

CLINICAL STUDIES**Electrophysiology**

Effective Prevention of Atrial Fibrillation by Continuous Atrial Overdrive Pacing After Coronary Artery Bypass Surgery

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- OBJECTIVES** The present study was aimed to evaluate the efficacy of a specific algorithm with continuous atrial dynamic overdrive pacing to prevent atrial fibrillation (AF) after coronary artery bypass graft (CABG) surgery.
- BACKGROUND** Atrial fibrillation occurs in 30% to 40% of patients after cardiac surgery with a peak incidence on the second day. It still represents a challenge for postoperative prevention and treatment and may have medical and cost implications.
- METHODS** Ninety-six consecutive patients undergoing CABG for severe coronary artery disease and in sinus rhythm without antiarrhythmic therapy on the second postoperative day were randomized to have or not 24 h of atrial pacing through temporary epicardial wires using a permanent dynamic overdrive algorithm. Holter ECGs recorded the same day in both groups were analyzed to detect AF occurrence.
- RESULTS** No difference was observed in baseline data between the two study groups, particularly for age, male gender, history of AF, ventricular function, severity of coronary artery disease, preoperative beta-adrenergic blocking agent therapy or P-wave duration. The incidence of AF was significantly lower ($p = 0.036$) in the paced group (10%) compared with control subjects (27%). Multivariate analysis showed AF incidence to increase with age ($p = 0.051$) but not in patients with pacing ($p = 0.078$). It decreased with a better left ventricular ejection fraction only in conjunction with atrial pacing ($p = 0.018$).
- CONCLUSIONS** We conclude that continuous atrial pacing with an algorithm for dynamic overdrive reduces significantly incidence of AF the second day after CABG surgery, particularly in patients with preserved left ventricular function. (J Am Coll Cardiol 2000;35:1411-5) © 2000 by the American College of Cardiology

Supraventricular tachyarrhythmias and particularly atrial fibrillation (AF) represent a common therapeutic challenge after cardiac surgery. Atrial fibrillation occurs in 30% to 40% of the cases, with a peak incidence during the second postoperative day (1). Postsurgical AF can induce hemodynamic deterioration and increases the risk of stroke or

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ventricular arrhythmias (2,3). Moreover, AF may influence significantly the costs of surgical procedure due to its high incidence and its impact on hospital stay (4,5). Many

clinical trials evaluating the preventive efficacy of different antiarrhythmic drugs have been published. If digitalis (6) and verapamil (7) are not effective, prophylactic treatment with beta-adrenergic blocking agents, sotalol or amiodarone was shown to be useful, but these drugs may be contraindicated in many situations (6-8).

Atrial pacing with an implantable stimulator is one of the new methods under investigation to prevent recurrences of AF (9,10). Even though temporary epicardial wires have been proposed for many years for diagnosis and treatment of atrial arrhythmias after cardiac surgery (11), their use coupled with continuous overdrive pacing to prevent post-coronary artery bypass graft (CABG) AF has not been evaluated extensively. The aim of our study was to test the hypothesis that continuous atrial dynamic overdrive pacing through temporary epicardial wires, performed on the second day after surgery, could reduce significantly the incidence of postoperative AF.

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Manuscript received April 22, 1999; revised manuscript received September 22, 1999, accepted February 2, 2000.

Abbreviations and Acronyms

- AF = atrial fibrillation
- APB = atrial premature beats
- CABG = coronary artery bypass graft
- LVEF = left ventricular ejection fraction
- PAP = pulmonary artery pressure
- PCWP = pulmonary capillary wedge pressure

METHODS

Patient population. Ninety-six consecutive patients undergoing elective CABG surgery for severe symptomatic coronary artery disease were enrolled in the study on the basis of a sinus rhythm without any antiarrhythmic drug and a stable hemodynamic status the second day after surgery. The CABG was performed using single atrial cannulation and cardiopulmonary bypass. Patients with a permanent pacemaker, those having atrioventricular conduction abnormalities or treated with amiodarone before surgery were excluded. Treatment with any other antiarrhythmic drug, beta-blockers or digoxin had to be stopped before CABG.

