Predictors of Atrial Fibrillation After Conventional and Beating Heart Coronary Surgery
A Prospective, Randomized Study

Raimondo Ascione, MD; Massimo Caputo, MD; Giliola Calori, MD; Clinton T. Lloyd, FRCS; Malcom J. Underwood, FRCS; Gianni D. Angelini, FRCS

Background—Atrial fibrillation (AF) increases the morbidity of CABG. The pathophysiology is uncertain, and its prevention remains suboptimal. This prospective, randomized study was designed to define the role of cardiopulmonary bypass (CPB) and cardioplegic arrest in the pathogenesis of this complication.

Methods and Results—Two hundred patients were prospectively randomized to (1) on-pump conventional surgery [(100 patients, 79 men, mean age 63 (40 to 77) years)] with normothermic CPB and cardioplegic arrest of the heart or (2) off-pump surgery [(100 patients, 82 men, mean age 63 (38 to 86) years)] on the beating heart. Heart rate and rhythm were continuously monitored with an automated arrhythmia detector during the first 72 hours after surgery. Thereafter, routine clinical observation was performed and continuous monitoring restarted in the case of arrhythmia. The association of perioperative factors with AF was investigated by univariate analysis. Significant variables were then included into a stepwise logistic regression model to ascertain their independent influence on the occurrence of AF. There were no significant baseline differences between groups. Thirty-nine patients in the on-pump group and 8 patients in the off-pump group had postoperative sustained AF ($P < 0.001$). Univariate analysis showed that CPB inclusive of cardioplegic arrest, postoperative inotropic support, intubation time, chest infection, and hospital length of stay were predictors of AF (all $P < 0.05$). However, stepwise multivariate regression analysis identified CPB inclusive of cardioplegic arrest as the only independent predictor of postoperative AF (OR 7.4; CI 3.4 to 17.9).

Conclusions—CPB inclusive of cardioplegic arrest is the main independent predictor of postoperative AF in patients undergoing coronary revascularization. (Circulation. 2000;102:1530-1535.)

Key Words: prevention ■ tachyarrhythmias ■ fibrillation ■ coronary disease ■ cardiopulmonary bypass
mia, left ventricular ejection fraction of <30%, recent myocardial infarction (MI) (<1 month), repeat operation, renal and respiratory impairment, previous stroke or transient ischemic attack, and coagulopathy. Patients with coronary disease involving branches of the circumflex artery distal to the first obtuse marginal branch and posterior branches originating from the left system were also excluded from the study because these were believed to be technically difficult for adequate revascularization at the beginning of our experience with off-pump surgery.

The study was approved by the United Bristol Healthcare Trust Ethics Committee, and all patients gave informed consent.

### Management of Preoperative and Postoperative Medications

Preoperative medications including β-blockers, diuretics, antihypertensives, and calcium channel blockers were routinely omitted on the day of surgery. ACE inhibitors were withdrawn on the afternoon before the operation. On the first postoperative day, in accordance with the intensive care unit protocol (if heart rate >55 bpm, systolic blood pressure >110 mm Hg), β-blockers and antihypertensive drugs were restarted.

### Anesthetic Technique

In both groups, anesthetic technique consisted of propofol infusion at 3 mg·kg⁻¹·h⁻¹ combined with remifentanil infusion at 0.5 to 1 µg·kg⁻¹·min⁻¹. Neuromuscular blockade was achieved by 0.1 to 0.15 mg/kg pancuronium bromide or vecuronium and the lungs ventilated to normocapnia with air and oxygen (45% to 50%). Heparin was given at a dose of 300 IU/kg to achieve a target activated clotting time (ACT) of 250 to 350 seconds before commencement of CPB in the on-pump group. An additional 3000 IU of heparin was administered if required. In the off-pump group, heparin (100 IU/kg) was administered before the start of the first anastomosis to achieve an ACT of 250 to 350 seconds. On completion of all anastomoses, protamine was given to reverse the effect of heparin and return the ACT to preoperative levels.

