Vascular Reactivity in Young Adults and Cardiovascular Disease

A Prospective Study

Josef Coresh, Michael J. Klag, Lucy A. Mead, Kung-Yee Liang, and Paul K. Whelton

Cardiovascular reactivity in response to the cold pressor test has been associated with an increased risk of coronary heart disease in middle-aged men. We studied 905 white male medical students, median age 22 years, in the Johns Hopkins Precursors Study. Systolic blood pressure, systolic blood pressure change during the cold pressor test, smoking, cholesterol, Quetelet index, and family history of coronary heart disease were measured on enrollment during 1948–1964. Incidence of cardiovascular morbidity and mortality was ascertained by annual questionnaires and death certificates. There was no association between change in systolic blood pressure during the cold pressor test, whether examined as a continuous variable or a 20 mm Hg or more rise, and the risk of subsequent cardiovascular disease or coronary heart disease. These findings did not change after adjustment for cardiovascular disease risk factors. Previously reported associations may have been due to preexisting arteriosclerosis, which increases the rise in systolic blood pressure during the cold pressor test. We conclude that cardiovascular reactivity to the cold pressor test in young adulthood is not a strong predictor of future cardiovascular disease.

In a prospective study of 265 men, aged 47–57 years, a 20 mm Hg or greater rise in systolic blood pressure during the cold pressor test was associated with the development of myocardial infarction or death from coronary heart disease over 23 years of follow-up. The incidence of myocardial infarction or death from coronary heart disease was 27% among the 67 men with a 20 mm Hg or greater rise in systolic blood pressure during the cold pressor test. The incidence was only 11% among the remaining 198 men (relative risk, 2.4; 95% confidence interval, 2.1–2.8). To our knowledge, no other prospective data on the association between the cold pressor test and coronary heart disease have been published.

The present study examined the association between reactivity to the cold pressor test during medical school in 905 men and the development of cardiovascular disease over the following 4 decades. Reactivity to the cold pressor test was analyzed both as a continuous variable, systolic blood pressure rise during the cold pressor test, and as a binary variable of hyperreactivity, a rise of 20 mm Hg or more. Survival analysis techniques were used to account for the variable duration of follow-up and for the confounding effect of known risk factors for cardiovascular disease.

Methods

Study Population and Baseline Measurements

The Johns Hopkins Precursors Study was started in 1947 by Dr. Caroline Bedell Thomas. The purpose...
Follow-up Procedures

Fatal and nonfatal myocardial infarction, angina, and stroke were assessed by annual questionnaires. The cardiovascular morbidity and mortality experienced by this cohort were divided into three categories. The first and most specific category included myocardial infarction (ICD-9 410 and 412) and sudden death (ICD-9 427.5 and 798.2). The second category, coronary heart disease, included all events in the first category as well as angina pectoris (ICD-9 413) and coronary artery disease requiring bypass graft surgery (ICD-9 414). The broadest category, cardiovascular disease, included coronary heart disease events as well as other cardiovascular disease, that is, hypertensive heart and renal diseases (402-404); pulmonary embolus (415); atrioventricular and other heart block (426.11, 426.30, 426.40, 426.50, 426.53); rhythm disturbances (427.1, 427.3-427.5); congestive heart failure (428); unspecified cardiovascular disease (429.2); cerebrovascular disease (430-436, 437.0-437.3, 438); and diseases of arteries, arterioles, and capillaries (440-442, 443.9, 444, 447.1).

Statistical Analysis

Frequency distributions of all variables were examined. The association between baseline characteristics and maximum systolic blood pressure response to the cold pressor test was tested using linear regression techniques. In this analysis, systolic blood pressure response to the cold pressor test was the dependent variable, and the effect of each baseline characteristic as an independent variable was estimated. The association between reactivity to the cold pressor test and the development of cardiovascular disease, included coronary heart disease events as well as other cardiovascular disease, that is, hypertensive heart and renal diseases (402-404); pulmonary embolus (415); atrioventricular and other heart block (426.11, 426.30, 426.40, 426.50, 426.53); rhythm disturbances (427.1, 427.3-427.5); congestive heart failure (428); unspecified cardiovascular disease (429.2); cerebrovascular disease (430-436, 437.0-437.3, 438); and diseases of arteries, arterioles, and capillaries (440-442, 443.9, 444, 447.1).
Table 1 shows baseline characteristics of the 905 medical students in the study. The overall risk profile was that of young, healthy individuals. Median age at entry was 22 years, with 95% of the subjects being younger than 28. The mean blood pressure was in the normotensive range, with only nine of the subjects having a systolic blood pressure above 160 mm Hg. Participants were, on average, lean, with moderately elevated average serum cholesterol levels as measured by the Bloor method. The Bloor method tends to overestimate serum cholesterol levels by 10-15% compared with the Abell-Kendall method. The high prevalence of cigarette smoking, 53%, was consistent with national averages during this time period. However, many of the subjects stopped smoking during the follow-up period. In 1970, only 31% of the subjects were smoking, and by 1980, the prevalence of cigarette smoking had decreased to 24%.