Preoperative clinical data were obtained from all patients by reviewing medical records and included age, gender, history of AF, previous myocardial infarction or cardiac surgery, and symptoms of heart failure. Left ventricular ejection fraction (LVEF) was calculated by cine-angiography and/or transthoracic echocardiography. P-wave duration was measured from lead II of the preoperative ECG. Aortic cross-clamp time was noted for each patient.

Eligible patients gave their informed consent orally and were randomized between atrial stimulation (group 1) and no stimulation (group 2). The study was approved by the Ethics Committee of our institution.

Study protocol. Two sets of epicardial wire electrodes (Medtronic model 6500; Medtronic Inc.; Minneapolis, Minnesota) attached, respectively, on the right ventricle and on the high right atrium, near the sinus node, were implanted in all patients as a routine practice in our institution.

The second day after surgery, an external pacemaker (Harmony; Vitatron Inc.; Dieren, The Netherlands) was connected to the atrial wires for 24 h continuous atrial pacing in AAI mode with a lower rate of 80 beats/min. A specific algorithm for dynamic overdrive was programmed, allowing the pacemaker to always stimulate just above the patient's own rhythm, to an upper limit of 125 beats/min. Thus, when a spontaneous beat is sensed, the algorithm increases the heart rate by shortening its escape interval by 50 ms. The pacemaker then increments gradually the interval by 5 ms per stimulus, reducing heart rate until the lower rate limit is reached or a new spontaneous beat is detected (Fig. 1).

A 24-h ECG recording was performed the same day in both patients with pacing and control patients with a Holter recorder (Avionics; Del Mar Inc.). The primary end point of the study was the occurrence, on the Holter ECG, of an episode of AF, considered as significant when sustained for at least 15 min. When necessary, AF was treated with antiarrhythmic drugs, without interrupting atrial pacing. A continuous infusion of amiodarone was used in most of the

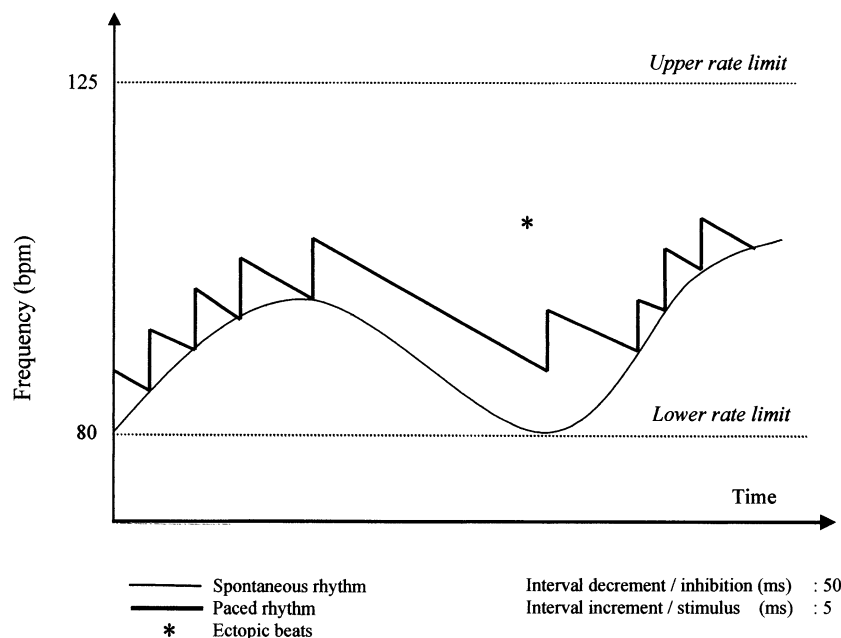


Figure 1. The dynamic overdrive pacing algorithm allows atrial pacing in the AAI mode, always just above the patient's own rhythm. When a premature beat is sensed, the algorithm increases the heart rate by shortening its escape interval by 50 ms to a programmed upper rate limit. The pacing cycle length is then gradually increased by 5 ms per stimulus until the lower rate limit is reached or another spontaneous beat is sensed.

