Hiroshima J. Med. Sci.
Vol.43, No.3, 93~103, September, 1994
HIJM 43-11

Prognostic Value of the Cold Pressor Test for Hypertension based on 28-year Follow-up

Fumiyoshi KASAGI

Department of Statistics, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732, Japan

ABSTRACT

Several stress tests have been used to predict the development of hypertension. No conclusion, however, has been reached on the effectiveness of these tests as a predictor of hypertension in later years.

The present study examines the prognostic values of blood pressure response to cold and resting blood pressure for future hypertension, based on a follow-up study over 28 years of 824 individuals (mean age: 35.8 ± 10.8 yr) whose resting blood pressure had been normal at baseline.

A significant determinant of blood pressure response to cold stimulus was age in these normotensive subjects. A higher response was observed as age increased. There was also a significant seasonal variation in blood pressure response to cold, suggesting the need to standardize a time to perform the cold pressor test.

Hypertension has developed in 343 individuals during the 28 years of follow-up, with a mean incidence rate of 24.6 per 10^3 person-years. Both systolic and diastolic responses were significant as a predictor of future hypertension after adjusting for attained age, resting blood pressure, and body mass index at baseline. However, a comparison between resting blood pressure and response to cold indicated that the cold pressor test is not as effective a predictor of hypertension as resting blood pressure. Radiation exposure was not significant either as a background risk or as a possible modifier of the relationship between the blood pressure response and the development of hypertension.

The current results suggest that blood pressure response to cold supplements resting blood pressure for predicting hypertension.

Key words: *Cohort studies, Cold, Hypertension, Prognosis*

Hypertension, a multifactorial disease involving many endogenous and exogenous factors, is a widespread disease affecting approximately 20% of Japanese adults. Many studies have shown this condition to be a major risk factor for cerebro-cardiovascular morbidity and mortality[13,21,27,29,41,54]. Therefore, early identification of the risk of hypertension would be important to its prevention.

Several stress tests, in which the response of blood pressure (BP) to some external stress is examined, have been employed in attempts to identify apparently normotensive individuals who might develop hypertension[5-7,12,20,48]. These stress tests are based on the hypothesis that a latent period of BP hyperreactivity precedes progression to sustained hypertension and that the increased response is evoked under stress. One such test is the cold pressor test, which measures the response of BP to the stimulus of cold. However, there are contradictory reports regarding whether this test is useful for predicting hypertension[2,15,23,25,50,56].

The cold pressor test was conducted in 1960 at the Radiation Effects Research Foundation (then the Atomic Bomb Casualty Commission, ABCC) on 1198 participants in the Adult Health Study in Nagasaki[44]. These participants have been subsequently followed for as long as 28 years. The follow-up data are an important resource if BP response to cold is considered in relation to the occurrence of hypertension. Few long-term prospective studies on so many subjects to examine the prognostic value of BP response to cold have been done so far. The present study will provide important findings in assessing the effectiveness of the cold pressor test as a predictor of hypertension.

MATERIALS AND METHODS

Subjects

The Adult Health Study (AHS) sample has been followed since 1958 to determine the late effects of exposure to atomic-bomb radiation. Of the sample 1198 men and women took part in a cold pressor test program at the Nagasaki ABCC facility during May to November in 1960. A brief description of these participants is as follows. Their ages at the time of examination (ATE) ranged from 15 to 81 yr. The study population comprised four groups: Group I consisted of 315 individuals who were within 2000 m of the hypocenter at the time of the bombing (ATB) and developed acute radiation symptoms; Group II consisted of 316 individuals who were within 2000 m of the hypocenter but did not develop acute radiation symptoms; Group III consisted of 293 individuals who were 3000–3999 m from the hypocenter; and Group IV consisted of 274 individuals who were not in the city (NIC) ATB. These four groups were matched by sex, age, and the month of examination. The descriptive statistics on the BP response to the cold pressor test in this study sample were reported previously, indicating no difference in response among the four groups[44].