### Operative Technique

#### On Pump

CPB was instituted with the use of ascending aortic cannulation and 2-stage venous cannulation of the right atrium. A standard circuit was used: a Bard tubing set, which included a 40-µm filter (Sorin Biomedica), and a hollow-fiber membrane oxygenator. Nonpulsatile flow was used, and flow rates throughout bypass were 2.4 L/m² per minute. Systemic temperature was kept between 34° and 36°C. Myocardial protection was achieved by using intermittent antegrade hyperkalemic warm blood cardioplegia.

#### Off Pump

The method of exposure and stabilization to perform the anastomosis consisted of the technique previously described by our group with or without the use of the Cardiothoracic System (CTS) retractor and stabilizer. The target vessel was then exposed and snared above the anastomotic site with a soft plastic snugger to prevent coronary injury. The coronary artery was then opened, and the anastomosis was performed. Visualization was enhanced by the use of a surgical blower-humidifier (Research Medical Inc).

### Postoperative Management

At the end of surgery, patients were transferred to the intensive care unit (ICU). The lungs were ventilated with 60% oxygen with volume-controlled ventilation and a tidal volume of 1 mL/kg with 5 cm H₂O of positive end-expiratory pressure. Adjustments in FiO₂ and respiratory rate were made according to routine blood gas analysis to maintain PaO₂ between 80 and 100 mm Hg and PaCO₂ between 35 and 40 mm Hg. Forced air warming was used until a stable nasopharyngeal temperature of 37°C was reached. Patients were extubated as soon as they met the following criteria: hemodynamic stability, no excessive bleeding (<30 mL/h), normothermia, and consciousness with pain control. Fluid management after surgery consisted of 5% dextrose infusate at 1 mL·kg⁻¹·h⁻¹, with additional colloid solution or blood to maintain normovolemia and hematocrit >24%. Potassium and magnesium deficiency was promptly treated as necessary to maintain electrolyte balance within the normal range.

### Monitoring and Definitions

Heart rate and rhythm were continuously monitored and displayed on a screen with an automated arrhythmia detector (Solar 8000 Patient Monitor, Marquette Medical Systems) during the first 72 hours after surgery. Automatic printing of the ECG was related to the inserted alarm levels and included heart rate >90 bpm and the presence of 6 consecutive normal R-R intervals varying by >100 ms. Twelve-lead ECG recordings were performed before surgery, 2 hours after surgery, and then daily thereafter until hospital discharge. After the first 72 hours, trained nurses performed clinical observations every 4 hours. An ECG was recorded on the basis of any clinical suspicion of arrhythmia. In the case of documented arrhythmia, continuous ECG monitoring was restarted.

Each episode of arrhythmias was printed out and interpreted by an independent intensive care physician. AF, atrial flutter, and atrial tachycardia were defined according to Kallman et al. AF was defined as nonsustained if lasting between 10 beats and 10 minutes and sustained if persisting for >10 minutes. For the purpose of the analysis, only a first event was recorded, provided its duration satisfied prespecified criteria.

Indications for temporary pacing were made by an independent intensive care physician, according to the ICU protocol, and included symptomatic bradycardia, unresponsive to treatment by drugs, acute

