Cold Pressor Test as a Predictor of Hypertension

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SUMMARY To determine the usefulness of the cold pressor test as a predictor of hypertension, we compared the blood pressure recordings available from 142 patients in 1979 with readings obtained during performance of two cold pressor tests, the first in 1934 when these subjects were children, and the second in 1961. Forty-eight subjects were hyperreactors to the tests in either 1934 or 1961, and 94 were normoreactors. At last follow-up, blood pressures in 14 of the hyperreactors were between 140 and 160 mm Hg systolic or 90 and 100 mm Hg diastolic (Stratum 1) and in 20 exceeded 160 mm Hg systolic or 100 mm Hg diastolic (Stratum 2). Ten normoreactors had casual blood pressures in Stratum 1 and eight in Stratum 2. Hypertension had thus occurred in 71% of the hyperreactors and 19% of the normoreactors. Fifteen hyperreactors were receiving antihypertensive therapy, and this reduced the severity of the casual blood pressure elevation in most patients to Stratum 1. Antihypertensive therapy had been started in three normoreactors. The duration of follow-up, 45 years, and the mean age at follow-up, almost 57 years, were greater in this study than in any previously reported study. Early hyperreactivity was related to future hypertension in enough subjects to suggest that an abnormal response to an external cold stimulus may be useful as an indicator of future hypertension.

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KEY WORDS • cold stimulus • blood pressure • hyperreactivity

Almost 50 years ago, Hines and Brown proposed that a period of vascular hyperreactivity preceded the development of sustained hypertension. They further suggested that vascular hyperreactivity manifested by an excessive pressor response to an external cold stimulus was a potential predictor of hypertension. Subsequent investigators have used the cold pressor test but have disagreed about its usefulness as a predictor of hypertension.

We report here the results of a 45-year follow-up study of 142 subjects who were originally studied by Hines, in an attempt to determine the value of the cold pressor test as an indicator of future hypertension.

Methods

In 1934, 300 Rochester, Minnesota, schoolchildren aged 7 to 17 years were studied by means of the cold pressor test. In 1961, 151 of the original subjects were again studied with use of a cold pressor test. The Mayo Clinic records of the 151 subjects who had been given cold pressor tests in 1934 and 1961 were reviewed in 1979 without knowledge of the test responses. Casual blood pressure recordings made during routine office visits were abstracted from each patient's record. In most instances, more than two blood pressure readings were available for each patient during the last year of follow-up. In this circumstance an average blood pressure was determined.

For the purposes of this study, a blood pressure level of less than 140/90 mm Hg is described as normotension. Higher pressures indicating hypertension were graded in the following manner: blood pressures of 140 to 159 mm Hg systolic or 90 to 99 mm Hg diastolic were classified in Stratum 1, and blood pressures of 160 mm Hg or more systolic or 100 mm Hg or more diastolic were classified in Stratum 2.

In addition, results of electrocardiograms, chest roentgenograms, and urinalyses were recorded, as were all index diagnoses of hypertension and coronary, cerebral, and renovascular diseases which had been entered on the master sheet of each patient's record. The presence of hypertension among the parents of each patient was also noted.

The cold pressor test performed in 1934 had been carried out according to Hines's protocol, and the same protocol had been used again in 1961. It is briefly described here. After the nature of the test was explained, each subject was asked to lie in a supine position in a quiet room. A blood pressure reading was
obtained at the beginning of the test; this was the casual blood pressure. Serial blood pressure readings were then taken at 10-minute intervals until three almost identical readings were obtained. The last of these measurements was designated the basal blood pressure.

The subject was then asked to immerse one hand to just above the wrist for 1 minute in ice water that was being kept at 4° to 5° C (39° to 41° F). During the period of ice-water immersion, blood pressure readings were taken in the opposite arm at 15-second intervals; the highest of these readings was designated the peak or ceiling blood pressure. The difference between peak and basal blood pressures determined the level of vascular reactivity. Subjects were then classified according to their response to the cold pressor test. Subjects were designated hyperreactors when they responded to the cold pressor test with an increase in blood pressure of at least 25 mm Hg systolic or 20 mm Hg diastolic; subjects with an increase less than that were designated normoreactors.

The subsequent incidence of hypertension among the two groups was compared in an effort to determine whether the cold pressor test had served as a useful indicator of future hypertension. Standard chi-square tests were used to determine differences in proportions. Stepwise linear regression and stepwise linear discrimination analyses were used to determine the predictors of the 1979 casual blood pressure.

Results

All children in the original cohort studied in 1934 were normotensive, and 10% of the children were hyperreactors. Among the 142 subjects for whom later information was available, the mean age of the 94 who had been normoreactors in 1934 was 11 years; 53 were boys (56%) and 41 were girls (44%). The mean age in 1934 of the 48 subjects who were or who became hyperreactors was 11.5 years; 23 of the hyperreactors were boys (48%) and 25 were girls (52%).

