Cardiovascular Reactivity to the Cold Pressor Test as a Predictor of Hypertension

Marilyn S. Menkes, Karen A. Matthews, David S. Krantz, Ulf Lundberg, Lucy A. Mead, Bahjat Qaqish, Kung-Yee Liang, Caroline B. Thomas, and Thomas A. Pearson

Cardiovascular reactivity to stress is hypothesized to be a marker for subsequent neurogenic cardiovascular disease, but few prospective studies of this hypothesis are available. We studied 910 white male medical students who had their blood pressure and pulse rate measured before and during a cold pressor test in the years 1948–1964. Hypertensive status (requiring drug treatment) was ascertained by annual questionnaires in the 20- to 36-year follow-up period. An association was observed between maximum change in systolic blood pressure and later hypertension, with a cumulative incidence of hypertension by age 44 of 6.7%, 3.0%, and 2.4% for a change in systolic blood pressure in the upper, middle two, and lowest quartiles, respectively (Kaplan-Meier, \( p < 0.02 \)). After adjustment for study entry age, Quetelet Index, cigarette smoking, pretest systolic blood pressure, and paternal or maternal history of hypertension in a Cox model, the association persisted. The excess risk associated with systolic blood pressure reactivity was not apparent until the population aged some 20 years and was most apparent among those in whom hypertension developed before age 45 (relative risk=2.5, 95% confidence intervals=1.47, 4.71 for a 20 mm Hg change). Diastolic blood pressure and heart rate changes were not associated with later hypertension. These data suggest that persons prone to later hypertension manifest an altered physiology at a young age. (Hypertension 1989;14:524–530)

Cardiovascular reactivity to stress has been hypothesized to be a marker for subsequent neurogenic hypertension. However, few studies have tested the link between responses to psychophysiological stimuli and later development of this disease in human populations. As one approach to evaluation of this hypothesis, studies have assessed the discriminative or prognostic value of "excessive" reactivity to a standardized cold stimulus, the cold pressor test. The empirical basis for the cold pressor test rests on observations by its originsators, Hines and Brown, and others who found: 1) that hypertensive persons show greater lability of blood pressure under various forms of stress than do normotensive persons, 2) that normotensive "hyper-reactors" to the cold pressor test are more likely to have a positive family history of hypertension than normotensive persons who are less reactive, and 3) that hyper-reactors to the cold pressor test may be predisposed to the development of essential hypertension at a later point in time.

However, other studies have been unable to confirm many of these observations, and few long-term prospective studies of this hypothesis are available. Previous prospective studies have been limited by incomplete or short duration of follow-up or by the small size of the cohorts initially tested for reactivity to the cold pressor test. In all of these studies, the analyses were based on arbitrary definitions of reactivity introduced by Hines or Brown. None took into consideration the impact of time or age in the estimation of risk of development of hypertension, and few controlled for confounding factors.

We report here on the results of a prospective survival analysis of the relation of cold pressor
reactivity to subsequent hypertension among a large cohort of medical students who have been followed since graduation for some 20 to 36 years; we took into account the effects of age and other important risk factors for hypertension.

Materials and Methods

Study Population and Baseline Measurements

In 1946-1947, a longitudinal investigation on risk factors in early adulthood for later cardiovascular and other chronic diseases was initiated by one of the authors (C.B.T.). The study population consisted of 1,130 white male medical students enrolled in the 1948 to 1964 graduating classes of the Johns Hopkins Medical School. More than 95% of eligible participants were enrolled. The age range of the total cohort at the initial examination was 19–49 years (mean, 23 years). Complete data for the cold pressor test-re-test correlations for the cold pressor test. They present study, three other investigations have reported pressure, diastolic blood pressure, and heart rate calculated: the maximum changes in systolic blood pulse rate were measured in the opposite arm at 4° C, during which time the blood pressure and observer. The blood pressure and pulse rate measurements were repeated until no further changes were noted (+4 mm Hg and 4 beats/minute), a common procedure in psychophysiological research to ensure that a reliable baseline value has been achieved. These control values were subsequently used for the calculation of the cold pressor reactivity measures. The right hand was immersed above the wrist for 1 minute in a bucket of ice water at 4° C, during which time the blood pressure and pulse rate were measured in the opposite arm at approximately 30 and 60 seconds and recorded. Three measures of cold pressor reactivity were calculated: the maximum changes in systolic blood pressure, diastolic blood pressure, and heart rate from the control values during the cold stimulus.