The average systolic blood pressure change during the cold pressor test was 12 mm Hg, with a standard deviation of 8 mm Hg and a mild skew toward higher values. One hundred and seventy-five (19%) of the subjects had a systolic blood pressure response of 20 mm Hg or greater. The diastolic blood pressure rise was slightly greater, at 15 mm Hg; the average increase in heart rate was 6 beats per minute. The magnitude of these responses is comparable to that of healthy adults in other studies.

Table 2 shows the association between the subjects’ baseline characteristics and the systolic blood pressure rise during the cold pressor test. Subjects with a higher systolic or diastolic blood pressure had a greater rise in systolic blood pressure during the cold pressor test. However, these associations were not very strong. The mean systolic blood pressure rise during the cold pressor test was only 0.54 mm Hg higher for each 10 mm Hg increment in baseline systolic blood pressure. A family history of premature coronary artery disease in the father was associated with a 1.3 mm Hg higher systolic blood pressure rise during the cold pressor test (p=0.05). A positive family history of hypertension in either parent was not associated with a significantly higher response to the cold pressor test. Reactivity to the cold pressor test was also not significantly associated with age, body mass index, or resting heart rate. However, the range of many of these variables was quite narrow in this young, healthy population.

Table 3 shows the number of cardiovascular disease end points ascertained. Eighty of the subjects died over a median follow-up period of 27 years. Twenty-four deaths were due to cardiovascular disease, and 18 of these were due to a myocardial infarction or sudden death. One hundred and fifty-three of the subjects had at least one cardiovascular disease event; 83 of these individuals experienced a coronary heart disease event, and 51 experienced myocardial infarction or sudden death.
The systolic blood pressure change during the cold pressor test was not predictive of future coronary heart disease or cardiovascular disease (Table 4). This was true whether the reactivity was modeled as a binary or continuous variable. Figure 1 shows a Kaplan-Meier plot of the cumulative incidence of coronary heart disease by age of the subjects for participants with a low (less than 6), intermediate (6-19), or high (20 or greater) systolic blood pressure response to the cold pressor test. It is evident from the graph that the cumulative incidence of coronary heart disease did not differ among the three groups ($p=0.82$). The incidence curves are overlapping until age 60. The rise in cumulative incidence above age 60 in the hyperreactors reflects the few events ($n=2$) among the small number of subjects ($n=26$) older than 60 years of age in this group. Adjustment for other coronary heart disease risk factors demonstrated that this lack of association was not due to confounding by these variables (Table 5). The adjusted relative risk associated with hyperreactivity to the cold pressor test (systolic blood pressure rise of 20 mm Hg or greater) was 0.91, with a 95% confidence interval of 0.5-1.8. Reanalysis of the data including the three individuals with extremely high cold pressor responses did not change the results.

The diastolic blood pressure and heart rate responses during the cold pressor test were also not associated with cardiovascular disease incidence (data not shown).

Discussion

To our knowledge, this is the largest prospective study examining the association between response to the cold pressor test and subsequent incidence of cardiovascular disease. The systolic blood pressure rise during the cold pressor test among the 905 young men in this study had a unimodal distribution, with no evidence for a distinct group of hyperreactors. The systolic blood pressure rise during the cold pressor test was minimally greater among individuals with a higher systolic or diastolic blood pressure. Reactivity to the cold pressor test, however, was not higher among people with a positive family history of hypertension.

Hyperreactivity to the cold pressor test was not associated with the incidence of overall cardiovascular disease or the more specific categories of coronary heart disease and myocardial infarction or sudden death. Modeling cold pressor reactivity as a continuous variable also yielded no association between cold pressor reactivity and disease. This lack of association was not due to confounding by other measured cardiovascular risk factors. Furthermore, the risk estimates were very close to 1.0, with narrow confidence intervals, giving strong evidence against a marked association between cold pressor reactivity and cardiovascular disease.

The rationale for using reactivity as a continuous variable in the present analysis was the unimodal distribution of reactivity. There was no evidence in our data or any of the other published studies for a distinct group of hyperreactors to the cold pressor test. The validity of the linearity assumption, which underlies the use of cold pressor reactivity as a continuous variable, was examined by dividing the reactivity into quartiles. There was no association between the reactivity quartiles and disease outcomes and no evidence for deviation from the linearity assumption. A quadratic term, systolic blood pressure change squared, also did not improve the fit of the model (data not shown).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction or sudden death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperreactivity ($\geq 20$ mm Hg)</td>
<td>1.24</td>
<td>0.6-2.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Systolic blood pressure rise (12 mm Hg)*</td>
<td>1.06</td>
<td>0.7-1.6</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Coronary heart disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperreactivity ($\geq 20$ mm Hg)</td>
<td>1.18</td>
<td>0.7-2.1</td>
<td>0.55</td>
</tr>
<tr>
<td>Systolic blood pressure rise (12 mm Hg)*</td>
<td>1.04</td>
<td>0.7-1.6</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperreactivity ($\geq 20$ mm Hg)</td>
<td>1.13</td>
<td>0.7-1.7</td>
<td>0.57</td>
</tr>
<tr>
<td>Systolic blood pressure rise (12 mm Hg)*</td>
<td>0.98</td>
<td>0.8-1.3</td>
<td>0.87</td>
</tr>
</tbody>
</table>