In 1961, 29 of the original group of 31 hyperreactors continued to show an excessive response to external cold stimulus. Additionally, 21 patients who had previously been normoreactors had become hyperreactors after 27 years. Four patients who had been hyperreactors in both 1934 and 1961 were found to be hypertensive in 1961, whereas none of the normoreactors had become hypertensive by 1961.

At follow-up study 45 years after the original cold pressor test had been performed, blood pressure data were available for 142 of the 151 patients who had had an additional cold pressor test in 1961. Of the 142 patients, 94 (66%) were normoreactors in both 1934 and 1961 and 48 patients (34%) were hyperreactors in either 1934 or 1961 (Figure 1).

A summary of the mean blood pressure data for normoreactors and hyperreactors is given in Table 1. There was no significant difference in casual or basal blood pressure between normoreactors and hyperreactors in 1934. There were significant differences between blood pressures of normoreactors and hyperreactors in 1961 and 1979 (Table 1). There was a distinct tendency for the level of casual blood pressure to rise with age (Figures 2 and 3).

The incidence of blood pressure recordings in the hypertensive range among normoreactors and hyperreactors at the last follow-up is summarized in Table 2. Of the 48 hyperreactors, 14 (29%) had blood pressures between 140 and 160 mm Hg systolic or 90 and 100 mm Hg diastolic (Stratum 1), and 20 (42%) had casual blood pressure recordings exceeding 160/100 mm Hg (Stratum 2). In marked contrast, only 10 normoreactors (11%) had casual blood pressure elevations of 140 to 160/90 to 100 mm Hg, and eight patients (8%) had hypertension exceeding 160/100 mm Hg. Therefore, the incidence of significant elevation of blood pressure (that is, blood pressure readings of 140/90 mm Hg or higher) was more than three times as common in patients who had previously demonstrated a marked pressor response to an external cold stimulus on at least one occasion during their lifetime (p < 0.001). Twenty-one of 31 patients (68%) who were hyperreactors in 1934 had significantly elevated casual blood pressures at the time of the last follow-up.

The time from the first recorded positive cold pressor test to the first abnormally elevated casual blood pressure ranged from 1 to 45 years (mean, 24.2 years). Importantly, 15 of the 48 hyperreactors were receiving antihypertensive therapy at the time of the most recent
TABLE 1. Comparison of Blood Pressure Recordings among 94 Normoreactors and 48 Hyperreactors to the Cold Pressor Test

<table>
<thead>
<tr>
<th>Year</th>
<th>Blood pressure recording</th>
<th>Normoreactor</th>
<th>Hyperreactor</th>
<th>Mean blood pressure, mm Hg (SD)</th>
<th>Normoreactor</th>
<th>Hyperreactor</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1934</td>
<td>Casual</td>
<td>110 (10)</td>
<td>113 (11)</td>
<td>64 (10)</td>
<td>66 (12)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basal</td>
<td>101 (8)</td>
<td>101 (9)</td>
<td>61 (9)</td>
<td>64 (11)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peak</td>
<td>112 (10)</td>
<td>124 (15)</td>
<td>74 (10)</td>
<td>88 (14)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>1961</td>
<td>Casual</td>
<td>117 (11)</td>
<td>125 (14)</td>
<td>71 (9)</td>
<td>77 (11)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basal</td>
<td>110 (11)</td>
<td>114 (14)</td>
<td>69 (9)</td>
<td>73 (11)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peak</td>
<td>123 (2)</td>
<td>151 (16)</td>
<td>80 (10)</td>
<td>99 (15)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>1979</td>
<td>Casual</td>
<td>128 (18)</td>
<td>145 (22)</td>
<td>79 (11)</td>
<td>89 (10)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

Hyperreactors included all patients with a positive response to the cold pressor test in either 1934 or 1961. The 1979 recordings were done on all subjects except for those who had died between 1961 and 1979. SD = standard deviations; NS = not significant.

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**Figure 2.** Frequency distributions of casual systolic blood pressure (SBP) in 1934, 1961, and 1979. The 48 hyperreactors were those subjects who had a positive response to the cold pressor test in either 1934 or 1961.

