Gender Disparity in the Development of Coronary Vasospasm Without Hemodynamically Significant Coronary Artery Disease

Ming-Yow Hung, Kuang-Hung Hsu, Ning-I Yang, Chi-Wen Cheng, Wen-Jin Cherng, Ming-Jui Hung

Short Title: Risk factor gender disparity in coronary vasospasm

Word count of body (4906), including references and tables (1,135); Word count of abstract: 238 words; Total number of tables: 5 tables

From the Second Section of Cardiology (M-Y. H.), Department of Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan; Graduate Institute of Clinical Medical Sciences (M-Y. H., M-J. H.), College of Medicine, Chang Gung University, Taoyuan; Laboratory for Epidemiology (K-H. H.), Department of Health Care Management, Chang Gung University, Taoyuan; and Section of Cardiology (N-I. Y., C-W. C., W-J. C., M-J.H.), Department of Medicine, Chang Gung Memorial Hospital at Keelung, Chang Gung University College of Medicine, Keelung, Taiwan

This work was presented in part at the 80th Scientific Session of the American Heart Association, Orlando, Florida, November 4-7, 2007, and published in abstract form (Circulation. 2007;116[suppl II]:II-639).

Correspondence to Ming-Jui Hung, MD, Section of Cardiology, Department of Medicine, Chang Gung Memorial Hospital at Keelung, 222 Mai-Chin Road, Keelung 20401, Taiwan. Tel: 886-2-24313131 ext 3168; Fax: 886-2-24335342. E-mail: miran888@ms61.hinet.net
Abstract

Objective: To determine gender differences in the risk factors for coronary vasospasm (CVs) and the effect of hypertension associated with inflammation on the prediction for CVs in patients without hemodynamically significant coronary artery disease (CAD).

Methods and Results: We examined 722 patients (39% women) who underwent diagnostic coronary angiography with or without proven CVs and without CAD (>50% stenosis) during an 8-year period. The levels of high-sensitivity C-reactive protein (hs-CRP), measured immediately before coronary angiography, were examined in a subset of 375 patients. For women, only the highest hs-CRP tertile (>3 mg/L) was independently associated with CVs (odds ratio [OR]: 3.21; 95% confidence interval [CI]: 1.28 to 8.07), while hypertension was negatively associated with CVs (OR: 0.42; 95% CI: 0.19 to 0.94). For men, age (>58 years) and the highest hs-CRP tertile were independently associated with CVs, with the highest tertile being the most significant factor (OR: 2.88; 95% CI: 1.35 to 6.18). The ORs (95% CI) of CVs in the highest hs-CRP tertile for both women and men reduced from 6.01 (1.45 to 24.88) to 1.48 (0.48 to 4.51), and 6.35 (1.96 to 20.56) to 2.69 (1.00 to 7.21), if they had hypertension, respectively.

Conclusions: We found gender disparity of risk factors for developing CVs; additionally, hypertension was negatively associated with CVs development. The study population had a negative interaction between hypertension and hs-CRP for CVs.

Key Words: gender, hypertension, smoking, high-sensitivity C-reactive protein, coronary vasospasm
Introduction

Traditional risk factors of atherosclerotic coronary artery disease (CAD) differ between women and men\(^1\) and CAD outcomes are less favorable in women than in men.\(^2\) In human coronary arteries, spontaneous contractile activity seems to be more frequent in older subjects,\(^3\) increasing the risk of vasospasm; however, only smoking has been demonstrated the major risk factor for coronary vasospasm (CVs), yet hypertensive subjects show a lower risk for CVs.\(^4\) Additionally, gene polymorphisms significantly associated with CVs differ between Japanese men and women.\(^5\) Both CVs and atherosclerotic CAD are reported to be inflammatory diseases, as indicated by the presence of elevated C-reactive protein (CRP),\(^6\) a biomarker of low grade inflammation. High-sensitivity C-reactive protein (hs-CRP) is also high in patients who had coronary vasospastic angina without hemodynamically significant CAD (>50% stenosis).\(^7-9\) A significant association between CRP levels and hypertension is reportedly present in both men and women, with the strongest association in Chinese population.\(^10\) Although hypertension is recognized as an important modifiable risk factor contributing to an increased risk of myocardial infarction,\(^11\) it was found more frequently in classic angina than in vasospastic angina.\(^12\) Prospective data demonstrate that CRP predicts incident cardiovascular events in people with and without previous CAD.\(^13,14\) Nonetheless, little is known about the effect of the relationship between hypertension and hs-CRP in terms of the risk for CVs. We thus hypothesized that there is interaction between these two factors in the development of CVs. Our primary goal was to determine whether there was a gender difference in the development of CVs and a secondary goal was to ascertain whether there was an interaction between hypertension and hs-CRP influencing the prediction of CVs development among patients without hemodynamically significant CAD.
Methods

