Atrial pacing for the prevention of atrial fibrillation after coronary artery bypass graft surgery: a review of the literature

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Atrial fibrillation (AF) occurs in 20–40% of patients after coronary artery bypass graft surgery (CABG) and contributes to increased morbidity and expenditure after CABG. The limited efficacy of pharmacological treatment to prevent post-CABG AF has stimulated research into alternative prophylactic strategies for the arrhythmia. This article critically reviews the trial evidence in the literature regarding the efficacy of epicardial atrial pacing to prevent post-CABG AF. Thirteen randomised controlled trials of either right, left, or biatrial pacing to prevent post-CABG AF were identified. Overall, prophylactic biatrial epicardial pacing appears to be effective prophylaxis against post-CABG AF and to reduce postoperative hospital stay. The efficacy of single site right or left atrial pacing is less clear. Further data are required to determine both the efficacy of single site atrial pacing and the cost effectiveness of pacing strategies to prevent AF after CABG.

METHODS

The literature was searched on Medline for English language articles published before March 2003. The search terms were used: “AF after CABG”, “atrial pacing for AF”, and “atrial pacing to prevent AF”. Abstract books from the major US and European annual scientific meetings from 1996 onwards were searched for relevant abstracts. Randomised, prospective studies with a control group were included. The primary end point was the incidence of postoperative AF. The secondary end point was duration of postoperative hospital stay.

The trial evidence: study method

Thirteen prospective, randomised, controlled trials (two published in abstract only) were identified for critical review (table 1). Study populations ranged from 21 to 161 patients. The majority of trials studied patients undergoing isolated CABG. In four trials up to 15% of patients underwent valve surgery, either alone or in combination with CABG.14–17 Trials compared control with either right atrial pacing (RAP),18–20 biatrial pacing (BAP),17 21 22 or both RAP and BAP.16 23 24 Two trials compared left...
atrial pacing (LAP) with control, RAP, and BAP. One study compared control with RAP and pacing at Bachmann’s bundle. A pacing protocol was AAT mode, AAI mode at 96 pulses/min, AAI mode set at 10–20 beats above the intrinsic atrial rate, DDD mode at a lower rate of 100 pulses/min, and atrial overdrive algorithms that paced the atrium consistently above the intrinsic atrial rate. Duration of pacing ranged from 24 hours to five days postoperatively and was not stated in one study.

In all trials the arrhythmia end point was AF except in two, which specified the combination of AF or atrial flutter as the end point. The duration of the arrhythmia to qualify as an end point varied from 1 minute to 1 hour. The requirement for treatment of the arrhythmia was included in some end point definitions. Intensity of monitoring for arrhythmia ranged from continuous telemetry as dictated by standard clinical care to pacemaker Holter monitoring. The follow up period ranged from a single 24 hour period on the second postoperative day to total in-hospital stay.

**THE TRIAL RESULTS**

The first four studies to be published (two in abstract only) all failed to find a significant difference in AF incidence between paced patients (whether BAP or RAP) and controls (table 1). In one of these studies, the incidence of AF lasting > 30 minutes was 18.2% with BAP compared with 29.5% in controls (not significant) (fig 1). There was, however, a significant reduction in the median duration of episodes of AF (12 v 48 hours; p = 0.008) in the paced group. Another of these trials that also compared BAP with control was aborted after the recruitment of only 21 patients of a planned 200 due to an excess incidence of AF (50% v 22%) in the BAP study group (fig 1). This excess was attributed to the development of sensing failure and asynchronous atrial stimulation.