<table>
<thead>
<tr>
<th>Variable</th>
<th>On Pump (n=100)</th>
<th>Off Pump (n=100)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63(40–77)</td>
<td>63 (38–86)</td>
<td>0.8</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>79/21</td>
<td>82/18</td>
<td>0.6</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6</td>
<td>5</td>
<td>0.7</td>
</tr>
<tr>
<td>Previous MI</td>
<td>30</td>
<td>41</td>
<td>0.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13</td>
<td>19</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48</td>
<td>62</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>70</td>
<td>77</td>
<td>0.3</td>
</tr>
<tr>
<td>Smoking</td>
<td>14</td>
<td>10</td>
<td>0.3</td>
</tr>
<tr>
<td>Priority</td>
<td>Routine admission</td>
<td>63</td>
<td>65</td>
</tr>
<tr>
<td>Unsuitable in hospital</td>
<td>37</td>
<td>35</td>
<td>0.7</td>
</tr>
<tr>
<td>Angina class</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>12</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>40</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>34</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>Good (&gt;50%)</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>Moderate (30–50%)</td>
<td>21</td>
<td>19</td>
<td>0.7</td>
</tr>
<tr>
<td>β-Blocker drugs</td>
<td>39</td>
<td>32</td>
<td>0.3</td>
</tr>
<tr>
<td>Diuretics</td>
<td>7</td>
<td>13</td>
<td>0.2</td>
</tr>
<tr>
<td>Nitrites</td>
<td>82</td>
<td>75</td>
<td>0.2</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>33</td>
<td>33</td>
<td>1.0</td>
</tr>
<tr>
<td>Parsonnet score</td>
<td>4 (0–15)</td>
<td>5 (0–34)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Data are presented as median with minimum-maximal values or number of patients (in parentheses).

*Mann-Whitney or χ² test.
conduction disturbances including second- or third-degree atrioventricular (AV) block, and bifascicular or trifascicular block. Indications for permanent pacemaker were made by an independent cardiologist and included second-degree (Mobitz type II) and third-degree AV block and long-lasting symptomatic bradycardia.

Intraoperative and postoperative data, including complications and adverse events, were recorded. Clinical diagnostic criteria for perioperative MI were new Q waves of >0.04 ms and/or a reduction in R waves >25% in ≥2 leads.

Chest infection was defined as the presence of purulent sputum associated with fever and requiring antibiotic therapy according to positive sputum culture.

**Statistical Analysis**

Arrhythmias such as atrial flutter, atrial tachycardia, or others were not considered in the same group of AF because their mechanism differs. Only sustained episodes of AF were included in the statistical analysis. The association of preoperative, intraoperative, and postoperative variables with postoperative AF was investigated with univariate analysis. The following factors, reported as predictors of AF by other investigators, were also included in the analysis: age at operation, preoperative use of β-blocker, left ventricular ejection fraction, previous MI, diabetes mellitus, surgery of the right coronary artery/posterior descending coronary artery (RCA/PDA), number of grafts, CPB and cardioplegic arrest, intubation time, chest infection, inotropic requirement, and blood loss. Because continuous data did not show a gaussian distribution, they were analyzed by the Mann-Whitney test. Categoric data comparison was made by χ² test. Data are expressed as median with minimum-maximal values or number (percentage) of patients.

Factors that turned out to be predictors of AF at univariate analysis were then included in a stepwise logistic multivariate regression model to ascertain their independent role. ORs and 95% CIs were calculated.

**Results**

Preoperative and operative characteristics are shown in Tables 1 and 2, respectively.

The two groups were similar with respect to age, sex, and severity of coronary disease, diabetes mellitus, angina class, and surgical data, including number of distal anastomoses.

There were 2 deaths in the on-pump group, both for multiorgan failure as a consequence of low cardiac output. Four patients in the on-pump group and 1 in the off-pump group had perioperative MI as per predefined criteria.

<table>
<thead>
<tr>
<th>Table 2. Intraoperative Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>CPB time, min</td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
</tr>
<tr>
<td>Gifts per patient, n</td>
</tr>
<tr>
<td>IMA to LAD or diag graft, n</td>
</tr>
<tr>
<td>SV to diag graft, n</td>
</tr>
<tr>
<td>RCA/PDA graft, n</td>
</tr>
<tr>
<td>Proximal Cx graft, n</td>
</tr>
<tr>
<td>Other arterial grafts†, n</td>
</tr>
</tbody>
</table>

Data are presented as median with minimum-maximal values or number of patients (in parentheses).

IMA indicates internal mammary artery; LAD, left anterior descending coronary artery; diag, diagonal branch of LAD; SV, saphenous vein; and Cx, circumflex artery.

*χ² test.

†This included the use of left and right IMA, radial artery, and gastroepiploic artery to coronary vessels other than LAD.