Study Population

From January 1999 to April 2007, 722 patients with suspected ischemic heart disease who underwent diagnostic coronary angiography and, thus, had no hemodynamically significant CAD were subjected to intracoronary methylergonovine testing. Inclusion criteria for CVs included spontaneous chest pain at rest associated with ST-segment elevation or depression on electrocardiogram and relieved by sublingual administration of nitroglycerin, no hemodynamically significant CAD after intracoronary nitroglycerin administration on coronary angiography, and/or positive intracoronary methylergonovine provocation testing. The control group consisted of patients who presented with atypical chest pain, had no hemodynamically significant CAD, and had negative intracoronary methylergonovine provocation tests (no CVs). Exclusion criteria were previous coronary angioplasty, hemodynamically significant CAD with myocardial infarction within the previous 6 months, inflammatory manifestations probably associated with noncardiac diseases (eg., infections and autoimmune disorders), associated liver disease/renal failure (serum creatinine level >2.5 mg/dl), collagen disease, or malignancy, coronary stenting follow-up without hemodynamically significant CAD, and loss of blood samples. This study was approved by the Chang Gung Memorial Hospital Institutional Review Board and all patients gave written informed consent.

Clinical Data

Patients were assessed for the presence of cardiac risk factors, cigarette smoking, diabetes mellitus, hypercholesterolemia and hypertension. Current smoking was defined as having smoked a cigarette within 3 weeks of the cardiac catheterization. Diabetes mellitus was defined from dietary treatment and/or medical therapy and hypertension as receiving the appropriate medical therapy or blood pressure of >140/90 mmHg. Hypercholesterolemia
was defined where serum total cholesterol was >200 mg/dl.

**Laboratory Analysis**

Blood specimens for measurement of hs-CRP were collected in citrate-treated tubes immediately before coronary angiography and after an overnight fast and were immediately centrifuged for ≥15 minutes. The plasma component was frozen and sent on dry ice to the core laboratory of the hospital, where samples were stored at -70°C until subsequent measurement. Serum hs-CRP was measured in duplicate by enzyme-linked immunosorbent assay on the basis of purified protein and polyclonal anti-CRP antibodies (IMMULITE hs-CRP, Diagnostic Products Corp., Los Angeles, California). The lower limit of this assay was 0.10 mg/L and coefficients of variation were ≤5% at 0.20 mg/L of CRP.

**Coronary Angiography and Intracoronary Methylergonovine Testing**

Coronary angiography was performed using the standard Judkins technique via a femoral or a radial approach. Nitrates and calcium antagonists were withdrawn for ≥24 hours before coronary angiography. The left ventricular ejection fraction was calculated using Simpson’s method. Selective left and right coronary angiography were performed in multiple axial and hemiaxial projections. Hemodynamically significant coronary stenosis was defined as ≥50% diameter reduction in lumen caliber after administration of intracoronary nitroglycerin (100 µg). Intracoronary methylergonovine (Methergin®; Novartis, Basel, Switzerland) provocation testing was performed in succession if no hemodynamically significant coronary stenosis was found. Methylergonovine was administered stepwise (1, 5, 10, 30 µg) first into the right coronary artery and subsequently into the left coronary artery. Provocation testing for CVs was considered positive where there was a >70% reduction in luminal diameter compared to post intracoronary nitroglycerin and there was associated angina and/or ST depression or elevation. After CVs diagnosis, the intracoronary methylergonovine administration was stopped with intracoronary nitroglycerin 50-200 µg (Millisrol®; G.
Pohl-Boskamp, Hohenlockstedt, Germany) administration for reversal. The observation of 
reversal change in the coronary artery diameter further confirmed the diagnosis of CVs. 
Spontaneous CVs was defined as the relief of >70% luminal stenosis after intracoronary 
nitroglycerin 50-200 µg administration.

