Absence of Association Between Infectious Agents and Endothelial Function in Healthy Young Men

Paul Khairy, MD, MSc; Stéphane Rinfret, MD, MSc; Jean-Claude Tardif, MD; Richard Marchand, MD; Stan Shapiro, PhD; James Brophy, MD, PhD; Jocelyn Dupuis, MD, PhD

Background—Although several studies have reported correlations between infections and coronary artery disease, associations with endothelial dysfunction, its precursor, have not been established. This study assessed whether infection with Chlamydia pneumoniae (CP), cytomegalovirus (CMV), Epstein-Barr virus (EBV), or Helicobacter pylori (HP) is associated with decreased endothelial function.

Methods and Results—Sixty-five male subjects, aged 20 to 45 years, with no risk factors or known coronary artery disease were enrolled in a seroepidemiological cross-sectional study. Endothelial function was determined by flow-mediated brachial vasodilation. Serum antibodies consisting of anti-CP IgG and IgM, anti-CMV IgG, anti-EBV nuclear antigen, and anti-HP IgG and markers of inflammation including high-sensitivity C-reactive protein were measured. Average age was 29.3 ± 5.5 years. Seroprevalence values were 65.1%, 34.9%, 88.9%, and 14.3% for CP, CMV, EBV, and HP, respectively. Average values for endothelium-dependent and -independent vasodilation were 9.4 ± 4.5% and 12.6 ± 5.0%. Despite adequate statistical power (82% for the primary end point), no association between endothelial function and seropositivity to individual infectious agents, infectious burden, or C-reactive protein was observed in regression analyses controlling for variables including age, blood pressure, and lipid parameters. Moreover, no dose-response trends between serum titers and endothelial function were found.

Conclusions—Lack of association between chronic infection with CP, CMV, EBV, or HP, or pathogen burden and endothelial function was observed, suggesting that these agents are not implicated as early etiologic triggers in the genesis of coronary artery disease. These results do not preclude active involvement at later stages of the pathophysiological process, such as acceleration of existing atherosclerosis and acute plaque rupture. (Circulation. 2003;107:1966-1971.)

Key Words: endothelium ■ vasodilation ■ infection

Numerous studies have suggested potential associations between coronary artery disease (CAD) and various infectious agents. Cytomegalovirus (CMV) has been associated with atherosclerosis, transplantation vasculopathy, vascular allograft rejection, and restenosis after angioplasty.1 Ebstein-Barr virus (EBV) has been shown to infect human endothelial cells and has been implicated in coronary aneurysm formation and isolated from cardiac and aortic tissues.2 Furthermore, both EBV and CMV have been positively correlated with angiographically determined CAD.3 Although controversial, Helicobacter pylori (HP) has been correlated with various forms of atherosclerosis.4-5 The body of evidence supporting an association between Chlamydia pneumoniae (CP) and CAD continues to grow at a rapid pace and includes seroepidemiological, histopathologic, and observational studies.6-10 Small clinical trials have focused on secondary prevention, and larger studies are underway.11

Despite these numerous reports, an association between seropositivity to infectious agents and endothelial dysfunction, an early event in the development of coronary atherosclerosis,12 has not been conclusively demonstrated. Identifying such an association may contribute to better defining the pathophysiological process and, perhaps, redirecting therapy toward primary prevention. The objective of this study was, therefore, to determine whether seropositivity to CP, CMV, EBV, or HP is associated with decreased endothelial function in young men with no known CAD or risk factors.

Methods

Overview of Study Design
A seroepidemiological cross-sectional study was performed at the Montreal Heart Institute between January 1999 and March 2001. After obtaining informed consent, a brief questionnaire was administered on relevant past medical history, blood pressure measurements were taken, and fasting blood samples were drawn. Serum
samples were divided into 500- or 1000-μL aliquots, frozen, and maintained at −80°C until dispatched on dry ice to participating laboratories. On the same day as blood sampling, brachial ultrasonography was performed. The institutional review board approved the study.

