Atrial fibrillation (AF) after coronary artery bypass surgery (CABG) constitutes the most common sustained arrhythmia.1–5 Postoperative AF is associated with strokes and a prolonged hospital stay.6–9 β-Adrenergic receptors and class III agents such as amiodarone confer some benefits in preventing post-CABG AF, but its incidence is still as high as 30% with these therapies.10–14

The pathogenesis of postoperative AF remains unclear and is presumably multifactorial. The transient nature of this problem seen after cardiac surgery suggests a reversible trigger; abnormal automaticity and atrial conduction delay are possible electrophysiological substrates. These would result in the occurrence of atrial ectopy and prolonged atrial activation, with lengthening of the P wave recorded by the ECG.15,16 However, a signal-averaged ECG of the P wave, which is a measure of regions of delayed atrial activation, is only moderately sensitive in predicting AF after CABG.17–19

Signal-averaged ECG P-wave dispersion has also been recently advocated as a novel measurement of the heterogeneity of atrial depolarization.20

High right atrial overdrive pacing for patients with paroxysmal AF reduces the recurrence of AF when compared with ventricular demand pacing in observational and controlled clinical trials.21–23 Biatrial pacing has been shown to be effective in preventing AF among patients with AF and advanced interatrial block through atrial resynchronization.24

The purpose of this prospective study was to evaluate the efficacy of biatrial pacing as a prophylactic measure against AF after CABG when compared with no (control) or single-site atrial pacing in either the left or right atrium. The impact of therapy on length of hospitalization was also examined. We also evaluated the effect of atrial pacing on mean P wave duration (Pdur) and dispersion (Pdis), as measured by 12-lead ECG.

### Methods

The study protocol was approved by the institution ethical research committee. From April 1998 to May 1999, 132 patients scheduled for CABG with cardiopulmonary bypass were enrolled. All patients gave informed consent. The diastolic left atrial diameter was measured from the M-mode echocardiogram at the level of the aortic root using electronic callipers. Ejection fraction was measured from the left ventriculogram obtained during preoperative cardiac catheterization. Patients were excluded if they had a history of supraventricular (including atrial flutter or AF) or ventricular tachyarrhythmias, if they required the use of antiarrhythmic therapy other than class III agents such as amiodarone, or if they underwent concomitant surgical interventions, such as reconstructive surgery for mitral regurgitation or mitral valve replacement.

A total of 132 patients who had no history of AF and who underwent CABG were randomized to 1 of the following 4 groups: biatrial pacing (BiA), left atrial pacing (LA), right atrial pacing (RA), or no pacing (control) in postoperative period. Overdrive atrial pacing was performed for 5 days. The incidence of AF was significantly reduced in the BiA group (12.5%) compared with the other 3 groups (LA, 36.4%; RA, 33.3%; control, 41.9%; P<0.05).

The mean length of hospital stay was significantly reduced in the BiA group. At baseline, the mean P-wave duration (Pdur) and dispersion (Pdis) were not prolonged. BiA pacing resulted in the most significant percentage of reduction in Pdis when compared with the LA or RA groups (BiA, 12.5%; LA, 13.6%; RA, 10.6%; P<0.05 for BiA versus LA or RA). No significant differences existed in mean Pdur and Pdis between patients who developed AF and those who remained in sinus rhythm at baseline. However, only those patients who remained in sinus rhythm had a significant reduction in mean Pdur and Pdis after pacing therapy.

### Conclusions

Biatrial overdrive pacing is more effective in preventing post-CABG AF than single-site atrial pacing; this therapy also results in a shortened hospital stay. The overall reduction in atrial activation time with BiA pacing was reflected in the reduction in Pdis. (Circulation. 2000;102:755-760.)

**Key Words:** arrhythmia ■ electrocardiography ■ pacing ■ surgery
TABLE 1. Clinical Characteristics and Surgical Data of the Patients