Statistical Analysis

Continuous variables were expressed as mean±SD, while log transformations were performed 
for variables with positive skewness for the subsequent Student’s t tests between two groups. 
Categorical variables were presented as number and percentage, and χ² tests were used for 
comparisons. Tertiles of hs-CRP were used to further analyze the subsequent effect with 
CVs, which were categorized as lowest (<1 mg/L), middle (1 to 3 mg/L), or highest (>3 mg/L) 
according to the AHA/CDC Scientific Statement for health care professionals.¹⁵ Multiple 
logistic regression model was used to identify independent risk factors for CVs in patients 
without hemodynamically significant CAD, hence multivariate-adjusted odds ratios and 95% 
confidence intervals were expressed. Model selection of multiple logistic regressions was 
based on the a priori knowledge and the significance of multivariate tests from variables of 
age, gender, body mass index (BMI), cigarette smoking, diabetes mellitus, hypertension, 
cholesterol, left ventricular ejection fraction (LVEF). Stratified analyses were conducted 
from a subset of 339 patients whose hs-CRP measurements were available to examine the 
interactions of hs-CRP tertiles and age group (cutoff point determined by the men age of 58 
years old) (model 1), smoking (model 2), and hypertension (model 3) on CVs. Data 
management and statistical analyses were performed using SPSS 11.0 for Windows (SPSS 
Inc., Chicago, Illinois). The level of significance was set at P<0.05 (2-sided).
Results

Baseline Characteristics of All Participants

Among the 722 patients who underwent diagnostic coronary angiography, the mean age was 58±12 years, and 39% were women. A total of 408 patients had CVs without hemodynamically significant CAD (CVs group) and 314 had no hemodynamically significant CAD and no CVs (control group). Compared to the controls, the CVs patients were likely to be older, men and current smokers (Table 1), and had a higher hs-CRP levels. The prevalences of BMI, diabetes mellitus, hypertension and hypercholesterolemia were similar for both groups. Single-vessel CVs was the most common finding in the CVs cases, and spasm was provoked mostly in the right coronary artery.

For women, traditional risk factors were comparable between the CVs and control subjects (Table 2). For men, age was significantly older and the prevalence of current smokers was significantly greater in subjects with CVs than in controls (Table 2). Among both women and men, CVs patients tended to have higher hs-CRP levels.

Variables Associated With CVs in Patients with hs-CRP Measurements

From multivariable analysis of women (Table 3), only the highest tertile of hs-CRP (>3 mg/L) was independently associated with CVs diagnosis. Hypertension was negatively associated with CVs.

Multivariable analysis of men showed that only age and the highest tertile of hs-CRP were independently associated with CVs diagnosis, with the highest tertile of hs-CRP being the most significant factor.

Gender-Specific Stratified Analyses of hs-CRP Tertiles and Major Risk Factors

The risk of CVs was found more likely in young, non-smoking and non-hypertensive subjects with high hs-CRP levels among women, while men’s risk of CVs was characterized as old, smoking and non-hypertensive subjects with high hs-CRP levels (Table 4). Significant
interactions were demonstrated between hs-CRP tertiles and age (model 1), smoking (model 2) or hypertension (model 3) for CVs risk. In the analysis of women, young subjects ≤58 years of age in the highest tertile of hs-CRP had a 4.7-fold higher risk for CVs compared to young subjects in the lowest hs-CRP tertile after adjustment for BMI, smoking, diabetes, hypertension, cholesterol, and left ventricular ejection fraction (model 1). Non-smokers with high hs-CRP had a 3.1-fold higher risk for CVs compared to those with low hs-CRP after adjustment for age, traditional risk factors, and left ventricular ejection fraction (model 2) (Table 4). Non-hypertensive women with high hs-CRP had higher risk of developing CVs than those with low hs-CRP (model 3) (Table 4).