Population
The study population consisted of male volunteers, 20 to 45 years of age. Inclusion was restricted to men given hormonal variations that limit reproducibility of endothelial function testing in premenopausal women.3 Because the primary focus was detection of endothelial dysfunction before development of CAD, patients with already established disease were excluded, as were those older than 45 years of age, given the greater likelihood of subclinical CAD. Subjects with any of the following were likewise excluded: family history of premature CAD (ie, first-degree male or female relative <45 or <55 years of age, respectively), known hypertension or systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg, dyslipidemia (LDL >5 mmol/L, total cholesterol/HDL >7 mmol/L, or fasting triglycerides >3 mmol/L), diabetes mellitus (known diabetes or fasting blood sugar >7 mmol/L), or cigarette smoking (≥1 cigarette/day currently or within the previous 5 years).

Endothelial Function
Endothelial function was assessed by brachial artery flow-mediated reactive hyperemia, with reproducibility >98% and a positive predictive value of 95% for coronary endothelial dysfunction.14 A 10% cutoff value has 91% sensitivity and 95% negative predictive value for functionally significant CAD.15 All studies were conducted by 2 trained research technicians (who previously performed 240 tests)16 and were reviewed by an experienced cardiologist (J.C.T.). Arterial diameter was assessed by high-resolution ultrasound with a standard 7.5-MHz linear transducer. A nontortuous segment of the brachial artery above the antecubital fossa was identified and scanned in a longitudinal fashion. Once depth and gain settings were adjusted to optimize images of the lumen to arterial wall interface, baseline scanning was performed with images magnified in a 20- by 20-mm viewing window. A pneumatic blood pressure cuff positioned above the elbow was then inflated to 60 mm Hg above systolic pressure for 5 minutes, after which the cuff was released and the artery imaged continuously for 5 minutes. Mean diameter of the 20-mm brachial artery segment was quantified by means of proprietary software. Frames from 3 consecutive cycles were taken at the R-wave peak, and results were averaged. Percent flow-mediated dilation measured 1 minute after cuff deflation was used as an index of endothelium-dependent vasodilation; percent dilation obtained 3 minutes after administration of nitroglycerin spray (400 μg) represented endothelium-independent dilation.

Laboratory Analyses
C-reactive protein (CRP) levels were quantified by an automated high-sensitivity enzyme immunoassay (Dade Behring).17 Anti-CP IgG and IgM antibodies were measured at National Microbiology Laboratories of Health Canada by microimmunofluorescence by using TWAR strain AR-39 as antigen (University of Washington Research Foundation).18 Lipopolysaccharide (LPS)-containing immune complexes were detected by 2 antigen-specific enzyme immunoassays.6 In short, for the LPS capture assay, microliter plates were coated with IgG2a mouse monoclonal antibody specific to chlamydia LPS. Sera were diluted 1:100, and alkaline phosphatase-conjugated anti-human IgM was used to detect antibody. Subjects were considered seropositive if anti-CP IgG was ≥1:64 with IgM <1:8.17 Sera were screened for CMV IgG antibodies at the Regional Virology Laboratory of Laval Hospital (Quebec, Canada) with an ELISA assay (Wampole Laboratories), with cutoff for seropositivity ≥1:10.20

Statistical Analyses
Sample size requirements were calculated with an independent t test for comparison of means assuming 50% seroprevalence of CP, 2-tailed α of 0.05, and flow-mediated endothelial dilation of 8.3±3.5%21 in seronegative controls. A total of 62 men were required to obtain a power of 80% to detect a 30% difference in endothelial function. Continuous data were compared with Wilcoxon rank-sum test and expressed as mean±SD or median with interquartile (25th and 75th) range. Discrete data, expressed as percentage, were compared with Fisher’s exact test. Multiple regression models for individual infectious agents and total pathogen burden assessed relationships and trends with endothelial function and markers of inflammation while controlling for potential confounders, baseline imbalances, and known risk factors for endothelial dysfunction. Jackknife residuals and Cook’s D statistics were used to identify potential outliers and influential observations. All analyses were performed with SAS software Version 8. A 2-tailed probability value <0.05 was considered statistically significant.

