur at a low incidence. Haissaguerre et al have documented a reduction in AF inducibility following catheter ablation in patients with WPW syndrome. Sharma et al found a reduction in AF inducibility after surgical ablation. Other studies have also demonstrated a reduction in AF inducibility after successful AP ablation. Indeed, ablation of the AP is very effective in the elimination of clinical episodes of AVRT and AF; however, it does not prevent recurrences of AF in certain patients. Therefore, it is very important to determine all possible mechanisms for the development of AF in the WPW syndrome patients. An explanation suggested, in certain patients, is the presence of an underlying intrinsic atrial disease.

In the absence of structural atrial disease, clinical electrophysiologic studies have not clearly defined atrial features that can predict spontaneous occurrence of AF. Some investigators have studied the atrial vulnerability showing that the induction of sustained episodes of AF was more frequent in patients with a history of spontaneous AF. Others have analyzed the atrial electrophysiological substrate that may predispose to AF. They evaluated atrial refractoriness, intra-atrial and interatrial conduction times, and several electrophysiological parameters elicited with programmed atrial stimulation with single extrastimulus. Important information about intrinsic atrial muscle vulnerability was obtained by atrial endocardial electrogams morphology recorded by atrial endocardial catheter mapping during sinus rhythm (Figure 2).

Atrial refractoriness. Nonhomogeneity of ERP of contiguous cells causes a slower conduction velocity of the stimulus that propagates through partially repolarized cells, allowing the genesis of unidirectional blocks and the appearance of multiple reentries. In experimental studies with a computer model of AF, Moe et al demonstrated that an atrial condition characterized by short and nonhomogeneous atrial ERP, associated to intra-atrial conduction disturbances, is considered an important factor in the appearance and maintenance of AF. These findings were later corroborated by other investigators. In a landmark paper from Allessie’s laboratory, Konings et al described various types of AF in humans with the WPW syndrome. They induced AF by rapid atrial pacing in 25 patients with WPW syndrome undergoing surgery for interruption of their AP. The free wall of the right atrium was mapped using a spoon-shaped electrode containing 244 unipolar electrodes. Based on the complexity of atrial activation, they defined three types of AF. In type I (40%), single broad wave fronts propagated uniformly across the RA. Type II (32%) was characterized by one or two nonuniformly conducting wavelets, whereas in type III (28%), activation of the RA was highly fragmented and showed three or more different wavelets that frequently changed their direction of propagation as a result of numerous arcs of functional conduction block. They found significant differences among the three types of AF in median intervals, variation in AF intervals, incidence of electrical inactivity, and reentry, and average conduction velocity during AF. Therefore, they could demonstrate that from type I to type III, the frequency and irregularity of AF increased, and the incidence of continuous electrical activity and reentry became higher. These various types of AF in humans appear to be characterized by different numbers and dimensions of the intra-atrial reentrant circuits. Clinical electrophysiology has identified several atrial features that may...
lead to the appearance and maintainance of AF, sometimes with conflicting results. These different results may be due to multiple factors, including different stimulation protocols and nonhomogeneous groups of patients. Some investigators reported short atrial ERP in patients with PAF, while others did not. Thus, it is controversial to utilize atrial ERP as a useful measure of atrial vulnerability. Several studies have shown conflicting results regarding refractoriness in AF. The measurement of atrial ERP in AF patients in only one site does not necessarily represent atrial refractoriness since these patients have a wide dispersion of atrial refractoriness. Therefore, it is not comparable in different sites of the atrium neither in different patients. It has been shown that the atrial ERP physiologically shortens with increasing heart rate. This rate adaptation is less evident in AF patients, as well as, in isolated cellular preparations. Riccardi et al evaluated the rate adaptation of ERP in WPW patients with and without AF, analyzing the gradient between two different atrial pacing cycle lengths. They found that the functional refractory period increased in most AF patients (81%) with an increase of the atrial stimulation rate, while this absent rate adaptation was observed only in few patients (24%) without AF. The functional refractory period expresses the time needed for the electrical stimulus to be conducted from the distal pair of electrodes to the proximal pair of electrodes, so it is a local intraatrial conduction parameter in a relative refractory condition. The fact that WPW patients with AF showed higher values of refractory periods which became even higher with increasing heart rate, suggests the concept of AF as based on slow conduction through partially recovered myocardium.