In the analysis of men, older subjects (>58 years of age) in the highest tertile of hs-CRP had a 4.6-fold higher risk for CVs compared to subjects ≤58 years of age in the lowest hs-CRP tertile after adjustment for BMI, smoking, diabetes, hypertension, cholesterol, and left ventricular ejection fraction (model 1). Smokers with high hs-CRP had a 4.7-fold higher risk for CVs compared to non-smokers with low hs-CRP after adjustment for age, traditional risk factors, and left ventricular ejection fraction (model 2) (Table 4). Non-hypertensive men with high hs-CRP had higher risk of developing CVs than those with low hs-CRP (model 3) (Table 4).

**Association between hs-CRP Levels and Other Variables under Different Gender**

In the analysis of women, no significant difference in the hs-CRP levels were observed comparing age groups (≤58 versus >58 years) and smoking status (Table 5). However, increased hs-CRP levels were found in subjects with hypertension ($P=0.012$ for hs-CRP tertiles and 0.006 for log-normalized hs-CRP levels, respectively).

In the analysis of men, hs-CRP levels were higher in subjects >58 years of age ($P=0.004$ for hs-CRP tertiles and 0.044 for log-normalized hs-CRP levels, respectively) and smokers ($P=0.006$ for hs-CRP tertiles and <0.001 for log-normalized hs-CRP levels, respectively).
Increased hs-CRP levels were also found in subjects with hypertension ($P=0.021$ for log-normalized hs-CRP levels).
**Discussion**

We found that there were not only gender differences in baseline characteristics of patients with CVs compared to controls, but also in their risk factors for CVs development. For women, only the highest hs-CRP tertile was independently associated with CVs diagnosis, while hypertension was negatively associated with CVs. Analysis of men showed that age and the highest hs-CRP tertile were independently associated with CVs diagnosis. A negative interaction was demonstrated between hypertension and hs-CRP in the development of CVs without hemodynamically significant CAD, suggesting that hs-CRP is one of independent risk factors contributing to CVs. These findings indicate that interaction between hypertension and hs-CRP may predict CVs development without hemodynamically significant CAD.

In general, since clinical manifestations of atherosclerotic CAD in women lag behind that of men by approximately 10 years and it has been shown that traditional risk factors of atherosclerotic CAD differ between women and men, the mechanism underlying the risk for this condition may differ by gender at each age. However, except for female hormonal status, no risk factor has been recognized as acting on one gender but not on the other. In our study, comparing all patients without hemodynamically significant CAD with and without CVs by gender, women with CVs were more likely to have higher hs-CRP levels, while men were more likely to be older, current smokers, and have higher hs-CRP levels. It has been demonstrated that the only major risk factor for CVs is smoking, with an adjusted OR of 2.41. In a study of premenopausal women, the OR for smoking and CVs was 7.7. In our investigation, cigarette smoking was not significantly associated with CVs when hs-CRP was added into the multivariable analysis, suggesting that hs-CRP is an important predictor in CVs.

In men, not in women, age was shown to be an independent predictor for CVs.
development in the present study. Aging is associated with endothelial dysfunction of nitric oxide (NO) production and reduced Ca$^{2+}$-activated K$^+$ channels in coronary smooth muscle; however, premenopausal women are protected against this deleterious effect by endogenous estrogen, which preserves NO availability by activating the L-arginine-NO pathway and keeps blood vessels from constricting, resulting in part the lower prevalence of atherosclerotic CAD and CVs in premenopausal women than men the same age.