Results
Completeness of Data
A total of 65 men were enrolled in the study. Two subjects were excluded because of misplaced serum samples. Complete information was available for the remaining 63 subjects, with the exception of one missing value for a high-sensitivity CRP, substituted by a standard assay measure. An excellent concordance between both assays has been previously demonstrated, with total imprecision <8%.22

Baseline Characteristics
Average age was 29.3±5.5 years. Mean lipid values were total cholesterol 4.6±0.9 mmol/L, LDL 2.9±0.8 mmol/L, HDL 1.3±0.3 mmol/L, and triglycerides 1.0±0.5 mmol/L. Endothelium-dependent vasodilation displayed considerable variability, with a mean of 9.3±4.5% and range of 1.1% to 20.0% (Figure 1). Baseline brachial artery diameter was 3.8±0.4 mm, with an average endothelium-independent vaso-
dilation of 12.6±5.0%. Seropositivity to CP, EBV, CMV, and HP was 65.1%, 88.9%, 34.9%, and 14.3%, respectively (Table 1). Baseline characteristics stratified by seropositivity status to CP are summarized in Table 2. Coexistence of infections was noted, with statistically significant pairwise correlations involving the 4 agents (Table 2). As previously reported, an inverse correlation between flow-mediated vascular reactivity and vessel size was noted (r=−0.274, P=0.0294).23

Markers of Inflammation
Fibrinogen levels were normally distributed (2.7±0.6 g/L), but CRP values were skewed leftwards (Figure 1) with a median of 0.57 mg/L. Fibrinogen and CRP were positively correlated (r=0.465, P<0.0001) but not associated with vascular reactivity. Although seropositivity to CP was associated with increased fibrinogen (r=0.296, P=0.0183), no association between any infectious agent and CRP was observed. Similarly, no association between endothelial function and markers of inflammation (ie, CRP, fibrinogen, leukocytes, and platelets) considered separately or collectively (F4,49=0.35, P=0.8447) was noted.

Infection and Endothelial Function
In univariate analyses, no correlation between infectious agents and vascular function was observed. On the basis of previously described relationships, the following known potential confounders were included in all multiple regression models: age, blood pressure, LDL, HDL, triglycerides, and baseline brachial artery diameter. Additional variables were considered if they displayed unequal distribution by seropositivity status. Overall, seropositivity to CP, CMV, EBV, or HP was not predictive of endothelial function. Endothelium-dependent flow-mediated vasodilation and parameter estimates are summarized in Table 3. Regression models were recreated with seropositivity to CP and EBV expressed ordinally and CMV continuously. No association between any infectious agent and endothelial function was noted. In addition, no trend between antibody levels and endothelial function was observed (Figure 2). Every possible cutoff value for seropositivity to each agent was retested, and no association with endothelial function was found.

In addition, the total infectious burden (ie, whether subjects were seropositive to 0, 1, 2, 3, or 4 infectious agents), depicted in Figure 3, had no bearing on endothelial function, with a trend in the opposite direction of the hypothesized effect (P=0.2535). All pairwise comparisons (eg, seropositivity to 0 versus 4 agents) were likewise not statistically significant.

### Table 1. Descriptive Analysis of Exposure Variables

<table>
<thead>
<tr>
<th>Variable/Coding</th>
<th>Descriptive Frequencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP IgG</td>
<td></td>
</tr>
<tr>
<td>Ordinal</td>
<td>0 1:16 1:32 1:64 1:128 1:256 1:512 1:1024</td>
</tr>
<tr>
<td>23.8% 4.8% 6.3%</td>
<td>9.5% 19.1% 27.0% 7.9% 1.6%</td>
</tr>
<tr>
<td>Dichotomous</td>
<td>65.1% positive (≥1:64)</td>
</tr>
<tr>
<td>EBNA</td>
<td></td>
</tr>
<tr>
<td>Ordinal</td>
<td>&lt;1:10 1:10 1:20 1:40 1:80 1:160 1:320 1:640</td>
</tr>
<tr>
<td>11.1% 6.4% 9.5%</td>
<td>11.1% 27.0% 25.0% 6.4% 3.2%</td>
</tr>
<tr>
<td>Dichotomous</td>
<td>88.9% positive (≥1:10)</td>
</tr>
<tr>
<td>CMV IgG</td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>84.2±214.0 AU/mL</td>
</tr>
<tr>
<td>Dichotomous</td>
<td>34.9% positive (&gt;15 AU/mL)</td>
</tr>
<tr>
<td>HP</td>
<td></td>
</tr>
<tr>
<td>Dichotomous</td>
<td>14.3% positive</td>
</tr>
</tbody>
</table>

