Metabolic Syndrome Is Associated With Faster Degeneration of Bioprosthetic Valves

Martin Briand, MS; Philippe Pibarot, DVM, PhD; Jean-Pierre Després, PhD; Pierre Voisine, MD; Jean G. Dumesnil, MD; François Dagenais, MD; Patrick Mathieu, MD

Background—Several studies have reported similarities between calcification of the native aortic valve and atherosclerosis. Recent studies also suggested that hypercholesterolemia may be a risk factor for calcific degeneration of bioprosthetic valves. The metabolic syndrome (MS) is associated with a higher risk of vascular atherosclerosis. We thus hypothesized that the atherogenic features of MS could accelerate bioprosthetic valve degeneration.

Methods and Results—We included 217 patients who underwent aortic valve replacement with a bioprosthetic valve in the study. Of these patients, 71 patients (33%) had MS defined according to the modified criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III. The annualized increase in mean transprosthetic gradient and the worsening of transprosthetic regurgitation measured by Doppler echocardiography were used to assess the deterioration of valve hemodynamic function. Patients with MS had higher progression of gradient (+4±5 mm Hg/year versus +2±2 mm Hg/year, \(P<0.001\)), higher proportion of ≥1/3 degree worsening of regurgitation (25% versus 12%, \(P=0.02\)), and higher proportion of valve function deterioration defined as regurgitation worsening and/or ≥3 mm Hg/year increase in gradient (41% versus 25%, \(P=0.02\)) when compared with patients without MS. On multivariate analysis, MS was an independent predictor of gradient progression (\(P=0.01\)), regurgitation worsening (\(P=0.02\)), and valve function deterioration (\(P=0.02\)). The other independent predictors were diabetes, renal insufficiency, and higher mean gradient at baseline.

Conclusions—This is the first study to report that the MS is independently associated with faster bioprosthetic valve degeneration. This study could pave the way for the development of a new medical therapy able to significantly reduce the structural valve deterioration of bioprostheses. (Circulation. 2006;114:[suppl I]:I-512–I-517.)

Key Words: heart valve prosthesis ■ metabolic syndrome ■ Doppler echocardiography

Bioprosthetic valves are composed of altered biological tissue that may undergo degenerative processes. Calcific degeneration of cusp tissue is responsible for approximately 75% of bioprosthetic valve failures. Several studies have reported important similarities between calcification of the native aortic valve and atherosclerosis.\(^1\)\(^2\) The development and progression of calcific aortic valve stenosis have been linked to various traditional risk factors for coronary artery disease. These findings support the notion that aortic stenosis is not a degenerative disease resulting from decades of repetitive mechanical stress, but rather an active disease related to atherosclerosis. Similarly, hypercholesterolemia, diabetes, and smoking have been associated with an increased risk of reoperation as a result of structural valve failure in patients with a bioprosthetic valve.\(^3\)\(^4\) Moreover, another recent study reported that statins could slow the progression of bioprosthetic valve degeneration.\(^5\)

These findings suggest that an active atherosclerotic-like process may also be involved in the calcific degeneration of bioprosthetic valves. Identification of new factors responsible for structural valve failure of bioprostheses could be useful in developing new therapeutic approaches with the aim of delaying or stopping this degenerative process and thereby avoiding the need for reoperation.

The metabolic syndrome (MS) is a cluster of atherogenic, inflammatory, and atherothrombotic abnormalities that are linked to abdominal obesity and insulin resistance.\(^6\) We recently demonstrated that the MS is a strong independent predictor of disease progression and occurrence of outcomes in patients with native aortic valve stenosis.\(^7\) We thus hypothesized that the proatherogenic and proinflammatory features of the MS could also accelerate the tissue degeneration of bioprosthetic valves. The objective of this study was thus to determine the impact of the MS on the deterioration of bioprosthetic valve hemodynamic function.

Methods

Patient Population

Between August 1997 and February 2004, a total of 1419 patients underwent an isolated aortic valve replacement with a bioprosthetic...
valve at the Quebec Heart Institute. Of this group, only the 317 patients who had their routine Doppler echocardiographic follow-up performed at the Quebec Heart Institute were considered for this study. Patients were included if they had a minimum of 2 echocardiograms separated by at least 6 months. Two hundred seventeen patients met these inclusion criteria.