In rat coronary arteries, contractile responses to serotonin increase with age but are decreased by hypertension. In contrast, the L-arginine/nitric oxide pathway remains unaffected. Furthermore, hypertension is associated with premature aging of the contractile machinery of vascular smooth muscle cells. Although hypertension is recognized as an important modifiable risk factor contributing to an increased risk of myocardial infarction, it was found more frequent in classic angina than in vasospastic angina. Our results showed that hypertension is negatively associated with CVs in women, consistent with a previous report. Gender has an important influence on blood pressure, with premenopausal women having a lower arterial blood pressure than age-matched men. In women, there is an age-related rise in systolic blood pressure after 59 years of age and in advanced ages hypertension prevalence is higher in women than in men, suggesting that CVs in women is more prevalent in younger than older women.

Hs-CRP has been demonstrated an independent predictor of CVs in patients without hemodynamically CAD. In our study, although baseline hs-CRP levels in CVs patients were similar in different genders, which was in contrast to a previous report in patients with stable angina, the OR, compared to controls, for developing CVs in the highest tertile seemed to be higher for women than men. For atherosclerotic CAD, hs-CRP was indicated as an independent predictor of increased coronary risk and the relative risks for cardiovascular events associated with CRP were also found higher for women than for
The addition of hs-CRP to traditional risk factors may reclassify up to 30% of individuals at intermediate risk into clinically relevant higher or lower risk categories in women. Meta-analysis of prospective population-based studies showed that, with a good inter-study consistency, a relative OR of 2.0 (95% CI 1.6 to 2.5) for major coronary events was observed for the upper tertile of hs-CRP with the lowest tertile used as the reference. These prospective studies included men, women, and the elderly. In general, most research showed dose-response relationships between the level of hs-CRP and risk of incident coronary disease.

Previous studies reported an association between blood pressure and CRP. The Women’s Health Study showed that CRP and blood pressure were independent determinants of cardiovascular risk, and their predictive value was additive. Investigators from the Atherosclerosis Risk in Communities study have shown that the highest tertile of CRP, in the setting of low-density lipoprotein cholesterol levels less than 130 mg/dL and elevated phospholipase A2 assay, identified persons at elevated risk for CAD events. In the present study, however, we demonstrated that there was negative interaction between hs-CRP and hypertension in the development of CVs for both women and men, suggesting that hs-CRP was one of the risk factors contributing to CVs. We also found a synergistic interaction between hs-CRP and smoking in the development of CVs. The interaction was linear and monotonic in male smokers, while in female non-smokers, hs-CRP had a threshold effect, suggesting an association relationship for hs-CRP in terms of CVs development among female non-smokers.

Most research shows no relationship between age (range, 20 to 70 years) and serum CRP concentrations, while in the present study, hs-CRP levels in men increased with age. CRP levels increased in cigarette smokers, and Yen et al reported that smoking was associated with increased levels of hs-CRP in a sample of healthy Chinese men in Taiwan.
We demonstrated this only in men in our study, which may have been due to the small sample of women smokers in our study. Our findings showed that hs-CRP levels was significantly associated with hypertension in both genders, consistent with a previous report.\textsuperscript{41}

**Limitations**

Since only total serum cholesterol was measured in the present study, rather than its components, which have opposing effects on the risk of CAD, this might underestimate the predictive ability of lipid concentrations and potentially overestimating the adjusted predictive value of hs-CRP concentration. Finally, the small sample of women who were current smokers might have resulted in underestimating the effect of the relationship between smoking and hs-CRP in terms of the risk for CVs in women.

**Summaries**

We found gender disparity among the risk factors for developing CVs without hemodynamically significant CAD, with the highest hs-CRP tertile in both men and women and age in men only. Since patients with high hs-CRP levels but without hypertension have the highest CVs risk, conventional risk factors play no major role in the pathogenesis of CVs. The study population demonstrated a negative interaction between hypertension and hs-CRP in the development of CVs. The current study demonstrates that analysis of the interaction between hypertension and hs-CRP may improve models for prediction of CVs and lead to better identification of individuals who might benefit from primary prevention.

**Acknowledgements**

We gratefully acknowledge supports from the Center for Healthy Aging Research (CHAR) of Chang Gung University.