The ablation technique utilized for the AP ablation may produce different results regarding atrial vulnerability and AF induction. Muraoka et al observed that the atrial ERP was prolonged, the zones of atrial vulnerability were narrowed and the induction rate of AF was reduced following elimination of the AP by surgical cryoablation. However, these parameters were unchanged in patients that had their AP ablated by radiofrequency catheter ablation. Although, they could not clearly explain these different findings with the different ablation techniques, they argued that the prolongation of the atrial ERP played a key factor in the decrease of the AF induction rate in those patients ablated by surgical cryoablation. Probably, the larger myocardial injury created by surgical cryoablation, or dissection of the atrioventricular sulcus may be related to the lower incidence of AF. Another factor that might have influenced is that the radiofrequency applications were mainly delivered on the ventricular side of the atrioventricular valve annulus, while surgical cryoablations were performed directly on the atrial tissue. Therefore, the injury of the atrial tissue was greater in this latter group of patients. The resulting prolongation of the atrial ERP may prevent capture of short coupled premature atrial excitation and, therefore, may result in prevention of atrial electrical disorganization and AF. Tsuji et al also showed that the occurrence of AF depends on a short atrial ERP, and AF mainly originated in the high right atrium regardless of the AP location.

Atrial response to programmed stimulation. The induction of AF during electrophysiological testing makes its evaluation difficult and may lead to the undesirable need for antiarrhythmic agents or electrical cardioversion. On the other hand, the induction of AF with programmed atrial stimulation with single extra-stimulus is not always successful even in patients with clinically documented AF. Besides the use of rapid burst pacing of the atrium may induce nonspecific AF. Therefore, the analysis of other atrial electrophysiological parameters is useful as indicators of potential atrial vulnerability. There are several atrial electrophysiological parameters relating to AF which are elicited with atrial programmed stimulation. The inducibility of AF, fragmented atrial activity, repetitive atrial firing, and intraatrial
conduction delay has been previously examined. With atrial programmed stimulation, transient AF was induced in 83% of the WPW patients with a history of clinically documented paroxysmal AF. 14

Although, for most WPW patients the AP ablation is a curative solution for the AVRT, sustained episodes of AF still occur in certain patients despite the disappearance of the AP. In order to clearly assess the intrinsic atrial vulnerability in WPW patients is necessary to perform a complete electrophysiologic study before and after AP ablation. Hamada et al 26 studied the existing electrophysiologic differences between WPW patients whose AF remained inducible, and those with AF that could not be induced following AP ablation. They demonstrated that WPW patients with AF had significantly longer maximal atrial conduction delay and wider conduction delay zone than controls. Considering only the patients with WPW syndrome and AF, ablation of the AP did not change the maximal atrial conduction delay and conduction delay zone in those patients whose AF remained inducible. However, AP ablation normalized the maximal atrial conduction delay and conduction delay zone in those patients whose AF remained noninducible. There was no significant difference in these parameters compared to controls. Therefore, they suggest that there is definitive electrophysiologic evidence of two different mechanisms for AF in the WPW syndrome, one

Figure 3: Induction of fragmented atrial activity (FAA)

An example of the induction of fragmented atrial activity (FAA) as defined in the text. Surface electrocardiographic lead V1 is shown together with intracardiac electrograms from the high lateral right atrium (HLRA), and distal coronary sinus (CSD). S1 and S2 are, respectively, the driving and premature stimulus artifacts. The basic drive cycle length (BCL) was 500 ms and the coupling interval (S1 S2 interval) was 230 ms. There is a prolongation of the duration of atrial activity from 110 to 200 ms in the HLRA. CD indicates interatrial conduction delay. Reprinted with permission from Konoe A, Fukatani M, Tanigawa M, et al. Electrophysiological abnormalities of the atrial muscle in patients with manifest Wolff-Parkinson-White syndrome associated with paroxysmal atrial fibrillation. PACE 1992;15:1040-1052.
is reversible and AP-dependent atrial vulnerability and the other is intrinsic and AP-independent atrial vulnerability. It is very interesting the finding that some WPW patients with AF that undergo AP ablation have their atrial vulnerability parameters normalized to the point that AF is no longer inducible. This strongly suggests the presence of reversible and AP-dependent atrial vulnerability as the mechanism for AF in the WPW syndrome. Now the question is why does the AP causes increased atrial vulnerability that is reversible in some patients but not reversible in others? There are only speculations to try to answer this question. The AP refractoriness might play a certain role. There is a tendency to shorter AP ERP in the anterograde and retrograde conduction in those patients whose AF remained noninducible. Nevertheless, it is difficult to understand how a small AP could have such a profound effect on overall atrial conduction. Although the mechanisms remain unexplained, it was demonstrated that WPW patients with AF appear to have both reversible and intrinsic AP-related atrial vulnerability. The WPW patients with AF have intrinsic atrial muscle abnormalities and most of them present abnormally prolonged and fractionated atrial electrograms that are recorded with atrial endocardial catheter mapping during sinus rhythm.