Doppler Echocardiography

Maximum transprosthetic flow velocity was determined by continuous-wave Doppler. Mean transprosthetic gradient was calculated using the modified Bernoulli equation. Annualized change in mean gradient (mm Hg/year) was calculated by dividing the difference between the first and last measurements of the follow-up by the time between examinations. Transprosthetic regurgitation was graded semiquantitatively by color Doppler echocardiography according to the following scale: 0, none; 0.5, trivial; 1, mild; 2, moderate; and 3, severe. Worsening of valve regurgitation was defined as an increase of at least 1 degree in the severity of regurgitation during follow-up compared with the value at baseline. In addition, we determined the number of patients who had a deterioration of their valve hemodynamic function during follow-up. This combined variable was defined as a rate of increase in mean gradient ≥3 mm Hg/year and/or ≥1/3 degree worsening of aortic regurgitation.

Clinical, Laboratory, and Operative Data

Clinical data included age, gender, history of smoking, and documented diagnoses of hypertension, diabetes, hypercholesterolemia, coronary artery disease, and renal insufficiency. Furthermore, blood pressure, fasting plasma lipid profile, and glycemia were measured in all patients before operation. Operative data as well as information on statin treatment were also recorded.

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). As waist circumference was not measured in this sample, body mass index was substituted for waist circumference as an index of obesity. Patients waist circumference was not measured in this sample, body mass index were considered to have the MS when 3 of the 5 following criteria were present: (1) body mass index ≥30 kg/m², (2) fasting glycemia ≥110 mg/dL, (3) triglycerides ≥150 mg/dL, (4) high-density lipoprotein (HDL) cholesterol <40 mg/dL in men and <50 mg/dL in women, and (5) systolic/diastolic blood pressures ≥130/85 mm Hg.

Statistical Analysis

Continuous data were expressed as mean±SD and compared using unpaired Student’s t test. Categorical data were expressed as a percentage and compared with the χ² test. A forward stepwise multiple linear regression analysis was used to identify the independent predictors of the progression rate of mean gradient. A forward stepwise multiple logistic regression analysis was used to identify the independent predictors of the worsening of valve regurgitation and the deterioration of valve hemodynamic function.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics

Of the 217 subjects, 71 (33%) met the clinical criteria of the MS. The baseline characteristics in the different groups are shown in Table 1. The group of patients with MS had a higher proportion of women, a higher prevalence of hypertension, diabetes, and obesity, and a higher Framingham score compared with patients without MS. As expected, patients with MS had significantly higher plasma levels of glucose and triglycerides and lower levels of HDL cholesterol. However, the plasma concentrations of total and low-density lipoprotein (LDL) cholesterol were not different between the 2 groups. With regard to operative data, patients with MS had a higher Parsonnet score and a smaller prosthesis size. There was, however, no difference between the 2 groups with regard to the type of bioprosthesis used for aortic valve replacement or the proportion of patients who had concomitant coronary artery bypass graft.

Predictors of Bioprosthetic Valve Degeneration

The average baseline mean gradient was 11±5 mm Hg and mean time interval between the first and last echocardiographic examination was 3.1±1.8 years (Table 2). The average rate of progression of mean gradient was +3±3 mm Hg/year. On univariate analysis, diabetes (P<0.001), MS (P<0.001), renal insufficiency (P=0.01), Framingham Score >8 (P=0.02), statin treatment (P=0.03), and prosthesis size (P=0.01) were associated with faster progression of mean gradient. There was also a trend (P=0.06) for more rapid progression in women, as well as in patients with hypertension. The progression rate of the gradient was twice as high among patients with the MS than among those without (Table 2). Patients receiving statin therapy had a significantly higher rate of progression of mean gradient (+4±6 versus +2±3 mm Hg/year; P=0.03).

In this series, 35 patients (16%) had a worsening of valve regurgitation (Table 2). The proportion of patients having a worsening of valve regurgitation was 2-fold higher in patients with MS compared with those without MS (25% versus 12%, P=0.02). Baseline mean gradient was the only other factor associated with regurgitation worsening (P=0.003).

