Atrial Fibrillation

Preservation of the Anterior Fat Pad Paradoxically Decreases the Incidence of Postoperative Atrial Fibrillation in Humans

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OBJECTIVES
The goal of this study was to determine if parasympathetic nerves in the anterior fat pad (FP) can be stimulated at the time of coronary artery bypass surgery (CABG), and if dissection of this FP decreases the incidence of postoperative atrial fibrillation (AF).

BACKGROUND
The human anterior epicardial FP contains parasympathetic ganglia and is often dissected during CABG. Changes in parasympathetic tone influence the incidence of AF.

METHODS
Fifty-five patients undergoing CABG were randomized to anterior FP preservation (group A) or dissection (group B). Nerve stimulation was applied to the FP before and after surgery. Sinus cycle length (CL) was measured during stimulation. The incidence of postoperative AF was recorded.

RESULTS
Of the 55 patients enrolled, 26 patients were randomized to group A, and 29 patients were randomized to group B. In all of the 55 patients, the FP was identified before initiating cardiopulmonary bypass by CL prolongation with stimulation (865.5 ± 11006 ms vs. 957.9 ± 147.9 ms, baseline vs. stimulation, p < 0.001). In group A, stimulation at the conclusion of surgery increased sinus CL (801.8 ± 166.4 ms vs. 890.9 ± 155.1 ms, baseline vs. stimulation, p < 0.001). In group B, repeat stimulation failed to increase sinus CL (853.6 ± 201.6 ms vs. 841.4 ± 198.4 ms, baseline vs. stimulation, p = NS). The incidence of postoperative AF in group A (7%) was significantly less than that in group B (37%) (p < 0.01).

CONCLUSIONS
This is the first study demonstrating that direct stimulation of the human anterior epicardial FP slows sinus CL. This parasympathetic effect is eliminated with FP dissection. Preservation of the human anterior epicardial FP during CABG decreases incidence of postoperative AF. (J Am Coll Cardiol 2004;43:994–1000) © 2004 by the American College of Cardiology Foundation

Atrial fibrillation (AF) after coronary artery bypass grafting (CABG) prolongs hospital stay and increases cost of care by an estimated 900 million U.S. dollars per year (1–4). The incidence of postoperative AF ranges from 20% to 45% (5). Risk factors for AF include advanced age, gender, and depressed left ventricular function. However, risk stratification has done little to prevent postoperative AF (6–8).

Antiarrhythmic medications have been used to suppress AF, but their effectiveness remains limited (9–11). In contrast, several large trials have shown a decrease in postoperative AF in patients receiving beta-receptor antagonists prooperatively (12–14). As these medications are known to decrease sympathetic tone, attention has focused on the potential role of the autonomic nervous system in the mechanism of postoperative AF.

The effect of vagal stimulation on atrial refractoriness is well described. Atrial refractoriness shortens, and heterogeneity of refractoriness increases, thereby increasing susceptibility to AF. However, it is unknown if the parasympathetic nervous system plays a role in postoperative AF.

The human epicardial fat pads (FPs) contain parasympathetic ganglia (15). Vagal pathways in the two posterior epicardial FPs have recently been characterized. The FP located at the superior vena caval-atrial junction (superior vena caval-atrial FP) contains postganglionic fibers that lead to the sinoatrial (SA) node. The FP located at the pulmonary vein-left atrium (pulmonary vein-left atrium FP) contains postganglionic fibers that lead to the atrioventricular node (16–18). These FPs are analogous to the epicardial FPs previously characterized in dogs (19–22). It has recently been determined that dogs also possess a third, anterior FP that contains the vagal neurons that lead to, and possibly, control the two posterior FPs. Ablation of this third FP disrupted vagal influences to both the SA and atrioventricular nodes, and decreased the susceptibility of the dog to AF by presumably removing vagal effects on the atria (23). A FP

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in humans analogous to the third FP in dogs has not yet been characterized.