**Sources of Funding**

This research was supported by Grant CMRPG23011 and CMRPG 250131 from Chang Gung Memorial Hospital at Keelung and by Grant NSC 95-2314-B-182A-058 from the National
Science Council, Taiwan.

**Disclosures**

None
References


<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls (n=314)</th>
<th>CVs (n=408)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56±12</td>
<td>59±12</td>
<td>0.004</td>
</tr>
<tr>
<td>Male gender</td>
<td>153 (49)</td>
<td>284 (69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26±4</td>
<td>26±4</td>
<td>0.47</td>
</tr>
<tr>
<td>Current smoker</td>
<td>72 (23)</td>
<td>188 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>62 (20)</td>
<td>79 (19)</td>
<td>0.87</td>
</tr>
<tr>
<td>Hypertension</td>
<td>142 (46)</td>
<td>173 (42)</td>
<td>0.37</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>206±40</td>
<td>202±41</td>
<td>0.30</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %†</td>
<td>68±12</td>
<td>66±10</td>
<td>0.22</td>
</tr>
<tr>
<td>hs-CRP, mg/L ¤†</td>
<td>1.58 (0.75, 4.09)</td>
<td>3.67 (1.07, 7.46)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Provoked coronary artery

Left anterior descending artery | 113 (28) |
Left circumflex artery         | 76 (19)  |
Right coronary artery          | 286 (72) |

Number of provoked spastic artery

1-vessel spasm | 343 (86) |
2-vessel spasm | 18 (5)   |
3-vessel spasm | 38 (10)  |

CVS indicates coronary vasospasm; and hs-CRP, high sensitivity C-reactive protein.

Values are expressed as numbers of patients (%) or mean±SD.

¤ Median (interquartile range). hs-CRP samples were collected in a subset of 375 patients, with 146 and 229 in the control and vasospasm groups, respectively.
†Log-transformed values were used in analyses.
Table 2. Baseline Characteristics of 285 Women and 437 Men

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Women (n=285)</th>
<th>Men (n=437)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls (n=161)</td>
<td>CVs (n=124)</td>
</tr>
<tr>
<td>Age, y</td>
<td>58±10</td>
<td>58±11</td>
</tr>
<tr>
<td></td>
<td>0.976</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.7±4.3</td>
<td>26.2±3.8</td>
</tr>
<tr>
<td></td>
<td>0.269</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>9 (6)</td>
<td>12 (10)</td>
</tr>
<tr>
<td></td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35 (22)</td>
<td>24 (19)</td>
</tr>
<tr>
<td></td>
<td>0.622</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>73 (45)</td>
<td>58 (47)</td>
</tr>
<tr>
<td></td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>210±39</td>
<td>206±43</td>
</tr>
<tr>
<td></td>
<td>0.462</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>69±12</td>
<td>68±10</td>
</tr>
<tr>
<td></td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>hs-CRP, mg/L †</td>
<td>1.59 (0.81, 3.94)</td>
<td>3.40 (0.90, 7.18)</td>
</tr>
<tr>
<td></td>
<td>0.038</td>
<td></td>
</tr>
</tbody>
</table>

CVs indicates coronary vasospasm; and hs-CRP, high sensitivity C-reactive protein.

Values are expressed as numbers of patients (%) or mean±SD.

† Median (interquartile range). hs-CRP samples were collected in a subset of 375 patients, with 71 and 68 in the control and vasospasm groups in women, and 75 and 161 in the control and vasospasm groups in men, respectively.
†Log-transformed values were used in analyses.
Table 3. Multivariable Analysis of Variables Associated With Coronary Vasospasm in Women and Men With hs-CRP Measurements