*Cold pressor test response was analyzed as a continuous variable. Relative risk (RR) for development of cardiovascular disease was calculated for a 12 mm Hg rise in systolic blood pressure during cold pressor test. This value represents the difference between the 75th and 25th percentile of the systolic blood pressure change in this study population.
Besides the absence of a biological relation between reactivity to the cold pressor test and incidence of cardiovascular disease, there are several alternative explanations for the failure to demonstrate such an association. Manual measurement of the rise in systolic blood pressure during the cold pressor test is imprecise. This imprecision could have resulted in misclassification, which would decrease the observed association. However, the cold pressor reactivity measures in this study have been shown to predict the development of hypertension, with a comparable number of end points \( n = 105 \).\(^\text{16}\) Higher systolic blood pressure reactivity to the cold pressor test was associated with an excess risk of developing hypertension before the age of 45 (relative risk, 2.6; 95% confidence interval, 1.5-4.7 for 20 mm Hg or greater rise in systolic blood pressure). Given that the cold pressor test reactivity predicts the development of hypertension in this study, it is even more surprising that reactivity is not associated with cardiovascular disease. If hypertension is in the causal pathway between cardiovascular reactivity and the development of cardiovascular disease, then pharmacological treatment of hypertension with the attendant risk reduction may explain the lack of association between reactivity and cardiovascular disease.

Another possible explanation for our negative results is that the association between reactivity to the cold pressor test and incidence of cardiovascular disease is too small to be detected in our study. The confidence intervals around the risk estimate associated with hyperreactivity show that a relative risk greater than 1.8 for cardiovascular disease is unlikely. However, a small increase in risk of 1.8 or less cannot be ruled out. Given that this study included 905 individuals followed for a median period of 27 years, it seems unlikely that a larger prospective study of the cold pressor test will be conducted. Longer follow-up on this cohort will result in more cardiovascular end points and will allow for an examination of any smaller risk associated with cold pressor hyperreactivity. However, many of the incident cases of premature coronary heart disease in this cohort have already occurred, because the median age of individuals in the study is now 60 years old. The previous study\(^\text{3}\) that demonstrated a relation between reactivity to the cold pressor test and subsequent coronary heart disease studied a much older population than that in the present study. People with arteriosclerosis exhibit a greater systolic blood pressure rise during the cold pressor test than those without arteriosclerosis, independent of the presence of hypertension.\(^\text{17,18}\) This finding suggests that measurement of reactivity to the cold pressor test in middle age may be a marker for existing atherosclerosis. As a result, the predictive value of reactivity to the cold pressor test performed in middle age is difficult to interpret. The association found by Keys et al\(^\text{1}\) could have resulted from a higher prevalence of

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### Table 5. Risk of Coronary Heart Disease Associated With Several Baseline Characteristics: Multivariate Cox Proportional Hazards Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperreactivity (≥20 mm Hg)</td>
<td>0.91</td>
<td>0.5-1.8</td>
<td>0.77</td>
</tr>
<tr>
<td>Early* CAD in father</td>
<td>2.12</td>
<td>1.3-3.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Serum cholesterol (41 mg/dl)</td>
<td>1.53</td>
<td>1.2-1.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>2.11</td>
<td>1.2-3.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Quetelet index (2.6 kg/m²)</td>
<td>1.08</td>
<td>0.9-1.3</td>
<td>0.48</td>
</tr>
<tr>
<td>Systolic blood pressure (10 mm Hg)*</td>
<td>0.95</td>
<td>0.8-1.1</td>
<td>0.56</td>
</tr>
</tbody>
</table>

RR, relative risk; CAD, coronary artery disease.
*Before age 65.
subclinical arteriosclerosis among hyperreactors to the cold pressor test at the baseline visit.

The lack of association of cardiovascular disease with cold pressor response in this study should be generalized with caution to other stressors. Reactivity in response to various stressors is mediated through different physiological mechanisms. The systolic blood pressure response to the cold pressor test results from a vasoconstrictive response mediated predominantly by neurosympathetic pathways. The mean arterial pressure rise during the cold pressor test is correlated with a response to other physical, but not mental, stressors. Daytime variability in blood pressure measured with an intra-arterial catheter is associated with a response to mental, but not physical, stress. Thus, mental stressors may be more similar to the daily stimuli people encounter and may prove to be more predictive of the development of coronary heart disease.

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