Obesity and Metabolic Syndrome Are Independent Risk Factors for Atrial Fibrillation After Coronary Artery Bypass Graft Surgery

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Background—Postoperative atrial fibrillation (POAF) is a highly prevalent complication after cardiac surgery with substantial effects on outcomes. Previous studies have reported that obesity is a risk factor for POAF after cardiac surgery. However, it is unknown whether the metabolic syndrome (MS) also increases the risk of postoperative atrial fibrillation.

Methods and Results—We retrospectively analyzed the association between obesity and MS and the incidence of new-onset POAF in a total of 5085 patients who underwent isolated coronary artery bypass grafting surgery with no concomitant valvular surgery. Of these patients, 1468 (29%) were obese (body mass index \( \geq 30 \text{ kg/m}^2 \)) and 2320 (46%) had a MS as defined by the NCEP-ATPIII. POAF occurred in 1374 (27%) of the patients. Obesity was associated \((P<0.001)\) with increased incidence of POAF in the whole cohort as well as in patients \( \geq 50 \) years old but not in patients \( \leq 50 \) years old. In these patients, MS was the only metabolic factor to be significantly associated with higher incidence of POAF \((12\% \text{ versus } 6\%, P=0.01)\). In \( \geq 50\)-year-old patients, mild \((30 \leq \text{ body mass index} <35 \text{ kg/m}^2)\) and moderate–severe \((\text{body mass index} \geq 35 \text{ kg/m}^2)\) obesity were independently associated with a 1.4-fold (95% CI: 1.10 to 1.71; \(P=0.004\)) and 2.3-fold (95% CI: 1.71 to 3.13; \(P<0.0001\)) increase in the risk of POAF, respectively. In \( \leq 50\)-year-old patients, MS \((\text{relative risk [RR]}: 2.36; 95\% \text{ CI: 1.10 to 5.12}; P=0.02)\) but not obesity was independently associated with POAF.

Conclusion—This study demonstrates that obesity is a powerful risk factor for the occurrence of POAF after isolated coronary artery bypass grafting surgery in patients older than 50 years. However, in the younger population, this association is not observed and MS is the only metabolic risk factor to be independently associated with POAF. (Circulation. 2007;116[suppl I]:I-213–I-219.)

Key Words: atrial fibrillation ■ coronary artery bypass grafting ■ metabolic syndrome ■ obesity

Postoperative atrial fibrillation (POAF) is a highly frequent complication after cardiac surgery, occurring in 1% to 40% of patients undergoing coronary artery bypass grafting surgery (CABG) and in up to 50% of patients after valvular surgery. Although POAF is seen as a temporary problem related to surgery, it is associated with significant morbidity and mortality. The risk for perioperative stroke is 3-fold higher for patients with POAF. In their series, Almassi et al found that hospital mortality (6% versus 3%) and 6-month mortality (9% versus 4%) were significantly higher in patients with POAF compared with those with no POAF after cardiac surgery. Furthermore, the impact of POAF on hospital resources is substantial and was estimated to lengthen hospital stay by 4.9 days, with an extra cost of $10,000 to $11,500 in hospitalization costs in the United States.

Recently, 2 studies have demonstrated that obesity is an independent predictor of new-onset atrial fibrillation (AF) both in the general population and in the postoperative period after cardiac surgery. The metabolic syndrome (MS) is a cluster of metabolic perturbations largely resulting from an excess accumulation of abdominal fat and it is characterized by insulin resistance, hypertriglyceridemia, low high-density lipoprotein cholesterol, and the presence of small dense low-density lipoprotein particles. The metabolic perturbations of the viscerally obese patient are associated with an inflammatory state characterized by elevated circulating cytokines, resulting in an increased oxidative stress. Hence, given that obesity, as defined by the body mass index (BMI), and AF are linked and that inflammation might have a contributory role in the development of this arrhythmia, we hypothesized that...
the MS with its attendant metabolic perturbations would increase the risk of new-onset POAF after CABG surgery.

Methods

Study Population
The data of 5829 patients operated for a first CABG without concomitant procedure, at the Quebec Heart Institute between 2000 and 2004, were retrospectively analyzed. From this cohort, the data required to define the MS were available for 5304 patients. In addition, 219 patients were excluded from this group because they had a history of AF. Thus, our final study population consisted of 5085 patients. The anesthetic and surgical techniques were standardized for all patients and no Maze procedure was performed.

Data Collection
The preoperative and operative data of all patients undergoing a cardiac surgery in our institution were prospectively collected and entered in a computerized database. A fasting plasma lipid profile, including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels, and blood pressure were also assessed in the resting state. Furthermore, waist circumference has been systematically measured since January 2000.