<table>
<thead>
<tr>
<th></th>
<th>BiA (n=32)</th>
<th>RA (n=36)</th>
<th>LA (n=33)</th>
<th>Control (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.3±7.7</td>
<td>67.0±6.1</td>
<td>65.5±7.5</td>
<td>62.5±8.7</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>75</td>
<td>69</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>50.5±12</td>
<td>52.0±11</td>
<td>53.0±8.4</td>
<td>51.1±9.2</td>
</tr>
<tr>
<td>Left atrial diameter, cm</td>
<td>3.7±0.5</td>
<td>3.7±0.7</td>
<td>3.5±0.5</td>
<td>3.6±0.4</td>
</tr>
<tr>
<td>No. of diseased coronary arteries/patient</td>
<td>2.8±0.4</td>
<td>2.7±0.6</td>
<td>2.7±0.5</td>
<td>2.7±0.5</td>
</tr>
<tr>
<td>Left main stem involvement, %</td>
<td>53</td>
<td>48</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>History of previous MI, %</td>
<td>22</td>
<td>27</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>Hyperlipidaemia, %</td>
<td>56</td>
<td>58</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td>Systemic hypertension, %</td>
<td>47</td>
<td>49</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>33</td>
<td>31</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>Preoperative use of β-blockers, %</td>
<td>66</td>
<td>64</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>Bypass pump time, min</td>
<td>118±40</td>
<td>117±42</td>
<td>114±22</td>
<td>120±37</td>
</tr>
<tr>
<td>Aorta cross-clamp time, min</td>
<td>66±25</td>
<td>66.5±17</td>
<td>66.7±14</td>
<td>67.8±21</td>
</tr>
<tr>
<td>Saphenous vein grafting, No./patient</td>
<td>2.1±0.8</td>
<td>1.7±0.6</td>
<td>2.1±0.7</td>
<td>1.8±0.8</td>
</tr>
<tr>
<td>Arterial grafts, No./patient</td>
<td>0.9±0.6</td>
<td>0.9±0.8</td>
<td>0.7±0.4</td>
<td>0.7±0.8</td>
</tr>
<tr>
<td>Postoperative use of β-blockers, %</td>
<td>56</td>
<td>52</td>
<td>56</td>
<td>52</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction.

β-blockers, or if they postoperatively developed significant events such as cardiogenic shock or ventricular tachyarrhythmias that precluded the use of atrial pacing. All medications, including β-blockers, were continued until surgery. Postoperatively, these medications were used according to clinical indications. In our institute, β-blocker therapy was continued after CABG for those who had a radial arterial graft inserted.

Patients underwent CABG on standard cardiopulmonary bypass with myocardial protection provided by blood cardioplegia. Epicardial pacing wires (Flexon-0, Davis-Geck) were placed at the epicardium of the right atrial appendage and at the roof of the left atrium at the end of surgery. Patients were randomly assigned to 1 of the following 4 groups: biatrial pacing (BiA), right atrial pacing (RA), left atrial pacing (LA), or no pacing (control). On arrival in the surgical intensive care unit, the sensing and pacing thresholds of the right atrial appendage and at the roof of the left atrium were determined. No pacing was used in 12 patients, either because of markedly raised pacing thresholds (n=5), poor sensing (n=3), or both (n=2). All patients were included in an intention-to-treat analysis. The mean age was 64.6±7.8 years, and 70% of the patients were male. The mean ejection fraction was 46.3±10.6%. The clinical characteristics in each group were similar and well matched (Table 1). A total of 66% and 54% of patients were taking β-blockers before and after the operation, respectively, and this was not significantly different among the 4 groups.

Postoperative Standard ECG Measurement Methodology

In the immediate postoperative period, ECGs were obtained with 12 leads simultaneously at a signal size of 10 mm/mV and paper speeds of 25 mm/s and 50 mm/s during sinus rhythm (SR) and atrial pacing, respectively. P-wave analysis was manually measured by a single investigator who was blinded to the clinical outcome of the patients. The P-wave onset was defined as the first atrial deflection from the isoelectric line, and the offset was the return of the atrial signal to the baseline. Mean P'<sub>dur</sub> was calculated as the mean value of P-wave duration in each lead. The difference between the maximum and minimum P'<sub>dur</sub>, expressed as a percentage of mean P'<sub>dur</sub>, was defined as P-wave dispersion (P'<sub>disp</sub>).

Statistical Analysis

All continuous variables were expressed as mean±SD. Continuous variables were compared by means of 2-tailed Student’s t-tests, and discrete variables were compared using the χ² test. For univariate predictors associated with P<0.1, stepwise logistic regression analysis was performed; the odds ratio and 95% confidence interval were calculated to ascertain significant predictors of AF. Linear regression models for length of hospital stay were performed to identify important independent predictors. Effects of possible outliers on length of hospital stay were examined and identified as standardized residuals beyond 3 SDs from the mean. P<0.05 was considered statistically significant.