**Figure 3.** Frequency distributions of casual diastolic blood pressure (DBP) in 1934, 1961, and 1979. The 48 hyperreactors were those subjects who had a positive response to the cold pressor test in either 1934 or 1961.
TABLE 2. Incidence of Hypertension among Normoreactors and Hyperreactors to the Cold Pressor Test

<table>
<thead>
<tr>
<th>Level of 1979 blood pressure</th>
<th>Normoreactor</th>
<th>Hyperreactor</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (&lt;140/90 mm Hg)</td>
<td>76 (81)</td>
<td>14 (29)</td>
</tr>
<tr>
<td>Stratum 1 (140-160/90-100 mm Hg)</td>
<td>10 (11)</td>
<td>14 (29)*</td>
</tr>
<tr>
<td>Stratum 2 (&gt;160/100 mm Hg)</td>
<td>8 (8)</td>
<td>20 (42)*</td>
</tr>
<tr>
<td>Total</td>
<td>94 (100)</td>
<td>48 (100)*</td>
</tr>
</tbody>
</table>

Hyperreactors included all patients with a positive response to the cold pressor test in either 1934 or 1961.

*p < 0.001.

follow-up. This had the effect of reducing the severity of the casual blood pressure elevation to the range of 140 to 160 mm Hg systolic and 90 to 100 mm Hg diastolic in most patients. Antihypertensive therapy had been initiated in only three of the 94 normoreactors during the 45 years of follow-up.

Stepwise linear regression analysis identified several variables that correlated with future blood pressure. Predictors of the 1979 casual blood pressure included the casual systolic pressure in 1961 (r = 0.52, p < 0.05) and the peak systolic blood pressure in 1961 (r = 0.50, p < 0.05). A less useful predictor of the 1979 casual blood pressure was the peak systolic blood pressure in 1934 (r = 0.52, p < 0.5). No other blood pressure recordings in youth or early adult life proved useful in predicting the 1979 casual blood pressure.

The incidence of a positive family history of hypertension was significantly higher among hyperreactors (58%) than among normoreactors (19%; p < 0.01). A positive family history of hypertension was more than twice as common in hypertensive hyperreactors as in hypertensive normoreactors (62% vs 28%).

A stepwise linear discrimination analysis was carried out for all data available from the 1934 cold pressor test. This analysis was used to determine which variables would classify subjects correctly according to their level of normotension or hypertension at the time of last follow-up in 1979. The presence of a positive result on the cold pressor test and a positive family history of hypertension correctly classified 80% of subjects who were normotensive and 60% of subjects who were hypertensive in 1979. When this same type of analysis was carried out on data from the 1961 cold pressor test in addition to the data from the 1934 test, little additional predictive power was noted. Analysis of the combined 1934 and 1961 data resulted in correct classification of 81% of subjects who in 1979 were normotensive and 60% of those who were hypertensive.

Using stepwise linear discrimination analysis, we determined the additional univariate predictors of the 1979 casual blood pressure from results of the 1934 and 1961 cold pressor tests. Univariate variables capable of predicting the 1979 casual blood pressure from the 1934 cold pressor test results were, in order of predictive power, peak systolic blood pressure, peak diastolic blood pressure, casual systolic blood pressure, change in systolic blood pressure, and change in diastolic blood pressure. When all available data from both 1934 and 1961 cold pressor tests were analyzed by means of stepwise linear discrimination to determine which univariate variables would predict the 1979 casual blood pressure, we found that the most important single variable was the presence of a positive cold pressor test in 1934. This was followed in order by the peak systolic blood pressure in 1934, the casual systolic blood pressure in 1961, the casual diastolic blood pressure in 1961, the change in systolic and diastolic blood pressure in 1961, and a positive family history of hypertension.

Although the numbers are too small for statistical analysis or comparison, three of the 48 hyperreactors had suffered myocardial infarction or stroke, but only one of the 94 normoreactors had suffered a myocardial infarction and none had suffered a stroke. In each group, three patients had angina pectoris and three patients had noninsulin-dependent diabetes mellitus.

Discussion

Essential or fixed hypertension in adulthood may begin in adolescence. Several approaches have been used to identify patients in whom sustained hypertension might develop. The two basic methods used in the search for potentially hypertensive patients consist of the application of descriptive characteristics gained from statistical analyses of cohorts of patients followed up in longitudinal studies and the application of provocative tests designed to gauge the response of the blood pressure to some external stimulus. Provocative testing is based on the premise that an excessive response to some external stimulus is indicative of future hypertension. Another potential predictor of hypertension that utilizes a direct laboratory test has recently been described. In vitro studies of erythrocyte cation transport suggest that laboratory testing may be an alternative method of identifying potentially hypertensive patients.6,7

The cold pressor test, a provocative test developed by Hines, is considered to be a potentially useful indicator of future hypertension.1 Hines and Brown1 proposed that a hyperreactive response of blood pressure to an externally applied cold stimulus was an inherited trait and that a period of vascular hyperreactivity preceded the development of fixed hypertension. These investigators also hypothesized that the pressor reaction to a cold stimulus was mediated through a neurogenic reflex arc and that repeated pressor episodes led to fixed hypertension. The cold pressor test was validated by Hines over 3 years on 25 normal and 25 hypertensive subjects, before being applied to more than 500 subjects.1 The maximum blood pressure response was usually obtained within 30 seconds. After
termination of the test, basal blood pressure was achieved within 2 minutes in normotensive subjects, whereas a prolonged pressor response was displayed in hypertensive subjects. The responses of test subjects were constant over the 3 years, and the average variation of blood pressure response from test to test was less than 10%.