Deterioration of valve hemodynamic function defined as a worsening of valve regurgitation and/or a rate of increase in mean gradient ≥3 mm Hg/year occurred in 65 of the 217 patients (30%) included in this study. The factors significantly associated with a higher occurrence of valve function deterioration were female gender (P=0.03), MS (P=0.02), coronary artery disease (P=0.02), stented bioprosthesis (P=0.009), prosthesis size (P=0.01), and higher mean gradient at baseline (P=0.002). The proportion of patients having a deterioration of valve hemodynamic function was higher in patients with MS (41%) compared with those without MS (25%, P=0.02; Table 2).

With regard to plasma lipid and glycemic profile measured at the time of operation, there was a weak correlation between glycemia (r=0.30, P=0.02) and progression rate of gradient. There was, however, no other significant association between the indices of bioprosthetic valve degeneration and the plasma levels of total, LDL, or HDL cholesterol.

On multivariate analysis, diabetes (P=0.004), MS (P=0.01), and renal insufficiency (P=0.02) were the only factors independently associated with faster progression of mean gradient (Table 3). Among patients without diabetes, the patients with the MS had a faster progression of gradient compared with those with no MS (P=0.02, Figure 1). This difference was also observed in patients with diabetes, but it was not statistically significant (P=0.08). The combination of MS and diabetes was associated with a rapid progression of mean gradient, which was approximately 2.5-fold higher than in those without these 2 factors.
Moreover, MS was an independent predictor of worsening regurgitation and valve function deterioration (Table 3). The other independent risk factors were higher mean gradient at baseline for worsening of valve regurgitation and prosthesis size ≤21 mm for deterioration of valve function.

Discussion

The contribution of the present study is to provide, for the first time, evidence that the MS is a strong independent predictor of bioprosthetic valve degeneration. These findings are clinically relevant, given that MS is a frequent and

### TABLE 1. Baseline Patients Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients (n=217)</th>
<th>No MS (n=146; 67%)</th>
<th>MS (n=71; 33%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71±8</td>
<td>71±8</td>
<td>70±8</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>139 (64)</td>
<td>102 (70)</td>
<td>37 (52)</td>
<td>0.02</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.78±0.18</td>
<td>1.77±0.18</td>
<td>1.82±0.17</td>
<td>0.04</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27±5</td>
<td>26±4</td>
<td>31±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow-up duration, y</td>
<td>3.1±1.8</td>
<td>3.1±1.8</td>
<td>2.9±1.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Risk factors**

- Hypertension 140 (65) 76 (52) 64 (90) 0.001
- Diabetes 57 (26) 21 (14) 36 (51) 0.001
- Obesity 70 (32) 19 (13) 51 (72) 0.001
- History of hypercholesterolemia 162 (75) 107 (73) 55 (77) NS
- History of smoking 26 (12) 17 (12) 9 (13) NS
- Coronary artery disease 144 (66) 98 (67) 46 (65) NS
- Renal insufficiency 22 (10) 11 (8) 11 (15) NS
- Framingham score 8.8 3.2 7.7 2.6 11.0 3.1 0.001

**Laboratory**

- Glycemia, mg/dL 108±35 98±17 129±51 <0.001
- Triglycerides, mg/dL 134±68 108±45 188±76 <0.001
- Total cholesterol, mg/dL 181±42 178±35 187±53 NS
- HDL cholesterol, mg/dL 48±14 51±13 44±14 <0.001
- LDL cholesterol, mg/dL 106±35 106±31 106±44 NS
- Total cholesterol/HDL cholesterol 3.9±1.2 3.7±1.0 4.5±1.4 <0.001

**Operative data**

- Stented porcine bioprosthesis 118 (54) 82 (56) 36 (50) NS
- Stented pericardial bioprosthesis 45 (21) 31 (21) 14 (20) NS
- Stentless porcine bioprosthesis 54 (25) 33 (23) 21 (30) NS
- Bioprosthesis size, mm 24.0±2.1 24.3±2.2 23.6±1.9 0.03
- Coronary artery bypass graft 136 (63) 91 (62) 45 (63) NS
- Parsonnet score 19±10 18±10 21±11 0.01

Values are expressed as mean±SD or n (%). NS indicates not significant.