The incidence of perioperative arrhythmias is presented in Table 3. The overall incidence of AF was 28% (56 patients), with 45 patients in the on-pump group and 11 patients in the off-pump group (P=0.001). Of these, 39 in the on-pump group and 8 in the off-pump group had sustained episodes of AF (P=0.001), and the average of their duration was similar between the two groups (Table 3). Atrial flutter occurred in 2 patients in the on-pump group and 1 patient in the off-pump group. Temporary pacing was required in 7 patients in the on-pump group (1 transient second-degree AV block and 6 transient symptomatic bradycardia) over the first 24 hours after surgery. One patient was temporarily paced in the off-pump group because of transient second-degree AV block (P=0.03, on versus off pump). One patient in each group was affected by third-degree AV block requiring a permanent pacemaker.

Postoperative clinical data are reported in Table 4. The off-pump group showed reduced inotropic usage, chest infec-
TABLE 4. Postoperative Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>On Pump (n=100)</th>
<th>Off Pump (n=100)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>2</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>MI</td>
<td>4</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Chest infection</td>
<td>22</td>
<td>8</td>
<td>0.006</td>
</tr>
<tr>
<td>Transient stroke</td>
<td>2</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Inotropic requirement</td>
<td>23</td>
<td>6</td>
<td>0.001</td>
</tr>
<tr>
<td>Total blood loss, mL</td>
<td>900 (90–4220)</td>
<td>690 (110–2300)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Intubation time, h</td>
<td>8 (3–192)</td>
<td>6 (3–21)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ICU length of stay, d</td>
<td>1 (1–8)</td>
<td>1 (0–6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hospital length of stay, d</td>
<td>7 (5–17)</td>
<td>5 (4–23)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Data are presented as median with minimum-maximal values or number of patients (in parentheses).

*Mann-Whitney or \( \chi^2 \) test.

Discussion

AF is the most common complication occurring after cardiac surgery.\(^1\,^2\) Despite advances in CPB, cardioplegic arrest, and surgical techniques, its incidence has paradoxically increased in recent years\(^3\) as the result of surgical patients being older and sicker and advances in ECG continuous monitoring technology.\(^3\) It is frequently not well tolerated, and patients may have symptoms including temporary hemodynamic instability, thromboembolic events, and shortness of breath or chest discomfort and has been shown to increase costs and to lengthen hospital stay.\(^1\,^3\)

Many preoperative and postoperative factors have been suggested to increase the incidence of postoperative AF after conventional CABG such as advanced age, hypertension,\(^3\) withdrawal of \( \beta \)-blocker drug,\(^19\) RCA stenosis,\(^4\) respiratory complications,\(^5\) and bleeding.\(^7\) Strategies directed toward reduction of postoperative AF have focused on several drugs, given prophylactically, such as \( \beta \)-adrenoceptor antagonists,\(^1,^9\) calcium antagonists,\(^9\) amiodarone, and propafenone,\(^10,^20\) with conflicting results.\(^1\) However, little is known about intraoperative mechanisms through which the incidence of postoperative AF could be reduced.\(^21\)

Recently, there has been a renewed interest in performing CABG on the beating heart.\(^11–14\) Several studies have reported improved myocardial and renal protection,\(^11,^22\) minimal inflammatory response,\(^2,^24\) excellent patency rate of the grafts,\(^13\) and decreased costs.\(^3,^25\) Furthermore, a reduction in postoperative AF has been reported in off-pump series,\(^12,^14\) although this remains an area of controversy.\(^15\) Buffalo and coworkers\(^12\) reported a significantly lower incidence of arrhythmias in a cohort of 1274 patients undergoing off-pump surgery when compared with patients undergoing CABG on pump. Abreu et al\(^14\) have also reported a trend toward a lower incidence of postoperative AF in patients undergoing CABG without CPB. Conversely, Cohn et al,\(^15\) in a very recent retrospective age-matched study, failed to demonstrate a lower incidence of postoperative AF among patients undergoing minimally invasive direct CABG than among those undergoing conventional CABG. This led the authors to conclude that mechanisms common to both groups must be considered as determinants of postoperative AF.

