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 ≥30 kg/m²) 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 ≥50 years old but not in patients ≤50 years old. In these patients, MS was the only metabolic factor to be significantly associated with higher incidence of POAF (12% versus 6%, P=0.01). In >50-year-old patients, mild (30 ≤ body mass index <35 kg/m²) and moderate–severe (body mass index ≥35 kg/m²) 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 ≤50-year-old patients, MS (relative risk [RR]: 2.36; 95% 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.

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 11% 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

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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-ATP III).12 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 to the end of the hospital stay. If AF was diagnosed, 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 prophylactic measures were used to prevent the development of POAF during the study period. However, as a general rule, patients who were on a beta-blocker medication preoperatively had a reintroduction 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 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.

Because AF is strongly age-dependent, and because the prevalence of AF doubles with each decade from the age of 50,13 we divided patients into 2 groups according to their age: (1) patients ≤50 years old and (2) patients >50 years old.

Statement of Responsibility
The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the article as written.

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 of 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=0.002) 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>Preoperative data</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>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>Triglycerides, mmol/L</td>
<td>1.02±0.2</td>
<td>1.05±0.3</td>
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<tr>
<td>Fasting glycemia, mmol/L</td>
<td>1.93±0.9</td>
<td>1.97±1.27</td>
<td>NS</td>
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<tr>
<td>ß-blockers medication, %</td>
<td>76</td>
<td>85</td>
<td>0.12</td>
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<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>
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<tr>
<td>Left main ≥50% coronary stenosis, %</td>
<td>2</td>
<td>13</td>
<td>0.07</td>
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<tr>
<td>Three-vascular 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>
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<th>Operative data</th>
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<th>&gt;50 Years Old (N=4583)</th>
<th>P Value*</th>
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<tr>
<td>Cardiopulmonary bypass time, min</td>
<td>75±21</td>
<td>72±25</td>
<td>NS</td>
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<tr>
<td>Aortic crossclamp time, min</td>
<td>53±19</td>
<td>48±19</td>
<td>0.11</td>
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<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>
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<table>
<thead>
<tr>
<th>Postoperative data</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>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<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=0.006) and moderate–severe obesity (RR: 2.30; 95% CI: 1.70 to 3.11; P<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, whereas mild obesity (BMI <35 kg/m²) and moderate–severe obesity (BMI ≥35 kg/m²) 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 hypertrophy, left atrial enlargement, and congestive heart failure. Previous studies have suggested that left atrial enlargement is the main mechanism responsible for the association between obesity and the risk of AF. 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. 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 excessive 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 perturbations. 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 consequences 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. 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 dilation 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 refractoriness and conduction, abnormal automaticity, and anisotropic conduction). It has been demonstrated that these latter processes act as potential substrates for POAF. Furthermore, there is now an increasing body of evidence that inflammation and oxidative stress play an important role in the pathogenesis of atrial remodelling. 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. The use of cardiopulmonary bypass in cardiac surgery is associated with an inflammatory response and the production of free radicals, 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. Circulating amount of free fatty acids has been related to ventricular arrhythmia and to sudden death. The proarhythmic 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.

Potential Mechanisms Responsible for the Association Between Obesity and Atrial Fibrillation

Because it is well established that atrial stretch and dilatation increases the vulnerability of the atrium to the development of AF, it has been reported that increasing BMI or adiposity is strongly correlated with left atrial enlargement. Increased left atrial volume is associated with an incremental deterioration of diastolic function and provides further predictive information in regard to the development of AF. Obesity is also associated with ventricular remodelling, elevated plasma volume, and ventricular diastolic dysfunction that may lead to left atrial enlargement. Also, inflammation, increased oxidative stress and lipoapoptosis, which are associated with increasing adiposity, may contribute to structural atrial changes increasing the risk of AF.

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, interventions consisting of either lifestyle interventions or pharmacological treatment, aimed at reducing the incidence of such risk factors, would potentially have a major impact in reducing morbidities after cardiac surgery. In addition, acute interventions during the perioperative period might also be considered. 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. 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 POAF in patients who are obese.9 It is possible that 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, an unmeasured effect of obesity rather than MS on POAF cannot be ruled out. Hence, future studies are needed to determine the causal mechanisms leading to left atrial enlargement.

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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