In the aortopulmonary window in humans, there is an anterior epicardial FP that is routinely dissected in CABG. This anterior FP is often completely dissected, as it is located where the aortic cross-clamp is placed. Although this FP has been shown to contain nervous tissue, its parasympathetic innervation has not been defined (5,24). We hypothesized that: 1) this FP contributes to the parasympathetic innervation of the human heart, and 2) if this FP is analogous to the third FP found in canines, dissection of this FP may subsequently decrease the incidence of postoperative AF.

METHODS

Patient population. Human studies were performed in consenting adults in the operating rooms of the participating institutions. The protocol was approved by the institutional review board of each hospital. Written, informed consent was obtained from all patients. From May 2001 to September 2002, patients undergoing CABG with no evidence of preoperative AF were screened for enrollment in this study. Of the 62 consecutive screened patients, 55 were enrolled in the study. The primary reasons for non-enrollment were patient refusal and operating room scheduling constraints. All patients underwent standard median sternotomy CABG. Patients undergoing other types of cardiac surgery, including minimally invasive surgery or valve replacement, were excluded. Patients with previous open-heart surgery, history of AF, or present use of class I or III antiarrhythmic medications were excluded. Patients taking digoxin, beta-receptor antagonists, or calcium channel blockers were included.

Epicardial FP identification. All patients underwent standard median sternotomy CABG. No patients received pancuronium (25). After the anterior surface of the heart was visualized, the anterior FP was identified (Fig. 1). Baseline nerve stimulation of this FP was performed as described below, while recording sinus cycle length (CL) (Fig. 2).

Experimental protocol. Nerve stimulation was performed on the anterior epicardial FP by means of a custom-designed electrode. This electrode was applied under direct visualization by the surgeon during CABG. The interelectrode distance was 5 mm. Nerves within the anterior epicardial FP were stimulated via a programmable stimulator (Grass, S-8800, Quincy, Massachusetts). Stimulation was performed for 20 s using a 0.5 to 0.8 ms pulse width, 40 mA current, and 50 to 80 ms interpulse interval. A Medtronic (Minneapolis, Minnesota) stimulus isolation unit was used to ensure constant current strength. Sinus CL was measured with continuous electrocardiographic recording during nerve stimulation. Nerve stimulation was performed over a minimum of two separate periods, and the sinus CLs were calculated by averaging 5 CLs before and during all stimulations. Venous cannulation was performed by way of the right atrial appendage. The aorta was then cross-clamped with attention to prevent damage to the anterior FP. If the patient was randomized to dissection, the anterior FP was dissected (20 to 40 s of electrocautery at 30 to 50 mA) before aortic cross-clamping (Fig. 3). To limit variability between dissection and surgical techniques, this study was limited to two surgeons. Cardiac protection was achieved with the administration of antegrade and, occasionally, retrograde cold blood oxygenated or crystalloid cardioplegia.

After the patient was off cardiopulmonary bypass, repeat nerve stimulation was re-applied to the area of the aortopulmonary window (dissected tissue or preserved FP) using...
the identical parameters and protocol as baseline. In three patients, repeat nerve stimulation was performed after intravenous administration of atropine (1 mg) to confirm the elimination of the parasympathetic response. All patients were followed during the postoperative hospital course. The incidence and duration of postoperative AF and AF burden were determined.

**AF.** All patients underwent continuous telemetry monitoring after surgery. All rhythm strips were reviewed and recorded. Cardiologists, blinded to the patient’s randomization group, analyzed all arrhythmias. Postoperative AF was defined as >30 s of AF or hemodynamically significant AF requiring intervention during the postoperative hospitalization. The type of arrhythmias, AF burden, and treatment of arrhythmias were documented in the form of rhythm strips and progress notes. During recording, AF was further defined as sustained (requiring active intervention, including but not limited to cardioversion or antiarrhythmic medication) or nonsustained (multiple self-limiting episodes of AF that were added to calculate AF burden).

**Statistics.** An a priori sample size analysis was performed. Using an effect size of 38%, it was determined that a sample of 54 patients was required to achieve a power of 80%. A paired Student t test was used to analyze the change in sinus CL with nerve stimulation compared with baseline. Incidence of postoperative AF in relation to preservation or dissection of the anterior FP was analyzed using a Fisher exact test. A multivariate regression analysis was also performed.