EBNA indicates anti-EBV nuclear antigen.

### Table 2. Distribution of Variables According to Seropositivity to *Chlamydia pneumoniae*

<table>
<thead>
<tr>
<th></th>
<th>CP Seronegative (n=22)</th>
<th>CP Seropositive (n=41)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>29 (25, 31)</td>
<td>30 (25, 32)</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>87 (83, 93)</td>
<td>87 (83, 93)</td>
<td>0.97</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>4.8 (4.1, 5.1)</td>
<td>4.6 (3.8, 5.4)</td>
<td>0.53</td>
</tr>
<tr>
<td>HDL</td>
<td>1.4 (1.3, 1.6)</td>
<td>1.3 (1.1, 1.5)</td>
<td>0.19</td>
</tr>
<tr>
<td>LDL</td>
<td>0.8 (0.6, 1.1)</td>
<td>2.8 (2.0, 3.6)</td>
<td>0.75</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.8 (0.6, 1.1)</td>
<td>0.8 (0.7, 1.2)</td>
<td>0.29</td>
</tr>
<tr>
<td>Creatinine</td>
<td>96 (84, 99)</td>
<td>100 (89, 106)</td>
<td>0.08</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.0 (4.8, 5.2)</td>
<td>5.1 (5.0, 5.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Markers of inflammation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.76 (0.31, 1.66)</td>
<td>0.50 (0.09, 1.17)</td>
<td>0.33</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2.39 (2.23, 2.93)</td>
<td>2.72 (2.37, 2.96)</td>
<td>0.16</td>
</tr>
<tr>
<td>WBC</td>
<td>5.6 (5.0, 6.2)</td>
<td>5.6 (4.6, 6.1)</td>
<td>0.49</td>
</tr>
<tr>
<td>Platelets</td>
<td>194 (177, 230)</td>
<td>196 (178, 238)</td>
<td>0.65</td>
</tr>
<tr>
<td>Infectious agents, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>68</td>
<td>100</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>18</td>
<td>44</td>
<td>0.054</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>0</td>
<td>22</td>
<td>0.0176</td>
</tr>
</tbody>
</table>

Continuous data are expressed as median, interquartile range (25th, 75th percentile). Dichotomous variables are expressed as percentage. WBC indicates white blood cell count.
Discussion
Seroprevalence rates of CP, EBV, CMV, and HP (65.1%, 88.9%, 34.9%, and 14.3%) were consistent with previous reports in young patient populations.7,24 Moreover, coexistence of these infections has been well-described.8 The endothelial function score of 9.3 ± 4.5 was likewise consistent with values of 8.3 ± 3.521 and 10.5 ± 0.615 in patients with no risk factors for CAD and negative exercise myocardial perfusion imaging, respectively.