For our purpose, excluded from the study were 289 persons who either had hypertensive diseases or a resting systolic blood pressure (SBP) higher than 140 mmHg and/or resting diastolic blood pressure (DBP) higher than 90 mmHg ATE. In addition, follow-up after the cold pressor test was not available for 60 individuals, and cold pressor test results were unknown for 11. The body mass index (BMI) [weight (kg) / height (m^2)], which is associated with the development of hypertension, was unknown for 14. A total of 824 individuals, after excluding these 374, were included in the present study. It should be noted that all of the study subjects had normal blood pressure ATE. The composition of the study subjects by sex and age is shown in Table 1.

Ascertainment of Hypertension

The follow-up study of these 824 individuals was conducted through the biennial AHS medical examinations, which include resting BP measurements and medical history questionnaires. Resting BP was measured in the sitting position with a standard mercury sphygmomanometer on the right arm. A single blood pressure reading was used for the present analysis. A medical history was taken to identify medically treated cases of hypertension that occurred between the AHS examinations. Hypertension, defined as having either SBP ≥ 160 mmHg and/or DBP ≥ 95 mmHg, or as receiving antihypertensive treatment, was recorded using the International Classification of Disease (ICD) code. In the present paper, cases of hypertension were identified by searching for the ICD code in the data base. The cutoff date of the follow-up was set as 30 June 1988. The follow-up period, therefore, is 28 years. The onset of hypertension was defined as the date midway between the examination when hypertension was first diagnosed and the previous examination.

Cold Pressor Test

After resting supine for at least 20 min in a room maintained at 25–30°C, the resting BP was measured in the right upper arm using a standard mercury sphygmomanometer. The left hand was then immersed to just above the wrist in water 3–5°C for 1 min, and during this time BP measurements were obtained at 30, 60, and 120 sec after immersion[44]. The maximum changes in SBP and DBP at the time of application of cold stimulus were defined as the systolic response and diastolic response, respectively. Systolic and diastolic responses were positive in most subjects except 8 cases of systolic response and 6 cases of diastolic response. The highest rise in SBP and DBP occurred in most subjects 30 sec after immersion of the hand in cold water. Fig. 1 shows the frequency distributions of the systolic and diastolic responses. As evident from Fig. 1, each response formed a right-skewed continuous distribution with no natural separation between normal and hyper responses. Therefore, a cutoff point, 15 mmHg, was arbitrarily selected to separate normal reactors and hyperreactors. Those subjects whose systolic (diastolic) response exceeded 15 mmHg were defined as systolic (diastolic) hyperreactors. Table 1 shows the resting BP, BP response, and the frequency of hyperreactors by sex and age.

Dosimetry System 1986 Dose

The estimated radiation dose received by A-bomb survivors is based on the Dosimetry System 1986 (DS86) introduced in March 1986 after reassessment of A-bomb doses. In the present study, the relationship between BP response to cold and radiation dose was not studied by a comparison of responses among the above-mentioned four groups, but by a comparison based on the DS86 dose assigned to each individual.

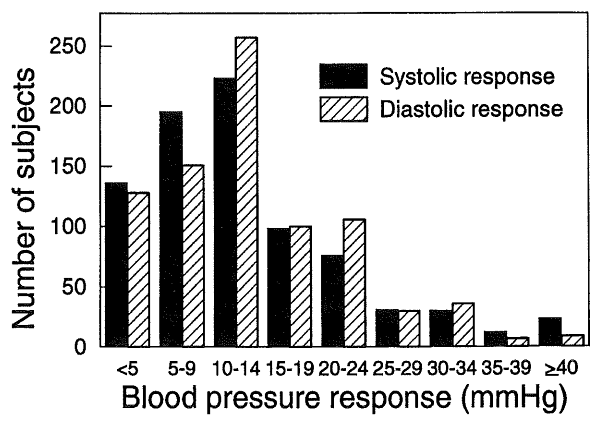

Fig. 1. Frequency distribution of systolic and diastolic response to cold

Table 1. The composition of study subjects, mean values of resting blood pressure, response to cold, and percentage of hyperreactors by sex and age at baseline