Results

Patient Data

Of the 132 patients, 32, 33, 36, and 31 were assigned to the BiA, LA, RA, and control groups, respectively. However, premature termination of pacing was required in 12 patients, either because of markedly raised pacing thresholds (n=7), poor sensing (n=3), or both (n=2). All patients were included in an intention-to-treat analysis. The mean age was 64.6±7.8 years, and 70% of the patients were male. The mean ejection fraction was 46.3±10.6%. The clinical characteristics in each group were similar and well matched (Table 1). A total of 66% and 54% of patients were taking β-blockers before and after the operation, respectively, and this was not significantly different among the 4 groups.
Incidence of Post-CABG AF
A total of 41 patients developed AF, with an overall incidence of 31.1%. There was a significantly reduced incidence of postoperative AF in the BiA group (12.5%) when compared with the other 3 groups (LA, 36.4%; RA, 33.3%; and control, 41.9%; P < 0.05) (Figure 1). AF developed a mean of 2.8 ± 1.2 days after surgery. If AF was not converted spontaneously to SR, either pharmacological means or electrical cardioversion was used to restore SR before discharge. After 4 weeks of follow-up, all patients remained in SR.

Length of Hospital Stay and Postoperative Outcomes
The mean hospital stay was 10.6 ± 4.0 days; the median stay was 8.2 days. The length of stay was most significantly reduced in the BiA group (7.0 ± 1.4 versus 9.6 ± 4.2 days in the control group; P = 0.003). The mean length of stay in the intensive care unit was also significantly reduced in the BiA group (2.8 ± 0.7 versus 4.6 ± 4.5 days in the control group; P = 0.04). Postoperative complications are shown in Table 2. Adverse cerebral events (including nonfatal stroke or transient ischemic attacks) occurred in 6 patients (4.5%); cerebral hemorrhage was excluded by brain CT examinations. The causes of cerebral events were believed to be embolic in 4 patients and secondary to cerebral hypoperfusion in 2 patients.

TABLE 2. Postoperative Complications

<table>
<thead>
<tr>
<th></th>
<th>BIA</th>
<th>LA</th>
<th>RA</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>3 (9.3)</td>
<td>1 (3.0)</td>
<td>2 (5.5)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2 (6.3)</td>
<td>2 (6.1)</td>
<td>1 (2.8)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>1 (3.1)</td>
<td>1 (3.0)</td>
<td>2 (5.6)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>3 (9.3)</td>
<td>3 (9.1)</td>
<td>2 (5.6)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1 (3.1)</td>
<td>1 (3.0)</td>
<td>1 (2.8)</td>
<td>1 (3.2)</td>
</tr>
</tbody>
</table>

Values are n (%). TIA indicates transient ischemic attack.

Discussion
Major Findings
We demonstrated that biatrial overdrive pacing is more effective in reducing the incidence of AF after CABG than control and single-site atrial pacing. This type of pacing was also associated with a significantly reduced length of hospitalization. Atrial overdrive pacing reduced the mean Pdur and mean Pdis significantly. BiA pacing resulted in the most significant reduction in Pdis. Prevention of AF was not (who also had AF). These events were significantly higher in those patients who developed AF (SR group, 1.1%; AF group, 12.2%; P = 0.005). Two patients (1.5%) with a disabling stroke received long-term anticoagulation.

Age was identified as the only significant predictor of the development of post-CABG AF (odds ratio, 1.06; 95% confidence interval, 1.01 to 1.12; P = 0.02). AF remained an important correlate for both intensive care unit stay and nursing ward stay. Patients with post-CABG AF stayed, on average, 1.8 more days in the intensive care unit and 2.1 more days in the nursing ward than those without AF (Table 3).

No significant effects of outliers could be identified (standardized residuals ranged from −1.62 to 2.97 from the mean length of hospitalization). The median hospital charges in the BiA group (estimated at $12 087 per patient), inclusive of direct surgical procedural charges, was significantly reduced by 14% compared with the median charges in the control group (estimated at $14 047 per patient; P < 0.001).