Although reliability data are not available from the present study, three other investigations have reported test-retest correlations for the cold pressor test. They range from 0.39 to 0.83 for systolic blood pressure changes, 0.23 to 0.75 for diastolic blood pressure changes, and 0.23 to 0.50 for heart rate changes across intervals of time from 2 weeks to 4 years.21-23 Among the samples most comparable to that of first year Johns Hopkins Medical School students (male and female undergraduates), the test-retest reliability of the cold pressor test was 0.83 for systolic blood pressure changes, 0.23 for diastolic blood pressure changes, and 0.50 for heart rate change.21

Follow-up Procedures

Since graduation, data on parental history were updated by questionnaires that were mailed to study participants each year. This follow-up information was used in the analysis to define the number of parents in whom the participants reported the development of hypertension before the age of 65, the age of the youngest parents of participants, thus allowing all parents to be at risk of becoming hypertensive. Participation during the long follow-up period has remained reasonably high, with response rates ranging from 68 to 78% for the return of any one set of questionnaires.

The incidence of disease events and mortality in this physician cohort were surveyed by questionnaire on an annual basis. For any 5-year period, 87–94% of any single class returned their morbidity questionnaires. Subjects who reported receiving drug therapy for hypertension were considered to be hypertensive for the purposes of this study. Other studies of the epidemiology of hypertension have used self-reports of hypertension as the outcome variable and have found the hypertension questions in the mail survey to have good sensitivity (82–98%) and specificity (98–99%).24,25 In addition, a small pilot study of 21 physicians enrolled in the present study showed that self-reports of systolic blood pressure, diastolic blood pressure, pulse rate, and weight were similar to (and not significantly different from) those measured by trained observers. By 1984, after 20–36 years of follow-up, 113 study subjects reported receiving treatment for hypertension; 105 of these had taken the cold pressor test. Thus, the statistical analysis was based on data from 910 study subjects, 105 of whom reported they were being treated for hypertension.

Statistical Analysis

The frequency distributions of the three cold pressor reactivity measures for the total population—maximum change in systolic and diastolic blood pressures and heart rate—were examined. The relation between reactivity to cold pressor and the incidence of hypertension during 20–36 years of follow-up was evaluated by an examination of Kaplan-Meier survival curves,26 with age to hypertension as the outcome. For this analysis, the reactivity variables were arbitrarily divided into three categories: the lower 25%, the middle 50%, and the upper 25% of the study population distribu-
tions. The middle two quartiles did not differ in risk of hypertension. The log rank test was used to assess the statistical significance of the difference between the three curves.27

The three cold pressor reactivity measures were also treated as continuous variables and were entered into separate Cox proportional hazards models28 to obtain unadjusted estimates of association with the development of hypertension. Estimates of relative risk with corresponding 95% confidence limits were obtained with the Cox model; these estimates were adjusted for baseline values of age, Quetelet Index ([weight [kg]/[height [m]]^2]), control systolic blood pressure, cigarette smoking, and the updated histories of maternal and paternal history of hypertension. Evidence for interaction between the cold pressor reactivity measures and family history of hypertension was sought with this model because family history of hypertension has been related to cold pressor reactivity in some studies.