<table>
<thead>
<tr>
<th>Variables</th>
<th>Women (n=139)</th>
<th>Men (n=236)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.99 (0.95-1.03)</td>
<td>0.649</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1.04 (0.95-1.15)</td>
<td>0.418</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.90 (0.50-7.32)</td>
<td>0.349</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.51 (0.19-1.36)</td>
<td>0.179</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.42 (0.19-0.94)</td>
<td>0.035</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>1.00 (0.99-1.00)</td>
<td>0.112</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.99 (0.99-1.00)</td>
<td>0.783</td>
</tr>
<tr>
<td>Tertile of hs-CRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 mg/L</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>1-3 mg/L</td>
<td>0.61 (0.24-1.60)</td>
<td>0.318</td>
</tr>
<tr>
<td>&gt;3 mg/L</td>
<td>3.21 (1.28-8.07)</td>
<td>0.013</td>
</tr>
</tbody>
</table>
Table 4. Hierarchical Analysis of Multivariate-Adjusted Odds Ratios (95% CIs) for Coronary Vasospasm with Gender, Tertiles of hs-CRP, and Anthropometric Measures of Age, Smoking, or Hypertension

<table>
<thead>
<tr>
<th>Model</th>
<th>Women (n=139)</th>
<th>Men (n=236)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile of hs-CRP</td>
<td>Tertile of hs-CRP</td>
</tr>
<tr>
<td></td>
<td>&lt;1 mg/L</td>
<td>1-3 mg/L</td>
</tr>
<tr>
<td>1 Age, y</td>
<td>≤58</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td></td>
<td>&gt;58</td>
<td>1.50 (0.38-6.04)</td>
</tr>
<tr>
<td>2 Smoking</td>
<td>no</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>2.73 (0.26-28.73)</td>
</tr>
<tr>
<td>3 Hypertension</td>
<td>no</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>0.79 (0.21-3.01)</td>
</tr>
</tbody>
</table>

Values are expressed as OR (95% CI).  Model 1: adjusted for body mass index, smoking, diabetes mellitus, hypertension, cholesterol and left ventricular ejection fraction.  Model 2: adjusted for age, body mass index, diabetes mellitus, hypertension, cholesterol and left ventricular ejection fraction.  Model 3: adjusted for age, body mass index, smoking, diabetes mellitus, cholesterol and left ventricular ejection fraction.

\* Data missing due to sparse data.
Table 5. Association of Tertiles of hs-CRP Levels and Anthropometric Factors of Hypertension, Smoking and Age Stratified by Gender among the Subset of Patients With hs-CRP Measurements

<table>
<thead>
<tr>
<th>Model</th>
<th>Women (n=139)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Men (n=236)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile of hs-CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ln(hs-CRP) (mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1 mg/L</td>
<td>1-3 mg/L</td>
<td>&gt;3 mg/L</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;1 mg/L</td>
<td>1-3 mg/L</td>
<td>&gt;3 mg/L</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>≤58</td>
<td>27.6%</td>
<td>31.0%</td>
<td>41.4%</td>
<td>0.738</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40.8%</td>
<td>25.5%</td>
<td>33.7%</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;58</td>
<td>32.9%</td>
<td>25.7%</td>
<td>41.4%</td>
<td>0.87±1.40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20.7%</td>
<td>41.4%</td>
<td>37.8%</td>
<td>1.18±1.33</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>no</td>
<td>32.3%</td>
<td>27.6%</td>
<td>40.2%</td>
<td>0.212</td>
<td>0.74±1.29</td>
<td>0.420</td>
<td></td>
<td></td>
<td></td>
<td>41.0%</td>
<td>32.0%</td>
<td>27.0%</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>8.3%</td>
<td>41.7%</td>
<td>50.0%</td>
<td>1.05±0.94</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22.1%</td>
<td>37.5%</td>
<td>40.4%</td>
<td>1.24±1.28</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>no</td>
<td>34.7%</td>
<td>36.1%</td>
<td>29.2%</td>
<td>0.012</td>
<td>0.49±1.22</td>
<td>0.006</td>
<td></td>
<td></td>
<td></td>
<td>32.6%</td>
<td>38.0%</td>
<td>29.5%</td>
<td>0.173</td>
<td></td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>25.4%</td>
<td>20.9%</td>
<td>53.7%</td>
<td>1.07±1.24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>27.1%</td>
<td>31.8%</td>
<td>41.1%</td>
<td>1.19±1.38</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as percentages or mean±SD.