### TABLE 2. Changes in Bioprosthetic Valve Hemodynamic Function During Follow-up

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients (n=217)</th>
<th>No MS (n=146; 67%)</th>
<th>MS (n=71; 33%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean gradient, mm Hg</td>
<td>11±5</td>
<td>11±5</td>
<td>12±5</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline aortic regurgitation</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>0</td>
<td>137 (63)</td>
<td>91 (62)</td>
<td>46 (65)</td>
<td></td>
</tr>
<tr>
<td>0.5+</td>
<td>18 (8)</td>
<td>13 (9)</td>
<td>5 (7)</td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>47 (22)</td>
<td>33 (23)</td>
<td>14 (20)</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>14 (6)</td>
<td>8 (5)</td>
<td>6 (8)</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Progression rate of mean gradient, mm Hg/y</td>
<td>3±3</td>
<td>2±2</td>
<td>4±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Worsening of valve regurgitation</td>
<td>35 (16)</td>
<td>17 (12)</td>
<td>18 (25)</td>
<td>0.02</td>
</tr>
<tr>
<td>Deterioration of valve hemodynamic function</td>
<td>65 (30)</td>
<td>36 (25)</td>
<td>29 (41)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or n (%). NS indicates not significant.
modifiable condition largely resulting from overweight/obesity and a sedentary lifestyle. Previous studies have reported that the prevalence of MS was estimated to reach ≈25% in the western world population. In our sample of elderly patients undergoing aortic valve replacement, the prevalence of MS was up to 33%. Furthermore, the fact that MS and diabetes were independent predictors of the deterioration of valve hemodynamic function supports the concept that active processes are involved in the tissue degeneration of bioprosthetic valves.

Comparison With Previous Studies
Because degeneration of bioprosthetic valves was generally considered to be a purely degenerative process, there have been few studies focusing on the association between metabolic risk factors and bioprosthetic valve degeneration. These studies reported that younger age at implantation, female gender, hypercholesterolemia, diabetes, smoking, and absence of statin therapy were associated with faster progression of bioprosthetic valve dysfunction and higher occurrence of structural valve deterioration requiring reoperation. In the present study, diabetes was also found to be an independent risk factor for faster progression of transprosthetic gradient.

It should also be pointed out that, as opposed to what was seen in these previous studies, only a small proportion of patients included in the present study had hypercholesterolemia at the time of operation. This is consistent with the fact that today patients with hypercholesterolemia are treated more aggressively and that more efficient therapies are available. As a matter of fact, although 75% of the patients of this series had a history of hypercholesterolemia, lipid-lowering therapy was successful in achieving the recommended goal of the NCEP-ATPIII, ie, an LDL cholesterol level <130 mg/dL, in 169 (78%) of these patients. This may help explain the absence of association between history of hypercholesterolemia and bioprosthetic valve degeneration in the present study.

Antonini-Canterin et al reported that statin treatment is associated with less bioprosthetic valve degeneration. In contrast, in the present study, the patients who were taking statins had faster progression of transprosthetic gradient. This discrepancy between these 2 studies might be due to the fact that there were relatively few patients with hypercholesterolemia in our series. In addition, it should be noted that patients at higher global risk of cardiovascular diseases generally require more aggressive therapy and are most often treated with statins. Hence, statin therapy may be a marker for other cardiovascular risk factors and concomitant diseases. And as a matter of fact, this factor did not emerge as an independent predictor of valve degeneration on multivariate analysis. Moreover, it should be emphasized that statin therapy was not able to slow valve degeneration in patients with MS (Figure 2).

Higher transprosthetic gradient at baseline and small prosthesis size were found to be independent risk factors for

<table>
<thead>
<tr>
<th>Variables</th>
<th>Progression Rate of Mean Gradient</th>
<th>Worsening of Valve Regurgitation</th>
<th>Progression of Valve Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>STD Coeff.</td>
<td>P</td>
<td>Odds Ratio (CI)</td>
</tr>
<tr>
<td>Prosthesis size ≤21 mm</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Baseline mean gradient, mm Hg</td>
<td>—</td>
<td>—</td>
<td>1.1 (1.02–1.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.22</td>
<td>0.004</td>
<td>—</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>0.19</td>
<td>0.01</td>
<td>2.7 (1.1–6.9)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>0.17</td>
<td>0.02</td>
<td>—</td>
</tr>
</tbody>
</table>

All the variables presented in Table 1 were tested in univariate and multivariate analysis. The progression rate of mean gradient was entered into the analysis as a continuous variable, whereas worsening of valve regurgitation and progression of valve dysfunction were entered as dichotomous variables (presence or absence). Only the variables that reached statistical significance on multivariate analysis are shown in this table. STD coeff. indicates standardized coefficient; CI, confidence interval.