Age a baseline	No. of Subjects	Basal SBP	Basal DBP	Response SBP	Response DBP	Hyperreactor SBP	Hyperreactor DBP
				Males			
≤ 29	105	118.1 (9.2)	66.0 (9.3)	10.7 (7.3)	12.9 (7.9)	24.8%	39.0%
30–39	104	115.6 (8.8)	69.0 (8.5)	12.5 (11.2)	11.8 (8.3)	31.7	33.7
40–49	56	116.9 (10.2)	71.7 (8.4)	14.2 (10.0)	13.0 (8.1)	39.3	39.3
≥ 50	61	120.8 (11.4)	74.5 (6.7)	19.3 (15.3)	14.8 (8.6)	54.1	41.0
Subtotal	326	117.6 (9.8)	69.5 (9.0)	13.5 (11.2)	12.9 (8.2)	35.0	37.7
				Females			
≤ 29	134	113.5 (10.7)	64.8 (10.5)	9.8 (8.0)	12.9 (10.7)	20.1	32.1
30–39	249	113.2 (9.9)	67.3 (8.9)	12.4 (9.8)	12.1 (9.0)	33.3	36.1
40–49	71	117.0 (9.5)	70.9 (7.4)	14.1 (9.0)	11.3 (8.9)	42.3	31.0
≥ 50	44	120.0 (11.7)	71.7 (6.9)	13.7 (9.8)	10.0 (6.5)	36.4	22.7
Subtotal	498	114.4 (10.4)	67.5 (9.3)	12.1 (9.3)	12.0 (9.3)	31.3	33.1
				Both sexes			
Total	824	115.7 (10.3)	68.3 (9.2)	12.6 (10.1)	12.4 (8.9)	32.8	35.0

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Response: Blood pressure response to cold stimulus. Standard deviation in parenthesis.

Table 2. Stratification of variables used in the Poisson regression analysis

Variables		Categories 1	2	3	4	5
Sex		Males	Females			
Age ATE		≤29	30–39	40–49	50≤	
Month ATE		6–8	9 or 10	5 or 11		
Follow-up period	(yr)	≤4	5–9	10–14	15–19	20≤
Exposure dose	(rad)	0	1–99	100–600	NIC	unknown
Body mass index	(kg/m^2)	≤17	18–23	24≤		
Resting SBP	(mmHg)	≤119	120–129	130–139		
Resting DBP	(mmHg)	≤69	70–79	80–89		
Systolic response	(mmHg)	≤14	15≤			
Diastolic response	(mmHg)	≤14	15≤			

NIC indicates subjects who were not in the city at the time of the atomic bombings.

Statistical Methods

The relation of BP response to incidence of hypertension was examined by Poisson regression analysis. When the data was stratified by sex, age ATE, month ATE, follow-up time, radiation dose, BMI, resting SBP, resting DBP, systolic response, and diastolic response, the number of those who developed hypertension, y, in each stratum is assumed to be an independent Poisson variable with the expected value of $E(y) = PY \times \lambda$, where PY and λ are the person-years at risk and risk function in each stratum. Stratification was done as shown in Table 2, giving a total of 2,308 strata.

A general risk function, λ, considered here is as follows:

$$\lambda = exp(X)[1 + \alpha(response)](1 + \beta_1 R_1 + \beta_2 R_2).$$

The term $exp(X)$ is an exponential background risk of hypertension defined in each stratum by a linear combination, X, of covariates such as sex, mean values of attained age, BMI, radiation dose, and resting DBP (SBP) in the case of a comparison of prognostic values between systolic (diastolic) response and resting SBP (DBP). The attained age is defined as age at baseline plus follow-up time (yr) in each stratum. The term "*response*" is dichotomized as 1 for systolic (diastolic) hyperreactors and 0 for systolic (diastolic) normal reactors. Thus, the coefficient α represents a relative risk of hypertension for hyperreactors, relative to normal reactors. The term "R_1" and "R_2" are indicator variables taken 1 for resting SBP (DBP) category of 120–129 (70–79) mmHg and of 130–139 (80–89) mmHg, respectively. Since both term "R_1" and "R_2" are 0 for resting SBP (DBP) category of ≤ 119 (≤ 69) mmHg, the coefficients β_1 and β_2 represent relative risks of hypertension for resting SBP (DBP) category of 120–129 (70–79) mmHg and for resting SBP (DBP) category of 130–139 (80–89) mmHg, respectively, to resting SBP (DBP) category of ≤ 119 (≤ 69) mmHg.

To compare the prognostic value of BP response to cold with that of resting BP, analyses were made based on the following three models: $\lambda = exp(X)$ (Model 1); $\lambda = exp(X)[1+\alpha(response)]$ (Model 2); $\lambda = exp(X)[1+\alpha(response)](1+\beta_1 R_1+\beta_2 R_2)$ (Model 3). The parameters α, β_1 and β_2 were estimated based on the maximum likelihood method, and the significance of parameters was based on the likelihood ratio test[42].

The factors related to BP response in the cold pressor test were examined by a multiple regression analysis and an analysis of covariance. The natural logarithm transformation of response values was necessary for ensuring normality. Here, for the positiveness of the argument and for better approximation to normal distribution, +23 was added to the systolic response values and +14 to diastolic values.

RESULTS

BP response to cold pressor test and related factors

For the 824 normotensive individuals (326 males, 498 females), the mean age ATE was 35.8 years and the mean resting BP was 115.7/68.3 mmHg. The mean systolic response was 12.6 mmHg (standard deviation [SD] ± 10.1) and the mean diastolic response was 12.4 mmHg (SD ± 8.9). No difference was observed between the two responses (Table 1).

The highest BP response to the cold pressor test was observed in the group for whom the test was conducted during summer, June to August, followed, in order, by the September-October group and the May/November group (Table 3). The analysis of covariance using sex, age, resting SBP, and resting DBP as covariates confirmed that the differences in the responses during these three periods were significant for both systolic response ($p = 0.03$) and diastolic response ($p = 0.01$).

Furthermore, to examine other factors related to BP response in the cold pressor test, a multiple regression analysis was done using sex, age ATE, resting SBP, resting DBP, BMI, the month of examination, and radiation dose categories as explanatory variables and the natural logarithm of BP response value as dependent variable (Table 4). Age ATE was significantly related to systolic and diastolic responses to cold stimulus, with the responses rising with age. Each BP response was inversely related to the corresponding resting BP. These two findings may seem contradictory because resting BP generally increases with age. However, this is not attributable to the inverse association of low resting BP and high response due to a "seasonal effect" as shown in Table 3. In

Table 3. Blood pressure response to cold by sex and the month of examination

Month of examination	No. of Subjects	Age ATE	Resting SBP	Resting DBP	Response SBP	Response DBP
			Males			
6–8	174	37.2 (13.5)	117.0 (10.2)	68.2 (9.2)	14.6 (11.7)	13.6 (8.6)
9–10	133	36.9 (11.7)	118.3 (9.1)	70.9 (8.6)	12.1 (10.9)	12.3 (7.9)
5 or 11	19	34.6 (12.6)	118.4 (10.9)	71.2 (7.9)	12.2 (7.9)	11.5 (6.7)
			Females			
6–8	270	35.2 (9.8)	113.9 (10.8)	65.8 (9.3)	13.2 (9.4)	13.8 (9.7)
9–10	206	34.8 (9.4)	114.7 (10.0)	69.4 (9.1)	10.8 (9.1)	10.2 (8.5)
5 or 11	22	35.4 (11.0)	118.1 (9.9)	70.7 (6.4)	10.1 (8.7)	7.1 (6.5)

ATE: At the time of examination; SBP: Systolic blood pressure; DBP: Diastolic blood pressure;
Response: Blood pressure response to cold stimulus.
Standard deviatioin in parenthesis.