Definition of Obesity
We divided the cohort into 4 categories according to their BMI (kg/m²): normal weight: BMI <25; overweight: 25 ≤BMI <30; mild obesity: 30 ≤BMI <35; moderate–severe obesity: BMI ≥35.

Identification of Patients with the Metabolic Syndrome
The clinical identification of patients with the features of the MS was based on the modified criteria proposed by the National Cholesterol Education Program—Adult Treatment Panel III (NCEP-ATPIII). Patients were considered to have the MS when 3 of the 5 following criteria were present: (1) waist circumference >102 cm in men and >88 cm in women, (2) fasting glycemia ≥6.1 mmol/L, (3) triglycerides ≥1.69 mmol/L, (4) high-density lipoprotein cholesterol <1.04 mmol/L in men and <1.29 mmol/L in women, and (5) hypertension.

Detection and Treatment of Atrial Fibrillation
The end point of this study was new onset of AF from the time of surgery until the hospital stay, and AF was defined as any sustained episode recorded during the postoperative hospital stay and requiring medical and/or electrical cardioversion. No systematic prophylactic measures were used to prevent the development of POAF during the study period. However, as a general rule, patients were on a beta-blocker medication preoperatively and had a reintroduction of this class of medication within the first 24 hours after surgery, and for those who were not previously on a beta-blocker medication, an introduction of such therapy was instituted in postoperative period if not contraindicated. A constant ambulatory electrocardiographic (ECG) monitoring was performed in all patients during the first 48 hours after surgery. Thereafter, a standard daily 12-lead ECG was recorded. In every patient suspected of an arrhythmic event, a standard 12-lead ECG was performed and the patient was monitored with continuous ambulatory ECG until 48 hours after resolution of the arrhythmia. Patients were treated with a standardized protocol for the administration of intravenous amiodarone. Patients with sustained AF not responsive to pharmacological treatment or patients with unstable hemodynamic had an electrical cardioversion.

Statistical Analysis
Continuous variables were expressed as mean±SD and were compared by using 2-sample t tests for independent samples. Differences in proportion were compared using a χ² test or Fisher’s exact test, as appropriate. A stepwise logistic regression analysis was then used to identify the independent predictors of POAF. We entered in the multivariate model age, gender, and all the variables with a probability value of ≤0.25 on univariate analysis. All the statistical analyses were performed using JMP software 5.1. A probability value of less than 0.05 was considered significant.

Results
From the study population (5085 patients), 2320 (46%) patients met the criteria for the MS and 31% had diabetes. Mean age was 64±10; 3900 (77%) were men; mean BMI was 27.9±4.7 kg/m²; and 377 patients (7%) had a BMI ≥35 kg/m². Fifty-three percent of the patients with MS were not obese (BMI <30 kg/m²). On the other hand, 14% of the patients with no MS were obese. These data underline the point that although there is an association between obesity and MS, these 2 entities are not necessarily equivalent.

Overall, the prevalence of POAF was 27% (1374 patients). Five hundred three (10%) patients were ≤50 years old and in this subset, the prevalence of AF was 8%, whereas it was 29% in patients >50 years old (P<0.0001). In the ≤50 years old group, the patients with POAF had a higher prevalence of MS (62% versus 42%; P<0.01) and a longer duration of hospital stay (Table 1). There was no other significant difference between the POAF and no POAF groups in the ≤50-year-old patients. In the >50-year-old patients, those who had POAF were older and had a significantly higher prevalence of obesity, hypertension, chronic obstructive pulmonary disease, and 3-vessel coronary artery disease, a lower high-density lipoprotein cholesterol and plasma triglyceride level, and a longer cardiopulmonary bypass time (Table 1). With regard to postoperative data, they had a higher 30-day mortality rate, a higher prevalence of prolonged intubation and postoperative infections, and a longer duration of hospital stay.

Postoperative Atrial Fibrillation in the Total Cohort of Patients
When compared with patients without MS, patients with MS had a higher incidence of POAF compared with those without MS: 29% versus 26% (P=0.01). When we stratified patients according to BMI, the incidence of AF increased significantly (P=0.02) and progressively with increasing BMI: 25% in normal weight, 26% in overweight patients, 29% in patients with mild obesity, and 34% in patients with moderate–severe obesity (Figure A).