In two further trials, 154 cardiac surgical patients (136 isolated CABG) and 132 CABG patients received either no atrial pacing (NAP), RAP, LAP, or BAP for 72 hours or five days, respectively, at 10–20 pulses/min above the native heart rate. In the first study, AF occurred significantly less frequently in the RAP group than in controls (8% v 37.5%; p = 0.002), but the incidence of AF was not significantly reduced compared with control in the LAP (20%) or BAP (26%) groups. Furthermore, postoperative hospital stay was shorter (5.6 v 7.8 days; p = 0.001) in the RAP group than in controls (table 2). By contrast, in the second study there was a significant reduction in the incidence of postoperative AF in the BAP group (12.5%) when compared with the other three groups (LAP 36.4%, RAP 33.3%, control 41.9%; p < 0.05). Mean hospital stay was also shorter (7.0 v 9.6 days;
p = 0.003) in BAP patients than in controls. The incidence of AF was again significantly lower in the BAP group than in the RAP group (both AAT mode) and control (10% v 28% v 32%, respectively; p = 0.02) among 118 cardiac surgical patients. This did not translate into a reduction in hospital stay, however. Levy et al also showed that BAP reduced AF lasting >1 hour detected by pacemaker Holter monitoring from 38.5% to 13.8% (p = 0.001) and reduced AF detected clinically from 33.8% to 10.8% (p = 0.002). The mean and median hospital stays in the BAP group were 7.7 days and 6 days, respectively, compared with 9.7 days and 7 days in the control group (not significant).

Neumann et al found that the incidence of AF detected by Holter monitoring during the first three days after CABG was lowest in patients randomised to AAT BAP (16%), but this was not significantly different (p = 0.31) from patients who received RAP (31%) or LAP (32%). Daoud et al randomly assigned 118 patients undergoing either CABG (n = 106), CABG plus aortic valve replacement (n = 5), or aortic valve replacement alone (n = 7) to NAP or BAP in AAI mode at a rate of 100 pulses/min. The mean pacing period was 78 hours. AF lasting >10 minutes on Holter monitoring occurred in 21% of patients in the BAP group compared with 35% of patients in the NAP group (p = 0.08). When patients undergoing CABG with or without aortic valve replacement (n = 111) were considered, the incidence of AF was significantly lower in the BAP group (19% v 35%; p = 0.05; odds ratio (OR) 0.38, 95% confidence interval (CI) 0.15 to 0.93). There was also a significant reduction in the amount of time spent on the intensive care unit among patients receiving BAP (37 v 50 hours; p < 0.05) but the total hospital stay was similar in the two groups (139 v 143 hours; p > 0.7).

Among 96 CABG patients randomly assigned to either RAP for 24 hours on the second postoperative day or to control, AF (during the second postoperative day) was reduced in the paced group compared with the control group (10% v 27%; p = 0.036). Whether the overall incidence of in-hospital AF was reduced was not reported. By contrast, however, when Chung et al randomly assigned 100 patients undergoing CABG to RAP at 10 pulses/min above the native heart rate for four days postoperatively or to control, there was no difference in the AF frequency between groups (25.5% v 28.6%, p = 0.90 at four days; and 27.5% v 28.6%, p = 0.90 at seven days).

Most recently, Goette et al randomly allocated 161 patients undergoing CABG to control, RAP, or pacing at Bachmann’s bundle. The incidence of AF was not reduced by pacing at either site (42% v 48% v 37%, respectively; not significant). The length of hospital stay was also not influenced by either pacing strategy (12.2 v 11.8 v 12.3 days, respectively; not significant), albeit in a health care system that tends to discharge patients later after CABG than in UK practice.

### DISCUSSION

Pharmacological treatment has limited effectiveness for the prevention of post-CABG AF. Atrial pacing has been shown to be effective at preventing AF in selected non-surgical patients with or without the need of a pacemaker. These factors together have stimulated considerable recent interest in atrial pacing as a preventive measure against post-CABG AF. We have reviewed the literature regarding its efficacy in preventing this arrhythmia.