The role of an atrial firing focus as a trigger for AF initiation in the WPW syndrome is not well documented yet. AF can also be initiated by ectopic beats originating from the pulmonary veins, and elsewhere. The pulmonary veins are well established as the dominant sources of triggers in paroxysmal AF, in addition to their contribution to maintenance of AF. However, there is no

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**Figure 4: Induction of interatrial conduction delay (CD)**

Atrial extrastimulus testing in a patient with paroxysmal AF showing atrial conduction delay (CD). S1 and A1 refer to the driving stimulus and the atrial electrogram, respectively, of the basic drive beat. S2 and A2 refer to the stimulus artifact and the atrial electrogram, respectively, of the induced premature beat. The atrial extrastimulus was programmed at a coupling interval of 190 ms with a driving cycle length of 500 ms. The S1-A1 interval in the distal coronary sinus was 135 ms. At the premature beat, S2-A2 interval prolonged to 230 msec. The maximum CD in this patient was 95 msec. This atrial CD led to repetitive atrial firing (RAF). HRA indicates high right lateral atrium; RAA, right atrial appendage; HBE, His bundle area; and Csd, distal coronary sinus. Reprinted with permission from Isomoto S, Centurión OA, Shibata R, et al. The effects of aging on the refractoriness and conduction of the atrium in patients with lone paroxysmal atrial fibrillation revealed with programmed atrial stimulation. Rev Soc Parag Cardiol 2005;3:29-30.
available data suggesting that firing from the pulmonary veins is the main source of recurrent AF in WPW patients that had their AP ablated. The elimination of triggers of AF requires spontaneous firing to be readily identifiable during an ablation procedure. Ablation targeting the pulmonary vein-left atrial junction is effective in isolating the left atrium from proarrhythmic pulmonary vein activity. Despite the latest progress in AF ablation, there is limited knowledge of how to identify, map, and ablate the culprit atrial substrate in an individual patient, because AF is generally associated with locally complex electrograms of undefinable timing and sequence [43]. This heterogeneity of substrate may explain why no single predetermined ablation technique is effective for all patients across the entire spectrum of AF. To the best of our knowledge, there is no detailed study addressing ablation of the pulmonary veins to suppress recurrent AF in WPW patients that had already undergone successful AP ablation.

**Fragmented atrial activity**

It is the widening of the local atrial electrogram in response to an atrial programmed extrastimulus testing. The mechanism producing fragmented atrial activity is not clear. Fragmented atrial activity might represent local continuous activity in response to premature beats. A single atrial extrastimulus delivered with a critical coupling interval often results in widening of the local atrial electrogram. Ohe et al. defined it as the occurrence of disorganized atrial activity ≥150% of the duration of the local atrial electrogram of the basic beat recorded in the high right atrium (Figure 3). Patients with WPW syndrome associated with AF have a wider fragmented atrial activity zone than those WPW patients without AF. This suggests that the widening of the fragmented atrial activity zone is closely related to the occurrence of AF in patients with WPW syndrome.

*Figure 5: Induction of repetitive atrial firing (RAF)*

An example of the induction of repetitive atrial firing (RAF) as defined in the text. Surface electrocardiographic lead V1 is shown together with intracardiac electrograms from the high lateral right atrium (HLRA), and distal coronary sinus (Csd). S1 and S2 are, respectively, the driving and premature stimulus artifacts. The basic drive cycle length (BCL) was 500 ms and the coupling interval (S1 S2 interval) was 230 ms. Reprinted with permission from Konoe A, Fukatani M, Tanigawa M, et al. Electrophysiological abnormalities of the atrial muscle in patients with manifest Wolff-Parkinson-White syndrome associated with paroxysmal atrial fibrillation. PACE 1992;15:1040-1052.
Atrial conduction delay

Interatrial conduction delay, measured from the stimulus artifact to the atrial electrogram at the distal coronary sinus level, reflects an actual interatrial conduction delay that is not influenced by local latency at the site of stimulation, since the stimulation is performed in the high right atrium. Interatrial conduction delay was defined as an increase in the S2 through A2 interval of the extrastimulus >20 ms compared with the S1 through A1 of the basic drive (Figure 4). Aytemir et al demonstrated a significant increased in the maximum P wave duration and P wave dispersion af-