Postoperative Atrial Fibrillation in Patients ≤50 Years
In patients ≤50 years old, there was no significant association between BMI and POAF (Figure B). However, when stratified according to the presence of the MS, the incidence of POAF increased significantly from 6% in those without MS to 12% in those with MS (P=0.01).
TABLE 1. Baseline Characteristics of Patients With New-Onset POAF Versus Those With No POAF in the Subset of Patients ≤50 and >50 Years Old

<table>
<thead>
<tr>
<th></th>
<th>≤50 Years Old (N=503)</th>
<th>&gt;50 Years Old (N=4583)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POAF (8%)</td>
<td>No POAF (92%)</td>
<td>P Value*</td>
</tr>
<tr>
<td>Age, years</td>
<td>46±4</td>
<td>45±4</td>
<td>NS</td>
</tr>
<tr>
<td>Gender, % of male</td>
<td>83</td>
<td>85</td>
<td>NS</td>
</tr>
<tr>
<td>Metabolic syndrome, %</td>
<td>62</td>
<td>42</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI, kg/m</td>
<td>29.4±5</td>
<td>28.8±5</td>
<td>NS</td>
</tr>
<tr>
<td>Normal weight (BMI &lt;25), %</td>
<td>19</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Overweight (25 ≤ BMI &lt;30), %</td>
<td>38</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>Mild obesity (30 ≤ BMI &lt;35), %</td>
<td>31</td>
<td>22</td>
<td>0.20</td>
</tr>
<tr>
<td>Moderate–severe obesity (BMI ≥35), %</td>
<td>12</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>101±16</td>
<td>100±14</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>55</td>
<td>47</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>31</td>
<td>22</td>
<td>0.20</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/L</td>
<td>1.02±0.2</td>
<td>1.05±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.93±0.9</td>
<td>1.97±1.27</td>
<td>NS</td>
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<td>Fasting glycemia, mmol/L</td>
<td>6.3±2.7</td>
<td>5.9±1.91</td>
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</tr>
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<td>ß-blockers medication, %</td>
<td>76</td>
<td>85</td>
<td>0.12</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, %</td>
<td>2</td>
<td>2</td>
<td>NS</td>
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<tr>
<td>Left ventricular ejection fraction, %</td>
<td>57±14</td>
<td>58±13</td>
<td>NS</td>
</tr>
<tr>
<td>Left main ≥50% coronary stenosis, %</td>
<td>2</td>
<td>13</td>
<td>0.07</td>
</tr>
<tr>
<td>Three-vessel coronary artery disease, %</td>
<td>44</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>55</td>
<td>52</td>
<td>NS</td>
</tr>
<tr>
<td>Previous stroke, %</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min</td>
<td>75±21</td>
<td>72±25</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic crossclamp time, min</td>
<td>53±19</td>
<td>48±19</td>
<td>0.11</td>
</tr>
<tr>
<td>Off-pump surgery, %</td>
<td>5</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>No. of bypassed vessels ≥3, %</td>
<td>81</td>
<td>73</td>
<td>NS</td>
</tr>
<tr>
<td>30-day mortality, %</td>
<td>0</td>
<td>0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Prolonged intubation &gt;48 hr, %</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative infections, %</td>
<td>0</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative stroke, %</td>
<td>0</td>
<td>0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital stay duration, days</td>
<td>7±4</td>
<td>6±4</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Mean±SD for continuous variables are shown.

*P value is for the comparison between POAF and no POAF groups among the patients ≤50 and >50 years old.

NS indicates not significant.

After adjusting for age, gender, BMI, diabetes, left main coronary stenosis, preoperative medication with beta-blockers, and aortic crossclamp time, the MS was the only significant predictor of POAF with a 2.36-fold (95% CI: 1.10 to 5.12; P=0.02) increase in the risk of PAOF.

Postoperative Atrial Fibrillation in Patients >50 Years

In patients >50 years old, the incidence of POAF was not significantly influenced by the presence of the MS: 30% versus 28% (P=0.06). However, the incidence of POAF was significantly higher (P<0.0001) in the group of patients with moderate–severe obesity (BMI ≥35 kg/m²) than in the other groups (Figure C). The association between obesity and the risk of POAF was observed in both males (P=0.002) and females (P=0.05), in patients with (P=0.006) or without (P=0.01) hypertension, and in patients with diabetes (P=0.0001) or without (P=0.01) diabetes.

On multivariate analysis, the independent predictors of POAF in the >50 years old group were: age, male gender, and obesity (Table 2). In this multivariate model, the risk of POAF was significantly increased by 1.38-fold 95% CI: 1.10 to 1.71; P=0.004) in the patients with mild obesity and 2.31-fold (95% CI: 1.71 to 3.13; P<0.0001) in the patients with moderate–severe obesity when compared with the normal-weight patients. In contrast, overweight was not
significantly associated with increased risk of POAF. Then, we constructed a second model in which BMI was entered as a continuous variable instead of categorical. In this model, increased BMI was independently associated with POAF (RR/per one-unit increase of BMI: 1.05; 95% CI: 1.03 to 1.06; \( P \leq 0.0001 \)).