Table 1. Clinical and Perioperative Characteristics of Paced and Control Groups

Variable (Mean ± SD)	All Patients (n = 96)	Paced (n = 48)	Control (n = 48)
Preoperative values			
Age (yr)	67 ± 9	66 ± 9	67 ± 8
Male gender (%)	76	79	73
Prior myocardial infarction (%)	48	52	44
LVEF (%)	57 ± 14	56 ± 14	57 ± 13
Heart failure symptoms (%)	7	8	6
History of AF (%)	1	2	0
Beta-blocker use (%)	59	62	56
P-wave duration (ms)	105 ± 13	108 ± 14	103 ± 12
Perioperative values			
Aortic cross-clamp time (min)	92 ± 23	89 ± 27	95 ± 20
No. of grafts per patient	2.6 ± 0.5	2.5 ± 0.5	2.6 ± 0.5
LIMA (%)	96	98	94
RIMA (%)	78	83	73
Postoperative values			
Peak of CPK release	889 ± 466	808 ± 384	966 ± 525
Peak of CPK MB release	39 ± 22	41 ± 23	37 ± 20
Thoracic drains still present (%)	74	77	72
Cardiac index on day 2 (liter/min)	2.91 ± 0.44	2.96 ± 0.48	2.86 ± 0.40

AF = atrial fibrillation; CPK = creatine phosphokinase; LIMA = left mammary artery; LVEF = left ventricular ejection fraction; RIMA = right mammary artery.

patients, at a dose of 900 to 1,200 mg/24 h. In addition, patients were monitored with telemetry and with a Swan-Ganz catheter for hemodynamic parameters. The ECG tracings were analyzed for arrhythmia with an analyzing system (Del Mar Avionics) and reviewed by the same cardiologist.

Statistical analysis. Results are presented as mean ± SD or proportions (percents). Categorical and numerical variables were compared between the two groups using chi-square or Wilcoxon rank sum test as appropriate. The influence of various factors on the onset of AF was studied by logistic regression with backward selection of variables by likelihood ratio test. The significance of selected parameters in the final model was assessed by the Wald test. All statistical tests are two-tailed. A p value <0.05 was required for statistical significance.

RESULTS

Patient characteristics. A total of 96 consecutive patients (73 men) with a mean (± SD) age of 66 ± 9 years (range, 39 to 80 years) have been enrolled in the study and were randomized to group 1 for atrial overdrive pacing (n = 48) or to group 2 (n = 48) as control. The mean (± SD) LVEF was 57 ± 14% and only 7.4% of the patients had a prior episode of heart failure. Beta-blockers were used preoperatively in 62% of the patients of group 1 and in 56% of group 2 (p = 0.67). No patients were treated with digoxin. Baseline characteristics of the two study groups are compared in Table 1 and no statistically significant differences were observed for any parameter.

Holter and ECG data. Significantly fewer patients of group 1 developed AF compared with group 2: 5 of 48 (10%) versus 13 of 48 (27%) (p = 0.036). However, the duration of AF episodes did not differ significantly (p = 0.27) between group 1 (median, 120 min; range, 16 to 780 min) and group 2 (median, 378 min; range, 18 to 800 min).

Preoperative P-wave duration was similar with a mean of 108 ± 14 ms for group 1 compared with 103 ± 12 ms for group 2 (p = 0.07). It was no more different between patients of both groups developing AF on day 2 after surgery (mean, 107 ± 14 ms) and patients not developing AF (mean, 105 ± 13 ms) (p = 0.65). However, P-wave length increased significantly during atrial pacing (116 ± 2 ms) compared with preoperative values (108 ± 2 ms) (p = 0.003).

As expected, mean (93 ± 11 vs. 87 ± 11 beats/min; p = 0.011) and lower (83.5 ± 6 vs. 73 ± 11 beats/min; p < 0.001) heart rates, including AF episodes, were higher in the group with pacing than in the control group, respectively. The maximum rate was only slightly and not significantly higher in the group with pacemakers (119 ± 24 beats/min) compared with control subjects (113 ± 18 beats/min) (p = 0.39).