Finally, since there was some suggestion from our data that cold pressor reactivity may be predictive of early rather than late onset of hypertension, a separate Cox model was developed to test this hypothesis. The model incorporated a time-dependent function, which had a value of zero or one, respectively, if hypertension developed in a subject before the age of 45 or at 45 years or later. By using this model, separate estimates of association between cold pressor reactivity and subsequent "early" or "late" hypertension were obtained. The model used in this analysis is described by the following equation:

\[
\lambda(t; \mathbf{x}_1, \mathbf{x}_2, z(t)) = \lambda_0(t) \cdot e^{\beta_1 x_1 + \beta_2 x_2 + \beta_3 z(t)}
\]

where

- \(\lambda_0(t)\) is the baseline hazard function;
- \(x_1\) is cold pressor maximum systolic blood pressure change;
- \(x_2\) is vector of the other covariates (baseline age, Quetelet Index, cigarette smoking, control systolic blood pressure, maternal and paternal history of hypertension);
- \(z(t)\) is time-dependent function; value = 0 or 1 when age is less than 45 or age is 45 or more years, respectively;
- \(\beta_1\) is log relative risk of cold pressor reactivity for early hypertension;
- \(\beta_2\) is difference of the log relative risks of cold pressor reactivity for early and late hypertension;
- \(\beta_3\) is vector of log relative risks for other covariates.

**Results**

Baseline characteristics of the study population undergoing the cold pressor test are presented in Table 1. The 220 subjects who did not complete the test had characteristics similar to the participants (p>0.10): mean age (23.4±2.7 years), mean Quetelet Index (23.0±2.5), smokers (59.8%), ex-smokers (1.1%), positive maternal or paternal history of hypertension (30.1%). About half of the study group smoked cigarettes and over 30% had at least one parent in whom hypertension developed before the age of 65.

The distribution of the three cold pressor reactivity measures approximated a normal curve with a mild skew toward higher values. The range of values of the three measures of reactivity were: -8 and 76, -6 and 50, -22 and 58 for the maximum change in systolic pressure (mm Hg), diastolic pressure (mm Hg), and heart rate (beats/min), respectively.

When age at follow-up was considered in the analysis, an association with incidence of hypertension was observed for one cold pressor reactivity measure: the maximum change in systolic blood pressure. Systolic blood pressure change was unrelated to control systolic blood pressure (r= -0.05, p=0.09). The cumulative incidence of hypertension by age, according to three levels of this reactivity measure (upper, middle two, and lower quartiles) are illustrated in Figure 1 and presented in more detail in Table 2. No association of hypertension with diastolic blood pressure or heart rate change was seen. The curves demonstrated that the cold pressor test does not distinguish between subjects who are at increased risk of development of hypertension until the population is allowed to age some 20 years or more. Table 2 illustrates that by using those with low cold pressor reactivity as a compar-

**Table 1. Baseline Characteristics of the Cardiovascular Reactivity Study Population**

<table>
<thead>
<tr>
<th>Subjects (N)</th>
<th>910</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (±SD)</td>
<td>23.1 (2.5)</td>
</tr>
<tr>
<td>Mean Quetelet (±SD)</td>
<td>22.9 (2.6)</td>
</tr>
<tr>
<td>Smoking history % (N)</td>
<td>53.3 (486)</td>
</tr>
<tr>
<td>Smokers</td>
<td>2.3 (21)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>17.3 (158)</td>
</tr>
<tr>
<td>Parental history of hypertension % (N)*</td>
<td>14.6 (133)</td>
</tr>
<tr>
<td>Maternal+</td>
<td>4.0 (36)</td>
</tr>
<tr>
<td>Paternal+</td>
<td>114.0 (10.4)</td>
</tr>
<tr>
<td>Both+</td>
<td>69.4 (8.0)</td>
</tr>
<tr>
<td>Mean control blood pressure and pulse (±SD)</td>
<td>72.3 (9.9)</td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>12.2 (8.7)</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>15.0 (9.1)</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>6.2 (8.7)</td>
</tr>
</tbody>
</table>