Obesity may also increase the risk of postoperative infectious complications and delay extubation, which could in turn increase the risk of POAF. In our series, obese patients indeed had significantly higher prevalence of postoperative infectious complications (5% versus 2%; \( P < 0.001 \)) and of prolonged intubation > 48 hours (4% versus 1%; \( P < 0.001 \)). In addition, these factors were significantly associated with increased risk of POAF (Table 1). However, after further adjusting for these postoperative variables, mild obesity (RR: 1.36; 95% CI: 1.10 to 1.69; \( P \leq 0.006 \)) and moderate–severe obesity (RR: 2.30; 95% CI: 1.70 to 3.11; \( P \leq 0.0001 \)) remain independently associated with the occurrence of POAF in the > 50 years old patients.

### Discussion

The present study included a large cohort of patients operated for isolated CABG and demonstrated that MS and obesity are powerful independent predictors of POAF. To our knowledge, this is the first study to report that the MS is an independent predictor of new-onset of AF after isolated CABG in young patients. In this population, the MS was indeed associated with a 2.36-fold increase in the risk of POAF. In patients > 50 years old, however, the MS was not significantly associated with POAF, whereas mild obesity (BMI \( \geq 35 \) kg/m\(^2\)) and moderate–severe obesity (BMI \( \geq 35 \) kg/m\(^2\)) were independently associated with a 1.4-fold and 2.3-fold increase in the risk of POAF, respectively.

### Obesity and Atrial Fibrillation

Obesity has reached epidemic proportions and has become a major health problem in Westernized societies. Obesity is associated with increased prevalence of hypertension, coro-
nary artery disease, diabetes mellitus, left ventricular hyper-
trophy, left atrial enlargement, and congestive heart failure.14
Previous studies have suggested that left atrial enlargement is
the main mechanism responsible for the association between
obesity and the risk of AF.9,10 On the other hand, the cause of
left atrial enlargement in obese individuals remains relatively
unknown and is probably multifactorial.

In the present study, we report a strong and independent
association between obesity (as defined by the BMI) and
POAF in a population of patients undergoing isolated CABG,
buttressing a previous study showing a similar observation in
a cardiac surgical population.9 The original contribution of
this study was to demonstrate that the association between
obesity and the risk of POAF is highly dependent on age.
Mild and moderate–severe obesity were associated with an
increased risk of POAF in patients >50 years old; however,
this association was not observed in younger patients.
Interestingly, in this younger population, the MS was found to be
the only significant predictor of POAF. The MS is a cluster of
metabolic abnormalities, which largely results from the ex-
cessive accumulation of visceral fat. The BMI alone is an
indicator of total body fat accumulation and does not take into
account adipose tissue distribution or its metabolic perturba-
tions. Obesity is a heterogeneous condition in which fat
distribution plays a crucial role in its pathophysiology and
associated complications. Thus, our findings support the
notion that fat distribution along with its metabolic conse-
quences affects development of POAF in an age-dependent
manner.

Potential Mechanisms Responsible for the
Association Between Metabolic Syndrome and
Atrial Fibrillation
Pathophysiology of AF is multifactorial, but the process
called atrial remodelling is critical for AF development and
seems to be the most significant factor underlying AF
recurrence and perpetuation in the general population.15
In particular, one cannot exclude, that as for obesity, left atrial
enlargement may have contributed to the association between
MS and POAF. Although, no previous study have reported a
link between MS and left atrial enlargement, it is nonetheless
possible that the metabolic and hemodynamic alterations
associated with the MS may lead to a dilatation of the left
atrium.

Atrial remodelling includes an anatomic substrate, which
refers to atrial architecture (atrial dilatation, fibrosis), and a
functional substrate, which refers to electrical inhomogeneity
(shortness of effective refractory period, dispersion of refrac-
toriness and conduction, abnormal automaticity, and aniso-
tropic conduction).16 It has been demonstrated that these latter
processes act as potential substrates for POAF.17 Further-
more, there is now an increasing body of evidence that
inflammation and oxidative stress play an important role in
the pathogenesis of atrial remodelling.18 Patients with the MS
have a condition characterized by a low-grade inflammatory
process, which could be exacerbated in the perioperative
period. Moreover, patients with the MS have increased
systemic oxidative stress, which is at least in part, attributable
to the increased oxidative transformation of low-density
lipoprotein to oxidized low-density lipoprotein.18 The use of
cardiopulmonary bypass in cardiac surgery is associated with
an inflammatory response and the production of free radic-
als,19 which might be amplified in patients with the MS,
thereby explaining a potential pathway by which MS affects
the incidence of POAF.