Whereas the above studies,\(^12,^14,^15\) by comparing conventional CABG with beating coronary surgery, are appropriate in terms of control group, in none of these was a prospective randomization undertaken.

To the best of our knowledge, the present study is the first prospective, randomized study to investigate the role of intraoperative factors such as CPB and associated techniques as determinants of postoperative AF in similar cohorts of patients undergoing CABG with or without CPB through a median sternotomy.

The main finding of the present study is that CPB inclusive of cardioplegic arrest is the main independent predictor for the development of postoperative AF, the risk being 7 times higher in the on-pump compared with the off-pump group. This could be related to the period of myocardial ischemia or to the inflammatory response after CPB itself, the required atrial cannulation, and the adverse effects of cardioplegia. Inadequate atrial protection has been postulated as the trigger responsible for the development of AF in vulnerable patients.\(^26,^27\) Myocardial damage has been reported to occur after cross-clamping of the aorta\(^28\) and cardioplegic arrest,\(^1,^2\) with its effects influencing myocardial ischemia and arrhythmias during both reperfusion and the early postoperative periods.\(^9\) In a recent study, we have shown a significantly higher troponin I release in patients undergoing conventional CABG when compared with beating heart revascularization.\(^11\)

Sympathetic activation may be important in the pathogenesis of AF after CABG.\(^2,^6\) and this underlines the importance of \( \beta \)-adrenoceptor blockade as prophylaxis. White and associates\(^19\) found a significant increase in the incidence of AF in patients in whom administration of \( \beta \)-adrenoceptor antagonists was ceased when compared with those whose drug treatment was continued after surgery. In the present study, preoperative \( \beta \)-blockers were administered until the day of surgery and restarted on the first postoperative day unless in the presence of slow heart rate or hemodynamic compromise.

In keeping with the findings of Kalman et al\(^2\) and Aranki et al,\(^3\) the univariate analysis of the present study showed that the need for postoperative inotropic requirement, ventilation time, chest infection, and hospital stay were all predictors of development of AF. However, when these factors were included in a stepwise logistic multivariate regression model, they did not appear to have an independent role.

In contrast with previous reports,\(^1,^2,^7\) this study failed to demonstrate advanced age as an independent predictor of postoperative AF, although overall a higher percentage of AF was observed in older patients.
The 39% incidence of sustained episodes of AF in the on-pump group is in the upper range of that previously reported when similar cardioplegia was used. This relatively high incidence may reflect the use of continuous monitoring during the first 3 postoperative days.

The relation between AF and postoperative bleeding reported by others did not quite reach statistical significance in the univariate analysis of the present study (\(P = 0.06\)). However, the blood loss of the on-pump group in this study is in keeping with other recently published data. A significant percentage of our patients were in-hospital referrals with unstable angina who were still receiving aspirin and low-molecular heparin. Furthermore, cell-savers, tranexamic acid, or aprotinin were not used in this study.

The limitation of the present study is the absence of continuous Holter ECG monitoring after the first 72 hours until discharge from the hospital. Although it is possible that short episodes of asymptomatic AF might have been missed, this is unlikely for sustained episodes, given the fact that patients were assessed every 4 hours. Furthermore, if there was any clinical suspicion of arrhythmia, an ECG was promptly recorded.

Conclusions
This prospective, randomized study clearly shows CPB inclusive of cardioplegic arrest as the main independent predictor of postoperative AF in patients undergoing CABG. The minimal incidence of AF in the off-pump group satisfies the modern demand of further improvements in perioperative patient treatment, reduction of costs and resources while maintaining quality of care, and patient satisfaction.

Acknowledgments
The Garfield Weston Trust and the British Heart Foundation supported this work.

References


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_Circulation_. 2000;102:1530-1535
doi: 10.1161/01.CIR.102.13.1530

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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