**RESULTS**

Of the 55 patients enrolled, there were 13 women and 42 men. Twenty-six patients were randomized to anterior FP preservation, and 29 were randomized to anterior FP dissection (usual care). There was no difference between groups in age, ejection fraction, perioperative beta-receptor antagonist use, hypertension, cardiopulmonary bypass pump time, number of bypass grafts, length of stay, or days monitored (Table 1). Five patients were excluded from evaluation of repeat nerve stimulation. Three of these patients received intravenous atropine before repeat nerve stimulation. Two patients were hemodynamically unstable, and repeat nerve stimulation was not feasible. Although repeat intraoperative nerve stimulation was not performed on these five patients, they were still randomized to FP preservation or dissection and followed for incidence of postoperative AF.

As shown in Figures 4a and 5, nerve stimulation significantly prolonged sinus CL in all patients from 865.5 ± 147.9 ms to 957.9 ± 155.1 ms (baseline vs. stimulation, p < 0.001). In patients in whom the anterior FP was preserved, nerve stimulation continued to prolong sinus CL from 801.8 ± 166.4 ms to 890.9 ± 178.2 ms (baseline vs.
stimulation, p < 0.001, Fig. 4b). In patients in whom the anterior FP was dissected, nerve stimulation failed to prolong sinus CL (853.6 ± 201.6 ms to 841.4 ± 198.4 ms, baseline vs. stimulation, p = NS, Fig. 4c). Every patient, at the onset of surgery, had a significant increase in his/her sinus CL with nerve stimulation. Also, selective SA nodal effect was seen, as there was no PR interval prolongation during nerve stimulation. Atrial fibrillation occurred in all patients within the first 72 h after surgery. Of the 26 patients randomized to anterior FP preservation, two developed postoperative AF. Both of these patients had nonsustained AF (∼30 s and ∼1 h). Of the 29 patients randomized to anterior FP dissection, 11 patients developed postoperative AF. Of these 11 patients, seven had sustained AF requiring intervention, while the remaining four had nonsustained AF (AF burden ∼30 s and ∼15 min).

Atrial fibrillation occurred within the first 72 h after surgery in all patients with postoperative AF. The incidence of postoperative AF was significantly greater in patients in whom the FP was dissected (37% vs. 7%, p < 0.01, Fig. 6). A multivariate regression analysis was performed on all variables listed in Table 1. Only FP dissection was predictive of postoperative AF (p = 0.002; odds ratio, 0.72; 95% confidence interval, 0.55 to 0.95).

**DISCUSSION**

This study is the first to evaluate and characterize the parasympathetic innervation of the anterior epicardial FP in humans. Also, it is the first study, to our knowledge, that systematically evaluates the role of this FP and its parasympathetic innervation in the incidence of postoperative AF. Increased vagal tone decreases atrial refractoriness, which increases susceptibility to AF. Dissection of parasympathetic nerve fibers (FP dissection) would be expected to decrease the incidence of AF. Conversely, FP preservation would be expected to increase the incidence of AF. This study demonstrated that preservation of the anterior FP did

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Anterior Fat Pad Preservation (n = 26)</th>
<th>Anterior Fat Pad Dissection (n = 29)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>61 ± 13</td>
<td>62 ± 12</td>
<td>0.83</td>
</tr>
<tr>
<td>Male</td>
<td>190 (73%)</td>
<td>22 (76%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.52 ± 0.13</td>
<td>0.47 ± 0.14</td>
<td>0.15</td>
</tr>
<tr>
<td>Perioperative beta-receptor antagonists</td>
<td>25/26 (96%)</td>
<td>27/29 (93%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Metoprolol 36 ± 18 mg BID (avg. dose ± SD)</td>
<td>4/29 (14%)</td>
<td>24/29 (83%)</td>
<td>0.60</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>3/26 (12%)</td>
<td>4/29 (14%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20/26 (77%)</td>
<td>24/29 (83%)</td>
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</tr>
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<td>Diabetes</td>
<td>9 (35%)</td>
<td>9 (31%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean number of grafts</td>
<td>3.3 ± 0.74</td>
<td>3.7 ± 0.97</td>
<td>0.11</td>
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<tr>
<td>Time of cardiopulmonary bypass (min)</td>
<td>100.6 ± 25</td>
<td>112.8 ± 29</td>
<td>0.11</td>
</tr>
<tr>
<td>Cold blood cardioplegia</td>
<td>15/26 (58%)</td>
<td>17/29 (59%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Days monitored postoperatively</td>
<td>6.38 ± 3.8</td>
<td>7.86 ± 4.7</td>
<td>0.21</td>
</tr>
</tbody>
</table>