The lipolytic activity of abdominal fat depot contributes to
generate important amount of free fatty acids.20 Circulating
amount of free fatty acids has been related to ventricular
arrhythmia and to sudden death.21 The proarrhythmic effect
of free fatty acids is particularly important during ischemic
events. Although the effect of free fatty acids on ventricular
arrhythmogenicity is well documented, it remains to be seen
if such proarrhythmic activity is implicated in the generation
of AF. Thus, although speculative for the moment, the
surgical stress encountered during CABG surgery along with
free fatty acids load generated by the hyperlipolytic visceral
fat depot could predispose to POAF.

Clinical Implications
Previous studies have shown the effectiveness of prophylactic
interventions to prevent POAF in patients undergoing a
cardiac surgery. However, the preventive treatment strategy
consisting in the systematic preoperative administration of
pharmacological agents such as amiodarone exposes a large
proportion of patients at variable risk for AF to potentially
serious adverse side effects of these agents. Because obesity
and the MS are frequent and potentially modifiable risk
factors, the impact of our findings on clinical practice is of
great relevance. Indeed, obesity and MS are highly prevalent
risk factors in the cardiac surgical population; thus, interven-
tions consisting of either lifestyle interventions or pharma-
co logical treatment, aimed at reducing the incidence of such risk
factors, would potentially have a major impact in reducing
morbidity after cardiac surgery. In addition, acute interven-
tions during the perioperative period might also be consid-
ered. In a recent randomized study, interventions aimed at
better control of the perioperative glycemia in patients with
diabetes undergoing CABG surgery have demonstrated a
substantial reduction of complications, including AF, in the
group with a tight glycemic control.27 On the other hand, it
remains to be determined if other acute interventions during
the perioperative period at targeting features of the MS or obesity would reduce the incidence of POAF. Actual pharmacological interventions (such as statins, angiotensin-converting enzyme inhibitors, and so on) have a minimal impact on the metabolic and inflammatory perturbation of the MS or obesity. However, newer therapeutic interventions targeting some key features of the MS have been recently proposed. Consequently, further studies are needed to understand potential mechanisms behind the association of obesity and MS with POAF. Such new knowledge could pave the way to tailored therapies aimed at reducing the incidence of POAF and its related complications.

Study Limitations
Patients were not monitored with a continuous recording throughout their entire hospitalization and therefore, possible short arrhythmic episodes could have been missed. However, the detection and treatment of clinically significant arrhythmia was part of a systematic protocol, which is routinely used for every patient in our institution, thus reducing potential bias.

The left atrial size, which was not measured in the present study, has been reported as an important determinant of POAF in patients who are obese. It is possible that left atrial enlargement may be, at least in part, responsible for the association between obesity or MS and POAF. Nonetheless, left atrial enlargement is most likely a surrogate marker for other abnormalities rather than an independent determinant per se. Hence, further studies are needed to identify the causal mechanisms leading to left atrial enlargement.

The apparent lack of significant association between POAF and some clinical factors in the subset of patients ≤50 years old may be a type II error attributable to the relatively smaller sample size and the lower incidence of POAF compared with the patients >50 years old. Nonetheless, this limitation does not affect the validity of the main result of this study, which is the demonstration of a strong association between MS and the risk of POAF in the patients ≤50 years old.

The length of time spent in the hospital as a result of postoperative complications may increase the chance to detect AF and therefore introduces a detection bias in obese and/or MS patients prone to complications. However, even after adjusting for hospital duration, obesity (mild obesity: RR, 1.34; 95% CI: 1.07 to 1.68, P = 0.009; moderate−severe obesity: RR, 2.26; 95% CI: 1.66 to 3.07, P < 0.0001), and MS (RR: 2.30; 95% CI: 1.07 to 5.0; P = 0.03) remained independent predictors of POAF in patients >50 and ≤50 years old, respectively.

Conclusion
Our study shows that, in subjects >50 years old, obesity is associated with increased incidence of POAF, whereas in subjects ≤50 years old, MS is associated with increased incidence of POAF. Thus, interventions focused at reducing the incidence of these conditions in patients with coronary artery disease would have, beyond reducing the overall cardiovascular risk, a potential benefit in reducing morbidity in the advent of a planned surgical revascularization. Studies aimed at a better understanding of the mechanism linking obesity and MS with POAF would possibly help at designing new therapeutic strategies to acutely reduce the incidence of POAF.

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Disclosures
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References


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