*Variable based on follow-up information to determine hypertension status of parents before age 65.
Cold pressor systolic blood pressure change was also observed to be significantly associated with risk of hypertension when it was treated as a continuous variable in a univariate Cox model (B = 0.027, SEM = 0.011, p = 0.01), and in multivariate analysis after adjustment for other important risk factors. Table 3 shows the regression coefficients and corresponding risk estimates for cold pressor reactivity and other major risk factors that were included in the multivariate model. The relative risk of hypertension for a cold pressor systolic blood pressure change of 20 mm Hg is 1.93 after adjustment for baseline age, Quetelet Index, pretest control systolic blood pressure, cigarette smoking, and maternal and paternal history of hypertension. A significant interaction was observed between maternal and paternal history in these data (relative risk of 8.12 for hypertension if both parents had hypertension). For this reason, a term was included in the model to take it into account. Cold pressor reactivity was not observed to be a stronger predictor in those with a positive maternal or paternal history of hypertension than in those without such history. Note that having two parents with hypertension is a stronger predictor of subsequent hypertension than having either parent with hypertension and that reactivity to the cold pressor test has a relative risk similar to that of control systolic blood pressure. Any comparison of relative risks between continuous and categorical variables (e.g., family history of hypertension vs. reactivity to the cold pressor test) is somewhat flawed because it depends on the arbitrary categorization of the continuous variables.

In addition, we examined the relation of cold pressor reactivity to incidence of hypertension, using Hines' definition of a hyper-reactor to the cold pressor test (a systolic blood pressure change of 20 mm Hg or greater) in a multivariate model that included the adjustment variables used previously. The association remained (relative risk = 1.76; 95% confidence interval = 1.12, 2.76), although it was somewhat weaker than that observed when reactivity was treated as a continuous variable.

We examined the possibility that the observed relation between cold pressor reactivity and incidence of hypertension differed for early (before 45 years) versus late (45 years or older) age of onset with a time-dependent multivariate survival model,

<table>
<thead>
<tr>
<th>Systolic blood pressure change to cold pressor test</th>
<th>Subjects at risk (n)</th>
<th>Events of hypertension (n)</th>
<th>Cumulative incidence (% of subjects) of hypertension Age at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (≤6 mm Hg)</td>
<td>257</td>
<td>28</td>
<td>2.4 at 44 years, 9.2 at 54 years</td>
</tr>
<tr>
<td>Moderate (7–17 mm Hg)</td>
<td>424</td>
<td>42</td>
<td>3.0 at 44 years, 9.5 at 54 years</td>
</tr>
<tr>
<td>High (≥18 mm Hg)</td>
<td>229</td>
<td>35</td>
<td>6.7 at 44 years, 15.4 at 54 years</td>
</tr>
<tr>
<td>Total</td>
<td>910</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>Subjects (n) contributing person years at each age cutoff</td>
<td></td>
<td></td>
<td>815 at 44 years, 346 at 54 years</td>
</tr>
</tbody>
</table>

Figure 1. Cumulative incidence of hypertension over 15–30 years of follow-up according to level of systolic blood pressure change during cold pressor test at baseline. Three groups are lowest quartile, (dots), middle two quartiles (solid line), and highest quartile (dashed line) according to baseline systolic blood pressure change. Incidence of hypertension in highest quartile is significantly different from other two groups (p = 0.021).
the results of which are shown in Table 4. For the 33 subjects who reported that hypertension had developed before age 45 years, the relative risk for a 20 mm Hg change in systolic pressure during the cold pressor test was 2.63, a strong and statistically significant association. In contrast, for the 72 subjects who reported the development of hypertension at age 45 years or later, the relative risk associated with a similar systolic change was 1.53, with a 95% confidence interval that included one.

Discussion

A significant independent association between blood pressure reactivity to the cold pressor test and incidence of subsequent hypertension was observed in this study. This is in agreement with the results of two previous prospective studies. Wood et al followed 47% of a study cohort of 300 school children for 45 years and found a 3.7-fold risk of hypertension for those classified as hyper-reactors at the time of the initial cold pressor test at either of two time periods. Barnett and associates followed a group of Hines' original cohort for 27 years and found a 10% (4/40) incidence of hypertension among patients classified as hyper-reactors at the time of the initial cold pressor test, but no hypertension among the patients originally classified as normoreactors. However, the low rate of follow-up and the lack of a uniform definition of test positives in the former study have been sharply criticized, and the low incidence of hypertension among high reactors provides rather weak support for the clinical usefulness of the cold pressor test.