avg. = average; BID = twice a day.

Figure 4. (a) Sinus cycle length (ms) at baseline and with nerve stimulation in all patients before coronary artery bypass grafting (CABG). Mean sinus cycle length (ms) with standard deviation at baseline and with nerve stimulation. (b) Sinus length (ms) at baseline and with nerve stimulation after CABG with anterior fat pad preservation. Mean sinus cycle length (ms) with standard deviation at baseline and with nerve stimulation. (c) Sinus cycle length (ms) at baseline and nerve stimulation after CABG with anterior fat pad dissection. Mean sinus cycle length (ms) with standard deviation at baseline and with nerve stimulation.
not increase AF but instead paradoxically decreased the incidence of postoperative AF.

Coronary artery bypass grafting routinely involves significant dissection of the epicardial FP in the aortopulmonary window before placing the aortic cross-clamp. We hypothesized that dissection of this FP destroyed the parasympathetic nerves within it, thus decreasing vagal tone. By decreasing vagal tone (increasing atrial refractoriness), dissection of the FP was expected to decrease susceptibility to AF. Davis et al. (24) previously evaluated removing the anterior FP in patients receiving off-pump and standard CABG. Their data demonstrated that patients with significant dissection in the aortopulmonary window had an increased incidence of postoperative AF. This finding was independent of reversible causes of AF such as pericarditis or infection, thus implying that postoperative AF may involve an autonomic mechanism. The current study was able to expand upon the findings of Davis et al. (24) by narrowing the study population to include only patients receiving standard median sternotomy on-pump bypass surgery, by providing single-blinded randomization, and by documenting true elimination of parasympathetic innervation via nerve stimulation.

To date, two epicardial FPs and their parasympathetic innervation of the heart have been described in humans. Quan et al. (16,17) previously identified and characterized the parasympathetic innervation of the two posterior FPs by applying direct nerve stimulation to both FPs. Nerve stimulation of the right pulmonary vein-atrial FP decreased atrial refractoriness and slowed sinus CL, demonstrating selective innervation to the SA node. Nerve stimulation of the inferior vena cava-left atrial FP decreased atrial refractoriness and induced complete heart block, demonstrating selective innervation to the atrioventricular node (16–18). These FPs are analogous to the posterior FPs previously described in the canine model (20–22,26–28). A third, more anterior FP has been found in dogs, but this FP has not yet been characterized in humans (23).

This anterior canine FP was recently characterized by Chiou et al. (23), who determined that its parasympathetic fibers course into the two posterior FPs. When this anterior FP was ablated, vagal nerve stimulation failed to have any parasympathetic effect on the SA or atrioventricular node. Nerve stimulation of the inferior vena cava-left atrial FP decreased atrial refractoriness and induced complete heart block, demonstrating selective innervation to the atrioventricular node (16–18). These FPs are analogous to the posterior FPs previously described in the canine model (20–22,26–28). A third, more anterior FP has been found in dogs, but this FP has not yet been characterized in humans (23).