Subsequent studies have failed to confirm the usefulness of the cold pressor test as a predictor of hypertension. Barnett and associates studied a group of Hines's original cohort and found a small incidence of hypertension among patients who had been hyperreactors at the time of the initial cold pressor test, whereas none of the normoreactors had become hypertensive after 25 years of follow-up. Thacker also found that the cold pressor test was positive in twice as many young college students with mild hypertension as with normotension. However, follow-up in this study was only 10 years, which makes it difficult to determine whether the cold pressor test was useful as an indicator of future hypertension.

A prospective study of naval aviators during an 18-year period failed to confirm the utility of the cold pressor test as a predictor of hypertension. Instead, the best indicator of future blood pressure was the basal blood pressure recorded before the cold pressor test was performed. Eich and Jacobsen also found that the cold pressor test did not reliably predict hypertension in a 10-year follow-up study of medical students who had taken the test.

Our study differs from previous studies in several important respects. First, the duration of follow-up in this study, 45 years, exceeded that of any other study. Second, the mean age of patients at the time of the most recent follow-up, almost 57 years, was slightly higher than that in other groups. Third, this was a heterogeneous group. The subjects composing the aviator cohort were preselected for their height and weight and had an initial blood pressure of less than 132/86 mm Hg. That study population was composed almost exclusively of men (94%). Fourth, although it is significant that in the aviator cohort the blood pressure seemed to stabilize after age 35, this finding differed from results in our study and from blood pressure trends recorded in other large epidemiologic studies.

In prospective longitudinal studies of blood pressure among adults, the baseline blood pressure has shown the strongest relation to the risk of future development of high blood pressure. Dispute remains about whether a documented level of blood pressure in a child is predictive of blood pressure in adulthood. Several longitudinal studies suggest that initial or baseline blood pressure recordings are indicative of future blood pressure levels. The results of our study also suggest that the initial blood pressure reading is an indicator of future blood pressure levels.

An additional indicator of the future development of high blood pressure is a family history of essential hypertension. Our results also support the relationship of a positive family history of high blood pressure to the future development of hypertension. However, when a family history of high blood pressure is examined in a multivariate analysis, it is less significant as a univariate variable than baseline blood pressure or, in our study, the response to an external cold stimulus.

The present study has some limitations. First, the number of hyperreactors discovered in 1934 was too small to allow statistically significant inferences to be drawn from this group of patients alone. We therefore combined the patients who demonstrated a hyperreactive response to an external cold stimulus in either 1934 or 1961. Because the two groups seemed to have similar characteristics, the conclusions drawn from the combined group seem valid. Second, although the study was prospective, additional information that might be helpful in the predictive sense was lacking. Specifically, at the time this study started, resting heart rates were not recorded, nor were indices of ponderosity available for use as additional variables in a multivariable analysis of factors that might predict the development of hypertension.

The use of provocative tests for the prediction of hypertension has been challenged on several fronts. All provocative tests are based on the assumption that repeated pressor episodes lead to the development of fixed hypertension. This assumption has not been adequately tested. The current study was not designed to test this hypothesis, but it does suggest that the development of fixed hypertension in most patients is preceded by a period of vascular hyperreactivity.

Other provocative tests have been associated with exaggerated blood pressure responses after the application of an external stimulus. In patients with mild hypertension, tilting caused a hypertensive blood pressure response. Psychologic stress has also been found to evoke a higher pressor response coupled with more catecholamine excretion in patients with borderline hypertension than in patients with normal blood pressure. There is some evidence that the response to psychologic stress can be predictive of hypertension among adolescents with borderline hypertension.

Investigations of pathophysiologic responses to the cold pressor test have shown that most normotensive and hypertensive subjects respond to the cold pressor stimulus with a predominant rise in total peripheral resistance; cardiac output showed a variable response. Younger patients generally responded with a profound change in cardiac output, whereas older patients showed a greater increase in cardiac output. Although these findings describe the physiological responses to the cold pressor test, they do not establish the mechanism of future development of hypertension in patients who show an excessive response to an external cold stimulus.

In conclusion, the results of this long-term follow-up study suggest that a positive response to the cold pressor test is a potentially useful predictor of hypertension. Other indicators of future hypertension are a positive family history of hypertension and baseline blood pressure recordings.
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