Four other prospective studies have not confirmed a positive association between cold pressor reactivity and later hypertension. One study was an 18-year follow-up study of a cohort of aviators, a group that may have been selected to be healthy and physically fit, including low, non-labile blood pressures and heart rates. By the end of the 18-year follow-up period, the mean age of the cohort was only about 41 years, an age that may have been too young to uncover many hypertensive cases. A second study of air force officers may have had similar selection biases and reported no correlation between cold pressor response and hypertension status after a follow-up period of only 7 years. Similarly, the remaining two studies, of university and medical student populations, determined the hypertensive status of their study subjects after only 5–10 years of follow-up, before most of them had reached their fourth decade of life. Since the prevalence of hypertension increases dramatically with age, our data suggest that assessment of this end point should not be made until the majority of the population reaches the age of 45 or 50 years if a fair test of the predictive value of the cold pressor test is to be made.

In addition to having followed a large proportion of the study cohort for a time span of up to three and a half decades, the present investigation differs from those previous to it with respect to the statistical methods of analyses that were used. Past investigations have examined cold pressor reactivity in relation to incidence of hypertension without taking the dimension of time or age into account in their analyses. When this analytic approach is applied to our own data, our study also shows no

### Table 3. Regression Coefficients and Relative Risks Relating Cold Pressor Systolic Blood Pressure and Other Risk Factors to Incidence of Hypertension Over 20–36 Years of Follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>β*</th>
<th>SE</th>
<th>Relative risk*</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>0.547</td>
<td>0.209</td>
<td>1.73</td>
<td>(1.15, 2.60)</td>
</tr>
<tr>
<td>Maternal hypertension</td>
<td>0.097</td>
<td>0.280</td>
<td>1.10</td>
<td>(0.64, 1.91)</td>
</tr>
<tr>
<td>Paternal hypertension</td>
<td>0.758</td>
<td>0.256</td>
<td>2.13</td>
<td>(1.29, 3.52)</td>
</tr>
<tr>
<td>Both parents with hypertension</td>
<td>1.239</td>
<td>0.438</td>
<td>8.12</td>
<td>(4.47, 14.10)</td>
</tr>
<tr>
<td>Control systolic blood pressure</td>
<td>0.036</td>
<td>0.009</td>
<td>2.04</td>
<td>(1.43, 2.90)</td>
</tr>
<tr>
<td>Cold pressor systolic blood pressure change (mm Hg)</td>
<td>0.033</td>
<td>0.011</td>
<td>1.93</td>
<td>(1.26, 2.98)</td>
</tr>
</tbody>
</table>

*Regression coefficients and relative risks estimated from a Cox Proportional Hazards Model that also includes baseline age (p>0.05) and Quetelet Index (p>0.05).

### Table 4. Relative Risks Relating Cold Pressor Systolic Blood Pressure Reactivity to Incidence of Subsequent Hypertension by Age at Follow-up

<table>
<thead>
<tr>
<th>Age at follow-up</th>
<th>Number of events of hypertension</th>
<th>Relative risk of subsequent hypertension (95% confidence interval)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45 years</td>
<td>33</td>
<td>2.63 (1.47, 4.71)</td>
</tr>
<tr>
<td>≥45 years</td>
<td>72</td>
<td>1.53 (0.86, 2.71)</td>
</tr>
</tbody>
</table>

*Relative risks estimated from a Cox Proportional Hazards Model with adjustments for baseline age, Quetelet Index, cigarette smoking, maternal and paternal history of hypertension, and control systolic blood pressure.

Relative risks estimated for an increase in systolic blood pressure of 20 mm Hg.
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independent association between cold pressor blood pressure reactivity and hypertension \( p > 0.10 \).\textsuperscript{16}

There are two points to be made in favor of the survival analyses we chose to use in our study. First, they are a preferred method of analysis for determination of the relation of prognostic factors to outcome over time in longitudinal studies.\textsuperscript{30} Secondly, since our data suggest that the importance of the cold pressor test as a predictor of hypertension varies with age, a consideration of time or age is crucial in the analysis.