We identified 13 randomised, controlled trials of prophylactic pacing for post-CABG AF. Several criticisms of these trials can be made. They had different exclusion criteria and the use of concomitant drugs, particularly β-blockers, varied, as did the intensity of monitoring for AF. Invariably they had low statistical power to detect a treatment effect. Despite the differences in study methods, two meta-analyses have pooled data from 10 (1473 patients) and 12 (1407 patients) randomised trials, respectively. The meta-analysis, the respective odds ratios (95% confidence intervals) for AF for paced patients compared with a control group were as follows: RAP, OR 0.68, 95% CI 0.39 to 1.19; LAP, OR 0.57, 95% CI 0.28 to 1.16; and BAP, OR 0.46, 95% CI 0.30 to 0.71. These odds ratios were essentially the same as those reported in the second meta-analysis (published in abstract only). The results of meta-analyses should be interpreted with caution but these data suggest that BAP, at least, is an effective preventive measure against post-CABG AF. Furthermore, data from trials that randomly assigned 744 patients to BAP or control showed a significantly reduced mean length of hospital stay by 1.54 days (95% CI −2.85 to −0.24), favouring pacing. Whether this reflects the reporting of hospital stay only in trials tending to show a benefit in paced patients is unclear.

The studies used a number of different pacing modalities (AAT, AAI, DDD, atrial overdrive algorithms) and different stimulation rates. It is probable that the effectiveness of atrial pacing in preventing AF after CABG is influenced by the pacing protocol in addition to the chamber(s) paced. BAP appears to be more effective than RAP or LAP, but the available data do not allow a definite conclusion to be drawn regarding the relative efficacies of pacing modality. Additional questions that remain unanswered relate to the feasibility, mechanism of benefit, and cost effectiveness of atrial pacing to prevent post-CABG AF.

### Feasibility

The duration of effective pacing that was actually achieved varied considerably between studies. For example, BAP was successfully maintained in all cases to 96 hours with no complications in one study, whereas in two other studies BAP was discontinued before the 72 hour protocol in 33% patients and in nine of 12 patients. Furthermore, successful pacing was achieved for a significantly shorter duration with the apparently more effective strategy of BAP than with
RAP, presumably because of its dependency on the integrity of two pairs of wires rather than one. Survival of the right atrial leads was significantly greater than for the left atrial leads (p < 0.001). In their BAP patients, Gerstenfeld et al. found that the left atrial wires had a significantly higher mean threshold than the right atrial wires, though no patients lost capture due to a large increase in threshold. Levy et al. reported lead failure in 20% of their BAP patients, evenly split between left and right atrial wires. In the study of Goette et al., atrial pacing was terminated early in 6 (10%) of 60 patients in the RAP group and in 3 (5.9%) of 51 patients in the Bachmann's bundle pacing group. Pacing thresholds were significantly higher in the RAP group than in the Bachmann's bundle group (p < 0.05), but there was no difference in atrial sensing. In the majority of cases, pacing was discontinued prematurely because of raised pacing thresholds, sensing failure, or diaphragmatic pacing. Such problems with the maintenance of the pacing regimens might have contributed to an underestimate of the efficacy of pacing, but they also raise issues about the feasibility of routine atrial pacing after CABG.

The major complication of atrial pacing other than lead failure is cardiac tamponade after removal of the epicardial wires. This is rare, particularly in non-antiagulated patients, and no such complications were reported in any of the trials. Nevertheless, at our institution epicardial pacing wires are removed before the day of discharge and with a surgeon available to perform open pericardial drainage when necessary.