Subsequently, they attempted to induce AF with programmed stimulation. As expected, they were less likely to induce AF in dogs with anterior FP ablation as compared with dogs without anterior FP ablation (23). This is consistent with the current understanding of vagal stimulation shortening atrial refractoriness and increasing susceptibility to AF. Additionally, Quan et al. (16,17) evaluated atrial refractoriness during nerve stimulation of the posterior epicardial FPs. It was demonstrated that atrial refractoriness decreased in areas of the atria that were densely innervated by parasympathetic nerves. Therefore, because vagal stimulation decreases atrial refractoriness, the incidence of AF would be expected to increase with FP preservation.
In humans, the existence of an anterior FP containing parasympathetic ganglia has been described in the aortopulmonary window. Although this FP is often dissected during CABG, its parasympathetic activity and role have not been well defined. In the current study, identification and characterization of the anterior FP were performed by direct visualization and stimulation. Sinus CL prolonged with nerve stimulation. This CL change occurred with stimulation parameters known to stimulate parasympathetic nerves. The gradual onset and gradual offset of CL change were typical of a parasympathetic and not a sympathetic response (16,17). Additionally, administration of atropine abolished this effect of nerve stimulation in three of three patients. Therefore, this CL change is due to parasympathetic nerve stimulation to the FP.

The slowing of sinus CL during nerve stimulation persisted after surgery in patients in whom the anterior FP was preserved. In contrast, stimulation of the FP in the aortopulmonary window failed to elicit any change in sinus CL in patients in whom the anterior FP was dissected. These data confirmed that the anterior FP provided parasympathetic innervation to the SA node, and that dissection of this FP eliminated its parasympathetic effect on the SA node.

Although previous studies have characterized the posterior epicardial FPs, this is the first study, to our knowledge, to identify and characterize the parasympathetic innervation of the anterior FP in humans. Because of its location and parasympathetic activity, it was suspected that this anterior FP may be analogous to the third FP found in dogs described by Chiou et al. (23).

Additionally, this study clearly demonstrated an increased incidence of postoperative AF in patients with anterior FP dissection as compared with patients with anterior FP preservation during CABG. The mechanism of this paradoxical response in the incidence of postoperative AF is unknown. Although parasympathetic tone has been associated with increased incidence of AF, preservation of parasympathetic innervation via the anterior FP paradoxically decreased incidence of postoperative AF in this study. The innervation of the heart is regulated directly by parasympathetic tone via the vagus nerve and indirectly by sympathetic tone. It is hypothesized that, by dissecting parasympathetic fibers of this FP, the balance between parasympathetic and sympathetic tone of the heart is altered. An imbalance in autonomic tone may increase the heterogeneity of atrial refractoriness, thus increasing susceptibility to AF. This is consistent with clinical observations that beta-receptor antagonist therapy after CABG decreases postoperative AF. As beta-receptor antagonists decrease sympathetic tone and, thus, decrease heterogeneity of atrial refractoriness, they may help restore normal parasympathetic/sympathetic balance.

Another potential, but less likely, mechanism to explain the increased incidence of postoperative AF in these patients is that changes in parasympathetic tone affect the firing of ectopic foci in the pulmonary veins. Recent studies have shown that sustained episodes of atrial arrhythmias in patients with ectopic pulmonary vein foci are dependent on variations in autonomic tone. These studies, however, did not evaluate patients in the postoperative state (29,30).

**Implications.** It is currently considered usual practice to dissect the FP (by blunt dissection or electrocautery) in the aorto-pulmonary window during CABG. This dissection aids in clearing the field of view and in securing the aorta cross-clamp. If these data are confirmed in future studies, they may affect operative technique during CABG before cross-clamping of the aortic root and may affect the management of postoperative AF. Although dissection of the anterior FP is considered usual practice, the surgeons involved did not have any difficulty preserving the anterior FP for this study.

**Study limitations.** A limitation of this study is its small sample size. Additionally, although atrial refractoriness is suspected of having a role in postoperative AF, this study did not directly measure atrial refractoriness pre- and postoperatively because of operating room time constraints. Additionally, heart rate variability analysis could not be performed preoperatively, because many patients were not stable for a full preoperative heart rate variability assessment.

**Conclusions.** This study is the first to evaluate and characterize the parasympathetic innervation of the anterior epicardial FP of the human heart. Also, it is the first randomized study to evaluate the role of this FP’s parasympathetic innervation in the incidence of postoperative AF. If confirmed, these observations may have an effect on CABG operative technique as well as treatment of postoperative AF.

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