Table 4. Multiple regression analysis of blood pressure response to cold

	Dependent variable			
	log (sustolic response +23)		log (diastolic response +14)	
Variables	Regression coefficient	Standard error	Regression coefficient	Standard error
Constant	3.726		3.768	
Sex	–0.0339+	0.0188	–0.0626*	0.0225
Age ATE	0.0047*	0.0008	0.0024*	0.0010
Resting SBP	–0.0020*	0.0009	0.0037*	0.0012
Resting DBP	ns		–0.0128*	0.0014
Season	–0.0458*	0.0151	–0.0601*	0.0184
BMI	ns		ns	
Dose category				
0.0	—		—	
0.1–0.9	–0.0145	0.0282	–0.0432	0.0338
1.0–6.0 Gy	0.0152	0.0292	0.0259	0.0349
NIC	0.0280	0.0268	0.0622+	0.0321
Unknown	–0.0167	0.0264	0.0030	0.0316

Season: The variable given 1 for June–August, 2 for September or October, and 3 for May or November for the month of examination;
Sex=0 for males, =1 for females; BMI: Body mass index; Gy: Gray;
NIC: indicates subjects who were not in the city at the time of the atomic bombing.
* $p<0.05$; + $0.05<p<0.10$; ns: not significant.

fact, regression analyses made individually in the three categories of the month of examination also showed a negative association between resting BP and response. Males had a higher BP response than females. This sex difference was suggestive for systolic response and significant for diastolic response. No significant association was observed between BMI and BP response.

Radiation dose was not significantly associated with systolic response (p = 0.53). On the other hand, the association between diastolic response and dose was suggestive (p = 0.06), but is attributable to the high diastolic response in the NIC group and is not evidence of a relationship between radiation dose and BP response.

Development of hypertension and prognostic values of blood pressure response to cold and resting blood pressure

Hypertension developed in 343 out of 824 normotensive individuals during the study period of 1960 to 1988. The crude incidence rate of hypertension was 24.6 per 10^3 person-years (28.3 for males and 22.3 for females). As the age ATE increases and as the resting SBP or DBP rises even within the normal ranges, the crude incidence rate of hypertension increases (Fig. 2).

The background risk of hypertension was considered based on attained age, not on age ATE, because the development of hypertension is more strongly related to attained age. The obtained background risk was significantly dependent on attained age, the square of attained age, resting SBP or resting DBP, and BMI (Model 1 in Table 5 and Model 1 in Table 6). Sex difference was not significant after resting BP was adjusted ($\chi^2(1)=0.74$). The dependence on radiation dose category was not significant ($\chi^2(4)=2.48$).

Table 5 shows a comparison of Poisson regression coefficients and deviances when resting SBP was included and not included in the risk model. As compared with systolic normal reactors, sys-

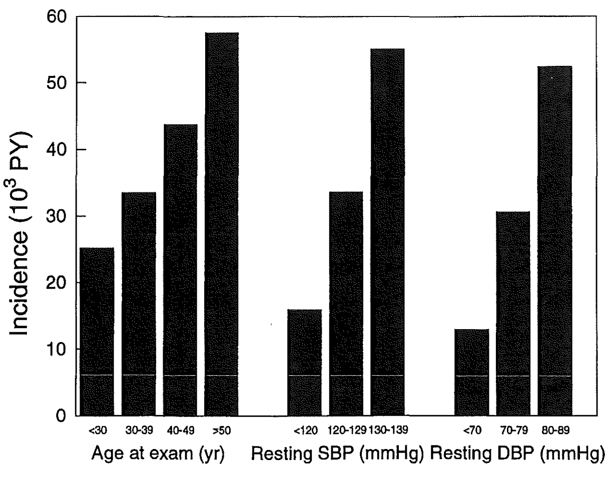

Fig. 2. Crude incidence of hypertension by age at baseline and resting blood pressure