Effect of Atrial Pacing on P-Wave Analysis
The baseline mean Pdur was 74.7 ± 9.6 ms, and the mean Pdis was 66 ± 24%. The mean Pdur and mean Pdis were significantly reduced with atrial pacing, irrespective of the mode of pacing (Figure 2). The percentage of reduction in mean Pdur among the 3 pacing groups was not significantly different (BiA, 19 ± 17%; LA, 17 ± 18%; and RA, 13 ± 21%; P > 0.3 for BiA versus LA or RA). BiA pacing resulted in the most significant percentage of reduction in mean Pdis when compared with the LA or RA groups (BiA, 42 ± 8%; LA, 13 ± 6%; and RA, 10 ± 9%; P < 0.05 for BiA versus LA or RA), as shown in Figure 3.

At baseline, no significant differences existed in the mean Pdur and Pdis between patients who developed AF and those who remained in SR for all 3 modes of atrial pacing. However, only those patients who remained in SR had a significant reduction in mean Pdur and Pdis after pacing therapy (Figure 4).
effective for patients whose mean P_dur and P_dis could not be reduced significantly, despite atrial overdrive pacing.

Prophylaxis Strategy for Post-CABG AF

Previous trials of prophylaxis for postoperative AF have mainly used β-blockers and sotalol; they have shown some benefits.9–13 Daoud et al14 demonstrated that preoperative oral amiodarone therapy was effective in reducing postoperative AF; this reduction was associated with a reduction in the duration and cost of hospitalization in patients undergoing cardiac surgery. Their study group included a heterogenous group of patients; 57% of these patients were undergoing valvular surgery, and the incidence of AF was still 25%, despite the use of amiodarone. Medical therapy as a prophylactic agent against post-CABG AF may be limited by other medical diseases, such as asthma, thyroid dysfunction, or liver function derangement.

Overdrive atrial pacing has been proposed for the prevention of AF recurrence in patients with bradycardia and paroxysmal AF.21 Single-site pacing in AF prevention, however, has not been shown to be effective in patients with paroxysmal AF.25 Dual-site atrial pacing, wholly from the right atrium, is effective in patients with drug-refractory AF and reduces AF recurrence.26 Biatrial pacing was introduced as a new pacing modality for the prevention of atrial tachyarrhythmias in patients with AF and advanced interatrial conduction block,24 but the actual incidence of advanced interatrial conduction block is rare in the general population, with a prevalence estimated at 1%.27 Because temporary pacing leads are routinely used after open-heart surgery, there have been some preliminary reports on the effectiveness of atrial pacing in preventing post-CABG AF.28,29 To our

Figure 2. Mean P_dur (A) and P_dis (B) were significantly reduced during atrial pacing, irrespective of mode of pacing. *P<0.05 for atrial pacing vs baseline values.

Figure 3. B/A pacing demonstrated the most significant percentage of reduction in P_dis. *P<0.05 when compared with either LA or RA.

Figure 4. Example of comparison of the change in mean P_dur (A) and mean P_dis (B) between patients who maintained SR and those who developed AF during B/A pacing. *P<0.05 for B/A pacing vs baseline.
knowledge, this is the first study reported that compares BiA pacing with single atrial pacing from either chamber.

**Role of Atrial Pacing in AF Prevention**

Previous animal studies demonstrated that dispersion of refractoriness and anisotropic conduction are 2 essential elements for sustaining atrial arrhythmia,\textsuperscript{30,31} and both have been implicated in the pathogenesis of postoperative AF.\textsuperscript{32} Pacing at a higher rate can suppress bradycardia-induced atrial premature contractions and may reduce the dispersion of refractory periods.\textsuperscript{33} The factor that distinguishes single- and dual-site pacing is the effect of each on the activation sequence. Unique pacing sites can “pre-excite” the abnormal substrate and, subsequently, increase the coupling interval of activation by a premature beat, thus preventing the initiation of reentry. Earlier excitation could potentially advance repolarization and the recovery of excitability. Papageorgiou and colleagues\textsuperscript{34,35} noted a conduction delay around the triangle of Koch and attributed this to nonuniform anisotropy in the region; they demonstrated that coronary sinus pacing eliminated the propensity of high right atrial extrasystoles to induce AF. Others have shown that slow conduction in either atrium with subsequent retrograde activation resulted in greatly delayed and inhomogeneous activation of the contralateral atrium and major intraatrial and interatrial asynchrony with prolonged regional refractoriness.\textsuperscript{36,37} Therefore, multisite pacing would provide the additional benefits of both improving local excitability and reducing the window of opportunity for AF initiation.