Our treatment of the indexes of blood pressure reactivity to the cold pressor test as continuous rather than categorical variables, unlike other investigators, increased the statistical power of our data to detect an association with incidence of hypertension. However, this difference in treatment of the exposure variable does not, by itself, explain the difference in results obtained between studies, since we also observed an independent association between the maximum cold pressor blood pressure change (or increment) when this variable was categorized according to similar criteria used by other investigators and analyzed with the Cox survival models. It is also important to note that the association with blood pressure change was independent of the basal level of blood pressure, since these data were adjusted for basal levels as well as other potential confounders in the models.

Although we did find a relation between systolic blood pressure response to cold stress and later hypertension, we did not observe a similar independent association for diastolic blood pressure or heart rate. These results appear to be in agreement with several studies,\textsuperscript{18-20} although they disagree with some of Hines’ work, who in later years based his definition of hyper-reactivity solely on diastolic pressor responses.\textsuperscript{31} Perhaps the nonsignificant results for diastolic blood pressure in the present study during the cold pressor test result from the low reliability relative to that of systolic blood pressure in this age group.\textsuperscript{21-23}

It is also important to note here that the cold pressor test elicits different hemodynamic mechanisms from stressors with a more substantial mental component. Results from two studies that measured blood catecholamine levels in response to two stress tests, the cold pressor test, and mental arithmetic test\textsuperscript{32,33} showed that the mental arithmetic test elicited higher heart rate responses and levels of plasma epinephrine than did the cold pressor test, whereas the cold pressor test was associated with higher levels of plasma norepinephrine and elevations in blood pressure comparable with those obtained during the mental arithmetic test. Norepinephrine levels were found to be more strongly correlated with blood pressure levels than with heart rates. Similarly, several investigators\textsuperscript{34-37} suggest that persons with a family history of hypertension in fact possess a heightened cardiovascular response potential expressed during the performance of tests that require “active coping” in the mental or psychosocial sense. Such tasks include the mental arithmetic test, shock avoidance, or other situational demands that trigger affective behaviors.\textsuperscript{34-38} Although some affective response is elicited by the cold pressor test, it is primarily a physical stressor that passively involves the participant.

The present study does not and cannot elucidate why episodic hyperresponsiveness is related to risk for hypertension. Hyperresponsiveness may represent one pathogenic mechanism in the development of essential hypertension, be a marker for a central defect in the autonomic control of the cardiovascular system, or reflect early changes in arterial compliance of future hypertensive individuals.\textsuperscript{36,39} One intriguing mechanism that has been proposed\textsuperscript{40-41} is that pressor hyper-reactivity is a manifestation of a widespread basic membrane transport disorder that disrupts cellular cation homeostasis. Sodium-lithium transport abnormalities have been observed in blood cell membranes of patients with essential hypertension,\textsuperscript{42,43} and a recent study\textsuperscript{44} has found that the cold pressor test elicited a greater sodium efflux in leukocytes of subjects with a positive family history of hypertension compared with those with a negative history.

Although the present study suggests that a state of hyperresponsiveness may precede essential hypertension and that the cold pressor test could be useful as a predictor of future hypertension in a young study population, the findings must be considered to be preliminary until they are replicated by other large, long-term prospective studies that are able to achieve complete follow-up. Even then, several factors would need to be considered, particularly if the test is ever to be used for screening purposes. First, the cold pressor test may not be a valid and reliable test in all populations. Second, the cold pressor test is reasonably acceptable to most study subjects and simple to administer. A final consideration is the relative strength of the association between cold pressor reactivity and incidence of hypertension. Although having two parents with hypertension is a stronger prognostic factor in this cohort and other cohort studies,\textsuperscript{6} the risk of hypertension associated with a 20 mm Hg increase in cold pressor systolic response is increased by over 90% and closely approximates the increased risk observed for a similar increase in basal systolic blood pressure.

In sum, the present study suggests that systolic blood pressure reactivity to the cold pressor test may prove to be an important independent predictor of early hypertension. The cold pressor tests may thus identify a subgroup of individuals with an occult physiological abnormality that predisposes them to hypertension decades later. Preventive interventions may be particularly warranted in these individuals.
Acknowledgments

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