Figure 6: Normal atrial endocardial electrograms

Examples of measurement of the duration (top), and the number of deflections (bottom) of the intraatrial electrogram. Surface electrocardiographic lead V1 is shown together with the right atrial electrogram (RA). In the top panel, the arrows show the onset and the end of the intraatrial electrogram. In the bottom panel, the arrows show the deflections of the intraatrial electrograms. Reprinted with permission from Konoe A, Fukatani M, Tanigawa M, et al. Electrophysiological abnormalities of the atrial muscle in patients with manifest Wolff-Parkinson-White syndrome associated with paroxysmal atrial fibrillation. PACE 1992;15:1040-1052.
ter AP ablation reflecting more inhomogeneous and prolonged atrial conduction in patients with the WPW syndrome and AF episodes. Therefore, this increased P max and higher P wave dispersion values in patients with previous clinical AF episodes suggest the important role of inhomogeneous and discontinuous propagation of sinus impulses in the development of AF in patients with the WPW syndrome. They demonstrated that the maximum P-wave duration and P-wave dispersion are independent predictors of recurrence of AF in patients with the WPW syndrome after successful radiofrequency catheter ablation of the AP. Hiraki et al. demonstrated in a prospective study that P wave signal-averaged electrocardiography predicts recurrence of AF in patients with WPW syndrome who underwent successful catheter ablation. In order to reduce interatrial conduction delay and decrease atrial vulnerability, bi-atrial pacing was developed as a technique of simultaneous activation of the right atrium and left atrium. It has been reported to prevent the recurrence of AF in paced patients with marked interatrial conduction delay. Thus, these facts indicate that the interatrial conduction delay can play an important role in the onset of AF. It was shown that WPW patients associated with AF have a wider interatrial conduction delay zone than those WPW patients without AF. This suggests that the patients with AF would have a greater tendency to develop slow interatrial conduction in the setting of WPW syndrome.

Repetitive atrial firing

Repetitive atrial firing is defined as the occurrence of two or more successive atrial complexes with a return cycle of <250 ms and a subsequent cycle length of <300 ms (Figure 5). The maxi-
maximum conduction delay refers to the maximum difference between the conduction time of the extrastimulus and that of the basic driven beat measured at the distal coronary sinus. These results suggest that the occurrence of repetitive atrial firing requires the presence of a short refractory period at the pacing site and prolongation of the maximum conduction delay. It was shown that WPW patients associated with AF have a wider repetitive atrial firing zone than those WPW patients without AF. This suggests that the patients with AF would have a greater tendency to develop repetitive atrial firing in response to an atrial premature contraction in the setting of WPW syndrome.

Abnormal atrial endocardial electrograms in sinus rhythm

The fractionated and prolonged duration of the abnormal atrial endocardial electrograms may indicate the presence of areas that possibly predispose the occurrence of reentrant circuits. At the time of atrial endocardial catheter mapping during sinus rhythm, the recording of an abnormally prolonged and fractionated right atrial electrogram may reflect slow and anisotropic conduction through a diseased atrial muscle. Tanigawa et al made the first attempt to define quantitative characteristics of normal atrial endocardial electrograms with a catheter electrode mapping technique of the right atrium during sinus rhythm. They recorded atrial endocardial electrograms from the anterior, lateral, posterior and medial aspects of the high, middle, and low right atrium. The duration of the atrial electrograms was defined as the time from the beginning of the earliest electrical activity that deviated from the stable baseline to the last point of the atrial electrogram that crossed the baseline. The number of fragmented deflections was measured by counting the number of downward deflections (Figure 6). An abnormal atrial electrogram was defined as that having a duration ≥100 ms and 8 or more fragmented deflections (Figure 7). In a pathological study of fatal cases with WPW syndrome and sudden cardiac death, Basso et al observed a 50% incidence of isolated atrial myocarditis. Sudden death was the first manifestation of the disease in 40% of the cases. This finding of atrial inflammatory infiltrates in patients with the WPW syndrome supports the hypothesis that atrial inflammatory foci may act as a trigger of AF, which in turn precipitates sudden cardiac death due to rapid ventricular conduction that degenerates into ventricular fibrillation.

Electrophysiological abnormalities of the atrial muscle in the WPW syndrome were identified by endocardial catheter mapping of the right atrium during sinus rhythm. Abnormally prolonged and fractionated atrial electrograms were frequently (83%) recorded in WPW patients associated with AF. However, these abnormal atrial electrograms were significantly less common (10%) in WPW patients without any evidence of AF. These electrophysiological abnormalities of the atrial muscle were more frequently and significantly found in the high right atrial sites distant from the atrioventricular groove and AF location. Since abnormally prolonged and fractionated atrial electrograms were also frequently found in patients with AF not associated to the WPW syndrome, it is suggested that the mechanism of abnormal atrial electrograms may not relate to the AP. Therefore, patients with the WPW syndrome associated with AF have a significantly high incidence of electrophysiological abnormalities of the atrial muscle which certainly play an important role in the occurrence of AF in these patients.