**Analysis of P\textsubscript{dur} and P\textsubscript{dis}**

The relationship between delayed atrial conduction times and P\textsubscript{dur} has led to an analysis of standard or signal-averaged ECG P\textsubscript{dur} as a prognostic index for the development of AF after cardiac surgery.\textsuperscript{16–19} We sought to determine if mean P\textsubscript{dur} and P\textsubscript{dis} from a standard ECG could provide a simple yet effective measurement of delayed and nonuniform atrial conduction in post-CABG AF. Because our group of patients, who had no clinical history of atrial dysrhythmia, did not demonstrate baseline intra-atrial conduction delay, atrial pacing of all 3 modes resulted in only a further shortening of mean P\textsubscript{dur} but no significant reduction among the 3 pacing modalities.

Previous studies have demonstrated that an abnormally prolonged and fractionated atrial electrogram is characteristic of patients with AF, suggesting that the inhomogeneity of electrical activity is related to delayed and nonuniform anisotropic conduction.\textsuperscript{38} By measuring P waves in different electrographic planes and calculating mean P\textsubscript{dis} from the surface ECG, we found that BiA pacing resulted in the most significant reduction in mean P\textsubscript{dis} when compared with single-site atrial pacing, which suggests that the most significant decrease in overall atrial activation time could be achieved by BiA pacing. Furthermore, patients who developed AF during atrial pacing did not achieve a significant reduction of mean P\textsubscript{dis} and P\textsubscript{dur}, which may reflect a failure of atrial pacing to pre-excite abnormal substrate in these cases, allowing for the initiation of AF.

**Length of Hospital Stay and Estimated Economic Impact**

The increased costs associated with the development of postoperative AF are largely related to the prolongation of hospital stay. With BiA pacing, the mean length of stay and its associated impact on cost were significantly reduced. Hospital resource use and the financial impact arising from elective CABG and its length of stay have been studied.\textsuperscript{8,39,40} Taylor et al\textsuperscript{40} examined the economic consequences of post-CABG complications and showed that AF was one of the least expensive but most common complications, occurring in 20% of patients. Respiratory failure and sternal wound infection were the most expensive complications, but they occurred in only 3% and 0.4% of patients, respectively. Aranki and colleagues\textsuperscript{8} examined the impact of post-CABG AF on hospital resources in 570 patients in whom the adjusted length of hospital stay attributable to AF was 4.9 days, which corresponded to an extra $10,055 to $11,500 per patient in hospital charges, or ≈2 million dollars for that cohort of patients. In this study, the finding of a significant excess of cerebral events among patients with postoperative AF confirms similar observations in other studies.\textsuperscript{6,7,9} Hogue et al\textsuperscript{41} determined that AF had no impact on the postoperative stroke rate unless it was combined with low cardiac output syndrome; this was evident in our 2 patients as well.

**Study Limitations**

Loss of capture from either atrial pacing wire during BiA pacing may be difficult to identify on ECG or telemetry monitoring; therefore, we performed daily assessments of the capture and sensing thresholds to ensure continuous capture by using an energy output 3 times the thresholds and by excluding those with marginal capture thresholds. Because the benefit of BiA pacing was superior to LA or RA pacing, any failure of BiA pacing would only have reduced the observed benefit of the BiA pacing mode. A transient period of incomplete overdrive pacing may be overlooked before adjusting the pacing rate should the patient’s intrinsic rate exceed the overdrive rate. The mean maximum sinus rate among the pacing groups, however, was not significantly different from the intrinsic rate of the control group. The P-wave analysis from surface ECG was performed manually and, with atrial pacing, the onset of the P wave may become more obvious, leading to the observed values of P\textsubscript{dis} and P\textsubscript{dur} reduction. However, a more substantial reduction of P\textsubscript{dis} on the pacing ECGs was observed in BiA pacing compared with other pacing modes, and P\textsubscript{dis} was only reduced in those patients whose AF was prevented by pacing therapy.

**Conclusions**

AF is commonly encountered after CABG, and it results in an increased hospital stay. BiA overdrive pacing is more effective in preventing post-CABG AF than single-site atrial pacing, and it results in a shortened length of hospitalization. Identifying patients at risk for developing post-CABG AF and using intensive prophylactic measures may be the optimal cost-effective strategy.
References


Effects of Biatrial Pacing in Prevention of Postoperative Atrial Fibrillation After Coronary Artery Bypass Surgery
Katherine Fan, Kathy L. Lee, Clement S.W. Chiu, Jan W.T. Lee, Guo-Wei He, David Cheung, Man Ping Sun and Chu-Pak Lau

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