Hemodynamic data. The mean cardiac index measured on the second postoperative day did not differ significantly in both groups (2.96 ± 0.48 vs. 2.86 ± 0.40 liter/min; p = 0.42). Furthermore, mean pulmonary artery pressure (PAP: 20 ± 4 vs. 21 ± 4 mm Hg), pulmonary capillary wedge pressure (PCWP: 12 ± 3 vs. 11 ± 2 mm Hg) and central venous pressure (9 ± 3 vs. 9 ± 3 mm Hg), were similar in

group 1 and in group 2, respectively. These parameters did not differ between AF and non-AF patients of both groups.

During AF episodes, hemodynamics deteriorated significantly in both groups with an increase of mean PAP (24 ± 3 vs. 27 ± 4 mm Hg; $p = 0.004$) and PCWP (13 ± 2 vs. 18 ± 3 mm Hg; $p < 0.0001$) and a decrease of systolic blood pressure (136 ± 22 vs. 116 ± 24 mm Hg; $p = 0.015$). Transcutaneous values of oxygen blood saturation also decreased below 93% in two patients during AF. No patient needed external electric cardioversion for AF due to hemodynamic compromise.

Initiation of AF. The onset of AF was studied in all patients. Atrial fibrillation followed an atrial premature beat (APB) in the 5 patients with pacing as well as in 13 control subjects, following a postextrasystolic pause in one of latter. During the 5 min preceding AF episodes, there were <15 APBs in three patients and >60 in the two others of group 1. In group 2, four patients had <15 APBs and two others had >60 ; seven patients had between 15 and 60 APBs. The mean coupling interval of APBs was 71% and 68% of the previous cycle length for group 1 and for group 2, respectively.

Multivariate analysis. In a multivariate analysis, the occurrence of AF in all studied patients was adjusted for different variables: age, LVEF, atrial pacing and their possible interactions. Thus, AF incidence was found to increase with age ($p = 0.051$), but not in patients with pacemakers ($p = 0.078$). It decreased with a better LVEF, but only in patients undergoing atrial pacing ($p = 0.018$). However, analysis of the same parameters in each group separately did not show any significant effect of age on AF incidence in the group undergoing pacing ($p = 0.89$). Furthermore, when patients with an LVEF $>50\%$ were analyzed, AF occurred in significantly fewer patients of group 1 (6%) than of group 2 (26%) ($p = 0.016$). For patients with a lower LVEF, the difference was not significant between group 1 (30%) and group 2 (33%) ($p = 1.0$), suggesting that atrial pacing was more effective with an LVEF superior to 50%.

DISCUSSION

Atrial fibrillation occurred in 10% of patients with pacemakers compared with 27% in control subjects during the 24 h of ECG recording performed on the second day after CABG. The overall incidence is similar to those in recent series (1,4).

It has been suggested that the pathogenesis of post-CABG AF is probably multifactorial with abnormal atrial conduction and a lack of uniformity of atrial repolarization as a substrate and with different triggers, including supraventricular premature contractions, pericarditis, electrolyte disorders, cardiopulmonary bypass and cardioplegia. Atrial ischemia and autonomic disturbances such as an increase in sympathetic tone after surgery or hypersensitivity

to adrenergic stimulation due to beta-blocker therapy withdrawal have also been incriminated (12,13).

Many investigators attempted to identify independent clinical and perioperative predictive or precipitating factors of post-CABG AF. The most important of them seem to be increasing age, male gender, history of AF, congestive heart failure or digoxin therapy (1,14). Moreover, prolonged P-wave duration and serum magnesium (15) or severe right coronary artery stenosis (16) have also been advocated. In our study, preoperative P-wave duration did not appear to be a risk factor for AF occurrence. This is in agreement with Frost et al. (17) who did not find any influence of P-wave duration on AF occurrence when adjusted for a patient's characteristics.