Potential mechanisms of benefit

The mechanisms behind any reduction in the incidence of postoperative AF due to atrial pacing are speculative. Experiments in animals and humans suggest that re-entry is the underlying electrophysiological mechanism in the majority of cases of AF. Persistence of AF requires that the depolarising wave fronts must continuously encounter excitable tissue, a circumstance favoured by slow atrial conduction. AF is characterised by re-entry circuits propagating around areas of either fixed or functional conduction block. Functional block is dependent on heterogeneities of cardiac tissue that may be caused by factors such as oedema due to manipulation of the heart at surgery, atrial ischaemia, changes in autonomic tone, and inflammatory changes due to pericarditis or cardiopulmonary bypass. Intra-atrial conduction and refractoriness may be modified in a favourable way by atrial pacing. In patients with intra-atrial conduction delay, for example, P wave duration was significantly increased (106 vs 187 ms; p < 0.0001) by BAP. In the study of Fan et al., the mean P wave duration and mean P wave dispersion were significantly reduced with atrial pacing irrespective of pacing site. The percentage reduction in mean P wave duration was similar in the three pacing groups but BAP resulted in a significantly greater reduction in mean P wave dispersion. By contrast, however, RAP prolonged P wave duration in the studies of Blommaert et al. and Goette et al. and prolongation of P wave duration during RAP was an independent predictor for postoperative AF in the latter study.

Atrial pacing may be expected to reduce bradycardia related AF. The presence of atrial extrasystoles progressively independently predicts the development of post-CABG AF. Furthermore, the frequency of atrial extrasystoles increases before the onset of AF after CABG and they are a common initiating factor for the arrhythmia. Overdrive atrial pacing algorithms have been shown to decrease the frequency of premature atrial complexes. However, Chung et al. found that not only was the number of atrial extrasystoles increased in the control patients who developed AF (2715 vs 232 in 24 hours; p = 0.023), but they were also increased in paced compared with non-paced patients (2106 vs 866 in 24 hours; p = 0.0001). Chung et al. concluded that atrial pacing in the postoperative period may actually be proarrhythmic. In this study, only the right atrium was paced, a strategy that may result in less favourable changes in intra-atrial conduction than with BAP. These contrasting findings highlight the limitations of our current understanding of the pathophysiology of post-CABG AF.

Conclusion

Prophylactic biatrial epicardial pacing appears to be effective prophylaxis against post-CABG AF but the effectiveness of single site RAP or LAP is less clear. It is not known whether (bi)atrial pacing is a cost effective strategy to prevent post-CABG AF. If the significant reduction in mean length of hospital stay of 1.54 days seen in patients randomly assigned to BAP in the trials can be reproduced in “real world” clinical practice, this approach to AF may reduce overall cost per patient. Further data are required to determine both the effectiveness of single site atrial pacing and the cost effectiveness of pacing strategies to prevent AF after CABG.

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REFERENCES
A 65 year old woman with hypertension and permanent atrial fibrillation had suffered two brief syncopal episodes. She was on losartan, digoxin, and aspirin. The ECG showed atrial fibrillation and incomplete left bundle branch block; the QT interval was 0.36 s and the QTc 0.414 s. The echocardiogram revealed mild dilatation and dysfunction of the left ventricle (ejection fraction = 40%). Laboratory tests were normal; serum potassium was 4.1 mEq, magnesium 2.2 mEq, and digoxin 0.95 ng/ml.

The Holter recording (right) revealed an episode of ventricular fibrillation (VF) occurring during sleep. Surprisingly, VF ceased after 1.16 mins; an asystolic pause of 16.08 s then ensued, followed by resumption of a supraventricular rhythm.

Ventricular fibrillation seldom terminates spontaneously, since several re-entrant wavefronts, independent from each other, coexist, and the simultaneous extinction of all the circuits is unlikely. In the present case, fibrillation waves are initially tall and regular, and later become irregular and reduced in voltage (third strip). From the second half of the fourth strip, however, the tracing shows again regular and high voltage waves. Although the term “ventricular fibrillation” is appropriate to describe this rhythm disorder, fragmentation of the electrical activity, as deduced from the ECG, is not very pronounced, to the point that in the section preceding termination the pattern resembles a fast ventricular tachycardia rather than a true VF. This may help to explain the unexpected spontaneous interruption of the arrhythmia.

A continuous two channel Holter recording. The top strip shows a short run of torsades de pointes; following the post-tachycardia pause, a single narrow beat occurs, and then a premature ventricular complex initiates ventricular fibrillation.