Despite documented associations, evidence implicating infectious agents in CAD pathogenesis is circumstantial. In this young population, despite having similar infection loads as older reported populations, no effect on endothelial function was found. These results are consistent with the lack of increased atherothrombotic risk reported by Ridker and colleagues in apparently healthy older men seropositive to CP25 and CMV.26 Similarly, a recent study in an elderly patient population found no association between infection to CP, HP, and CMV and increased risk of cardiovascular disease.27 Results of this study were robust in that, in this relatively homogeneous population, no correlation or trends were found with total infectious burden or individual antibody titers at predetermined threshold levels and all possible cutoff values. Moreover, effects of gender, smoking, and family history of premature CAD were controlled by restriction. Consistent with these findings, Sharma et al28 reported no significant correlation between CP and flow-mediated vasodilation in patients without CAD, diabetes, hypertension, or dyslipidemia. In a subgroup analysis of 86 patients with no angiographically significant CAD, Prasad et al29 found a significant correlation between total infectious burden to 5 investigated agents (CP, CMV, HP, hepatitis A virus, and herpes simplex virus) and decreased intracoronary endothelium-dependent vasodilation (P=0.03). This apparent discrepancy may be related, in part, to different patient populations, infectious agents studied, and methods of assessing outcome. Interactive effects between conventional risk factors and infectious agents could not be excluded in this older patient population (56 ± 1 years), in whom more than half were hypertensive and smokers and roughly 20% were diabetic. Because subjects with traditional risk factors were excluded from our study, interactions with infections could not be assessed.

Seropositivity to CP or CMV has been positively correlated with CRP in patients with carotid atherosclerosis30 and angiographically demonstrated CAD31 and in chronic peritoneal dialysis recipients,9 in whom a high prevalence of accelerated atherosclerosis is expected. However, the lack of association observed in this study is consistent with a report documenting no association between CP or CMV with CRP and interleukin-6 in healthy subjects.32 Independent of seropositivity status, CRP may increase as a result of vascular inflammation induced by atherosclerosis, whether or not it contributes to accelerating this process.33,34 Similarly, both fibrinogen and CRP were found not to be associated with endothelial function. A correlation between markers of inflammation and endothelial dysfunction has likewise not been clearly demonstrated in healthy young subjects, unlike in patients with CAD35 or insulin-dependent diabetes.36

Although results of this study argue against a chronic low-grade infection being responsible for initial injury that induces atherosclerosis, several possible scenarios remain. First, organisms may persist in vascular cells but not contrib-

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Simple linear regression plot of anti-CP titers with 95% confidence intervals around the slope and mean.

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Total infectious burden and endothelial-dependent vasodilation.

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**TABLE 3. Flow-Mediated Vasodilation by Infectious Agent**

<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>FMD Seropositive</th>
<th>FMD Seronegative</th>
<th>Parameter Estimate (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia pneumoniae</td>
<td>9.8 ± 4.5</td>
<td>8.5 ± 4.5</td>
<td>0.280 (−2.053, 2.613)</td>
<td>0.8151</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>9.5 ± 4.5</td>
<td>8.1 ± 4.2</td>
<td>0.159 (−0.432, 0.750)</td>
<td>0.6006</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>9.0 ± 4.5</td>
<td>9.5 ± 4.5</td>
<td>−0.806 (−3.403, 1.789)</td>
<td>0.5452</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>13.6 ± 4.4</td>
<td>8.7 ± 4.1</td>
<td>2.888 (−0.354, 6.129)</td>
<td>0.0888</td>
</tr>
</tbody>
</table>

FMD indicates flow-mediated vasodilation; CI, confidence interval.
TABLE 4. Power Calculations

<table>
<thead>
<tr>
<th>% SP</th>
<th>Ratio</th>
<th>Expected EDV in SP</th>
<th>Expected EDV in SN</th>
<th>Δ</th>
<th>Power, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>65.1</td>
<td>1.8636</td>
<td>8.09</td>
<td>11.56</td>
<td>3.47</td>
<td>4.5</td>
</tr>
<tr>
<td>34.9</td>
<td>0.5366</td>
<td>7.27</td>
<td>10.39</td>
<td>3.12</td>
<td>4.5</td>
</tr>
<tr>
<td>88.9</td>
<td>0.1250</td>
<td>8.88</td>
<td>12.68</td>
<td>3.80</td>
<td>4.5</td>
</tr>
<tr>
<td>14.3</td>
<td>0.1667</td>
<td>6.80</td>
<td>9.72</td>
<td>2.91</td>
<td>4.2</td>
</tr>
</tbody>
</table>

SP indicates seropositive; SN, seronegative; EDV, endothelium-dependent vasodilation; Δ, difference; and SD, standard deviation of the mean.