Figure 1. Rate of progression of mean gradient (MG) among the 2 groups separated according to the presence or absence of diabetes in patients with the MS (solid bars) and in those without the MS (open bars). *P<0.05 versus Group 1, †Group 2, and ‡Group 3.

Figure 2. Rate of progression of mean gradient (MG) among the 2 groups separated according to the presence or absence of statin therapy in patients with the MS (solid bars) and those without the MS (open bars). Symbols as in Figure 1.
bioprosthetic valve degeneration in the present study. One possible explanation for this finding is that these factors could be associated with higher mechanical stress on the valve cusps, which has been demonstrated to contribute to the tissue degeneration of bioprostheses.10

**Potential Mechanisms Responsible for the Association Between MS and Valve Degeneration**

There are compelling histopathological and clinical data suggesting that stenosis of the native aortic valve is an active disease process akin to atherosclerosis with lipoprotein deposition, production of oxidized LDL-cholesterol, chronic inflammation, and active calcification of valve cusp.1,2 The results of the present study as well as those of previous studies3–5,11 support the concept that these active pathological processes could also occur within the cusps of bioprosthetic valves. To this effect, several studies reported the presence of lipids and inflammatory cells in the cusps of bioprosthetic valves.11–14 It is thus conceivable that inflammation may play a pivotal role in the degeneration of bioprosthetic valves.11,13,14

There are several features of the MS that could be involved in the tissue degeneration of bioprosthetic valves. The reduction of HDL cholesterol, a powerful antioxidant agent, as well as the presence of small dense LDL particles associated with MS could predispose a person to the deposition of oxidized LDL within the valve cusp tissue. In turn, oxidized LDL is major initiating factor for inflammation and calcification.1,2,15 Furthermore, the expanded abdominal adipose depot in patients with MS is an important source of cytokine (eg, interleukin-6, tumor necrosis factor-α) production.16 Interleukin-6 has proinflammatory and proatherogenic effects, and it stimulates hepatic production of C-reactive protein.16 Hence, the presence of abdominal obesity in patients with MS could exacerbate the inflammatory or immune response to various environmental stimuli, including oxidized LDL.

**Clinical Implications**

The results of this study have important clinical implications. Indeed, MS is a potentially preventable and modifiable condition that often goes undiagnosed and untreated. Hence, in light of our results, patients with a bioprosthetic valve should be screened for the presence of MS and if it is present, they should probably be followed-up more closely with regard to the evolution of their valve function. Moreover, it should be emphasized that many of the features of the MS are not reversed by the pharmacological treatment of traditional risk factors (ie, statins, angiotensin-converting enzyme inhibitors, etc).6 Treatment of the features of the MS requires aggressive changes in lifestyle habits, such as increasing physical activity and implementing dietary changes that lead to weight reduction. Newer pharmacological approaches that specifically target some of the key causal mechanisms of the MS might also be considered in patients with a bioprosthetic valve.6,17 Additional prospective studies will, of course, be necessary to determine whether bioprosthetic valve degeneration can actually be slowed by a more aggressive treatment of MS.

At this point, it is not possible to determine whether the presence of the MS should be a factor in deciding which type of valve the patient receives, but the present results certainly provide impetus for future studies examining this hypothesis.

**Limitations of the Study**

This is a retrospective study. The waist circumference was not measured in this study. Alternatively, to identify patients likely to have the MS, we used a body mass index ≥30 kg/m². Body mass index alone is not necessarily a good marker of abdominal obesity and of the MS. Nonetheless, when combined with the other metabolic criteria of the NCEP-ATPIII guidelines, it is useful in identifying individuals with the MS.6,9

In conclusion, this is the first study to report that the MS is highly prevalent in patients undergoing aortic valve replacement and that it is a strong and independent predictor of bioprosthetic valve degeneration. These findings lead to new horizons of research and provide a strong impetus for the elaboration of prospective studies focusing on the aggressive treatment of the features of MS in patients with a bioprosthetic valve.

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**Disclosures**

None.

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