As suggested by one group, visualization and treatment needs further clarification.

The role of autonomic tone and advance age

Autonomic modulation of accessory pathway refractoriness and conduction became evident in experiments involving exercise, postural changes, and drugs. Time- and frequency-domain analysis of heart period variability performed in patients with paroxysmal AF suggests that autonomic modulation as abnormal cardiac sympathetic activity may be related to the onset of AF in patients with WPW syndrome. It is relatively frequent to observe in the clinical setting that the onset of AF is associated to exercise or emotional stress in patients with WPW syndrome. Honda T et al. demonstrated an increased sympathoadrenal activity in WPW patients associated with AF, and concluded that...
augmented sympathoadrenal activity seems to play an important role in the genesis of AF in this syndrome. Patients with overt pre-excitation and spontaneous AF appear to exhibit predominance of sympathetic activity and vagal withdrawal which is consistent with shorter accessory pathway effective refractory periods, shorter cycle length of orthodromic AVRT, and shorter pre-excited RR intervals during AF in these patients.

Demonstration of electrophysiologic changes in the atrial muscle with age is consistent with the concept that electrical functional changes are related to histologic changes of the conduction system of the aging heart. Becker AE found that the structural atrial changes are fibrofatty replacement and patchy replacement fibrosis that involve the myocardial sleeves on pulmonary veins and sites of rapid conduction, such as the terminal crest and Bachmann’s bundle. Dagres N et al studied 116 consecutive patients with manifest or concealed accessory pathways and documented paroxysmal AF who underwent radiofrequency catheter ablation, and demonstrated that the recurrence rate of AF following successful ablation shows an age-related increase, being low in patients younger than 50 years of age and high in the older patients. The incidence of recurrent AF showed a statistical significant increase in patients older than 50 years (35%) as compare to those younger ones (12%). The recurrence rate of atrial fibrillation was even higher in patients older than 60 years (55%).

Conclusion

AF has a different dimension in the context of the WPW syndrome. Indeed, it may be life-threatening if an extremely rapid ventricular response develops in the presence of a fast AP degenerating into ventricular fibrillation. Therefore, it is very important to clearly understand the mechanisms involved in the development of AF in the WPW syndrome. AF has a reserved prognostic significance in patients with the WPW syndrome, and its incidence is relatively high in the absence of any clinical evidence of organic heart disease. Several mechanisms responsible for the genesis of AF in WPW patients were hypothesized, namely, spontaneous degeneration of AVRT into AF, electrical properties of the AP, the effects of AP on atrial architecture, the increased sympathetic activity and vagal withdrawal, the influence of advancing age, and intrinsic atrial muscle vulnerability. The existence of a retrograde multiple or multifiber AP is strongly related to AF inducibility, and the complex excitation inputs into the atrium over the retrograde multiple or multifiber AP facilitate the development of AF in WPW patients. The decrease incidence of AF after successful elimination of the AP, suggest that the AP itself may play an important role in the initiation of AF. However, AF still occurs in some patients with the WPW syndrome even after successful definitive elimination of the AP. There is an important evidence of an underlying atrial muscle disease in patients with the WPW syndrome. Abnormally prolonged and fractionated atrial endocardial electrograms are observed with a significantly higher incidence in WPW patients with documented episodes of AF. These electrophysiological abnormalities of the atrial muscle certainly play an important role in the occurrence of AF in these patients. Furthermore, the electrophysiological findings of altered atrial refractoriness, increased induction of repetitive atrial firing and increased intraatrial conduction delay suggest an intrinsic atrial vulnerability as the mechanism of AF in certain patients with the WPW syndrome. The atrial vulnerability in the WPW syndrome seems to be either, reversible and AP-dependent, or intrinsic and AP-independent atrial vulnerability. It is very interesting the finding that some WPW patients with AF that undergo AP ablation have their atrial vulnerability parameters normalized to the point that AF is no longer inducible. These facts strongly suggest the presence of different mechanisms of AF development in different patients with the WPW syndrome. A detailed electrophysiological examination before and after AP ablation could shed insight into the understanding of the mechanism for the genesis of AF in individual patients with the WPW syndrome.

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