ute to pathological abnormalities.37 Another possible scenario that integrates results of the present study and previous reports is that one or more infectious agent, although not responsible for initial endothelial injury, may accelerate progression of atherosclerosis or promote plaque rupture. Mahony and Coombes38 have proposed an integrated model whereby CP has a contributory rather than causal role, persistently infecting T-cells, macrophages, and endothelial cells and contributing to a sustained inflammatory response. Thus, rather than initiating, infectious agents may promote, sustain, or accelerate atherosclerosis. Alternatively, they may be implicated in the final stages of vessel occlusion. Inflammatory infiltrates found in ruptured plaques suggest an immune component to plaque vulnerability. Infectious agents may act as extrinsic triggers by inciting an inflammatory reaction, activating macrophages and T-lymphocytes within the plaque, or attracting these cells toward the plaque.39 Production of cytokines may promote secretion of metalloproteinases that degrade fibrous capsules, resulting in plaque fissuring. Indeed, CP selectively upregulates 92-kDa gelatinase that actively destroys extracellular matrix.40

Limitations
The latency period between seropositivity to CP, CMV, EBV, or HP and measurable effects on endothelial function, if any, is unknown. Duration of infection before endothelial function testing could not be inferred from serological tests, because IgG antibodies reflect infection from birth until sampling.

The volunteer sampling method, in our opinion, is unlikely to have introduced selection bias. The true relationship between exposure and outcome will be biased only if eligible nonparticipants differ with regard to both seropositivity status and other risk factors for endothelial dysfunction. To guard against this theoretical scenario, the study population was narrowly defined with restrictive eligibility criteria and exclusion of subjects with factors known to be associated with endothelial dysfunction. If eligible nonparticipants differ only with respect to outcome, endothelial function tests in participants may differ from those in the targeted population. This is unlikely given endothelial function scores consistent with previous reports. Similarly, if eligible nonparticipants differ only with respect to seropositivity status, the strength of association will retain its validity but may overestimate or underestimate true population seroprevalence rates.

Endothelial function score and standard deviation were higher than anticipated, and seroprevalence rates deviated from an equally distributed pattern. Net effect on power calculations are summarized in Table 4. To detect the prespecified 30% difference in endothelial function, a power of 81.7% was obtained for CP. In contrast, power calculations of 73.1%, 54.3%, and 47.7% were obtained for CMV, EBV, and HP, respectively. Absence of trends between antibody titers and endothelial function and the confidence intervals obtained suggest that the lack of association observed is not simply the result of underpowering. Nevertheless, the purported risk associated with infection may be smaller than for traditional risk and produce changes in endothelial function of a magnitude below the detection threshold determined by the study power.

At the expense of generalizability, a relatively homogeneous population was deliberately selected to increase precision regarding inference about disease etiology and offer some protection against unmeasured variables, such as body mass index, diet, vasoactive substances, and exercise patterns, that may contribute to variability in endothelial function but are less likely associated with seropositivity status.41,42

Conclusion
In conclusion, this seroepidemiological cross-sectional study demonstrated a lack of association between prior infection to CP, CMV, EBV, or HP and endothelial function. Total infectious burden and high-sensitivity CRP were likewise not correlated with endothelial function. Because endothelial dysfunction is a precursor to CAD, these results suggest that a chronic low-grade infection with these agents is unlikely to be responsible for initiating CAD but do not preclude a role in later stages of the pathophysiological process, such as acceleration of atherosclerosis or plaque rupture.

Acknowledgments
This work was supported in part by a fellowship award (to Dr Khairy) from the Canadian Institutes of Health Research. Drs Dupuis and Tardif are senior scholars from the Fonds de la recherche en santé du Québec. The authors are indebted to Francine Poulin and Marie Gagnon for their excellent technical support and Dr Claire Bélieu for supervising laboratory analyses.

References


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_Circulation_. 2003;107:1966-1971; originally published online April 7, 2003; doi: 10.1161/01.CIR.0000064895.89033.97
_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

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