Preventive drug therapy. Several trials focusing on preventive drug therapy for post-CABG AF have been performed. In their meta-analysis, Kowey et al. (6) and Andrews et al. (7) found that only the use of beta-blocking agents alone, even at low doses or combined with digoxin, was the most effective prophylactic treatment, whereas digoxin used alone was ineffective. A beneficial effect of sotalol, a beta-blocker with class III properties, was suggested by some recent series (18,19) but is still debated (20). Furthermore, these drugs may be contraindicated in some cases and one may notice that most of the trials on prevention of postsurgical AF exclude older patients, those with poor left ventricular function or pulmonary problems. Thus, some other therapeutic options could be of major interest in the prevention of AF following cardiac surgery.

Prevention of AF by atrial pacing. Prevention of paroxysmal AF by continuous pacing has been investigated in studies involving patients with permanent pacemakers. However, most of these studies focused on the comparison of different modes of pacing (e.g., VVI vs. DDD, DDD vs. DDDR), sites of pacing (e.g., atrial or biatrial pacing) (10,21) or some specific algorithms. There are some data concerning the use of temporary epicardial wires for the diagnosis and the treatment of supraventricular arrhythmias after cardiac surgery (22).

However, our study is, to our knowledge, the first one assessing the efficacy of temporary atrial overdrive pacing for the prevention of post-CABG AF in a larger group of patients without the adjunction of drugs. For this purpose, we used a specific algorithm that reacts to APBs and allows permanent stimulation of the atria just above the patient's own rhythm. These two characteristics could be essential for influencing effectively the electrophysiologic substrate initiating AF. If a simple overdrive function at a fixed heart rate of 80 to 90 beats/min is used, the heart will be paced only for long period but without adequate intervention after APBs or during faster heart rates. In their article, Delfaut et al. (10) suggested that it was necessary to stimulate the atria $>80\%$ of the time to be effective. Our results support the hypothesis that prevention of AF probably requires permanent atrial overdrive pacing to obtain continuous modification of the electrical substrate. With the specific algorithm we used, an even higher percent-

age of stimulation, close to 90%, can be achieved. However, in some patients, factors other than instability of cycle length may be involved in initiating AF.

Analysis of the number of APBs before AF onset shows that in the control group with a higher incidence of AF, there are 7 of 13 patients who had between 15 and 60 APBs. In contrast, most of the patients in the group with pacing had either very few or a substantial number of APBs. This may indicate that dynamic overdrive pacing is best designed for this category of patients with a moderate number of APBs.

Role of ventricular function and age. Surprisingly, our results suggest that atrial dynamic overdrive pacing is less effective in patients with reduced preoperative LVEF. It has been suggested that fibrosis, atrial dilatation or structural changes may play a role in this phenomenon (4). However, hemodynamic parameters recorded in our patients some hours before the onset of AF do not seem to have any predictive value. This could be explained by the fact that these acute parameters do not reflect the real preoperative left ventricular function.

Another interesting finding in our study is that dynamic overdrive pacing was effective in older patients as well as in younger patients even though age was confirmed as a significant risk factor for AF occurrence in the whole study population. This suggests a particular interest of atrial pacing as preventive treatment of AF in the elderly, compared for example, with beta-blocker therapy that was found by Fuller et al. (14) to be of little benefit in preventing postsurgical AF in patients older than 65 years.

Limitations of the study. One limitation of the study is the monitoring period of atrial arrhythmias that is too short to assess long-term benefits of dynamic overdrive pacing. There is also a need for further studies to confirm the lack of efficacy of prophylactic atrial pacing in patients with low LVEF.

CONCLUSIONS

The use of temporary epicardial wires for continuous atrial pacing with a specific algorithm for atrial dynamic overdrive reduces significantly the incidence of AF on the second day after CABG surgery in the absence of antiarrhythmic therapy, particularly in patients with normal preoperative left ventricular function. This technique, in combination with antiarrhythmic therapy and low energy internal defibrillation when necessary, may enhance prevention and treatment of postoperative AF and could be useful to decrease hospital stay and thereby reduce costs. Technologic improvements of next-generation pacemakers could allow extension of this approach to patients with recurrent AF.

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