Table 5. Poisson regression coefficients of systolic response and resting systolic blood pressure for selected models of risk function

Variable		Model (1)	Model (2)	Model (3)
			Background risk	
Constant		–14.97	–15.23	–14.52
Attained age		0.1887*	0.1932*	0.2008*
Attained age squared		–0.0016*	–0.0016*	–0.0017*
BMI		0.0630*	0.0671*	0.0730*
Resting DBP		0.0675*	0.0675*	0.0486*
			Relative risk	
Systolic response				
Normal reactor			1.000	1.000
Hyperreactor			1.324*	1.383*
Resting SBP	≤119			1.000
	120–129			1.620*
	130–139			2.193*
Deviance		1731.80	1725.82	1699.34

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.
Attained age = age at baseline + follow-up time (yr); * p<0.05

Table 6. Poisson regression coefficients of diastolic response and resting diastolic blood pressure for selected models of risk function

Variable		Model (1)	Model (2)	Model (3)
			Background risk	
Constant		–17.37	–17.48	–16.01
Attained age		0.2065*	0.2065*	0.2048*
Attained age squared		–0.0017*	–0.0017*	–0.0017*
BMI		0.0627*	0.0629*	0.0620*
Resting SBP		0.0561*	0.0565*	0.0417*
			Relative risk	
Diastolic response				
Normal reactor			1.000	1.000
Hyperreactor			1.145^{ns}	1.278*
Resting DBP	≤69			1.000
	70–79			1.616*
	80–89			2.137*
Deviance		1729.14	1727.74	1708.68

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.
Attained age = age at baseline + follow-up time (yr); * p<0.05; ns: Not significant.

tolic hyperreactors had a significant relative risk of hypertension of 1.32 ($\chi^2(1)$=5.98), even if resting SBP was not included in the risk model (Model 2). And, there was little difference between the regression coefficients when resting SBP was included (Model 3) and not included (Model 2) in the risk model. This indicates that systolic response can be a significant and independent predictor irrespective of the level of resting SBP. On the other hand, the relative risks of hypertension for resting SBP were 1.62 at the level of 120–129 mmHg and 2.19 at the level of 130–139 mmHg, compared with the level of less than 120 mmHg. Thus, the rise in the relative risk of hypertension was steeper for resting SBP than systolic response. This fact was supported by an analysis based on systolic response divided into the three categories of ≤ 9, 10–19, and $20 \leq$ mmHg. The relative risks of hypertension were 1.33 at the level of 10–19 mmHg and 1.44 at the level of $20 \leq$ mmHg, compared with the level of ≤ 9 mmHg (data not shown).

Table 6 shows a comparison of the regression coefficients and deviances among three models of resting DBP and diastolic response. The risks of hypertension at the levels of 70–79 mmHg and 80–89 mmHg of resting DBP were 1.62-fold and 2.14-fold higher than the risk at the level of less than 70 mmHg (Model 3). These relative risks are similar to those for SBP. When resting DBP was not included in the risk model (Model 2), diastolic hyperreactors did not have a significant relative risk ($\chi^2(1)=1.40$). This is different from the case of systolic response. However, when resting DBP was included in the model (Model 3), diastolic response was significant. This means that the diastolic response itself is not significant as a predictor of the development of hypertension, and that it becomes significant only when resting DBP is taken into consideration.

Hence, it appears that BP response to cold stimulus is weaker than resting BP for the predictability of future hypertension and contributes as a predictor supplementing resting BP.

Multiplicative effect of systolic and diastolic response on the development of hypertension

Although there is a correlation between systolic and diastolic responses, there are systolic hyperreactors who are diastolic normal reactors and vice versa. Normal reactors for both systolic and diastolic responses accounted for 53% of the subjects studied, hyperreactors only for systolic response 14%, hyperreactors only for diastolic response 12%, and hyperreactors for both systolic and diastolic responses 21%. It would be interesting to know whether hyperreactors for both systolic and diastolic response have a much greater risk of hypertension than the others. Therefore, the risks of hypertension of four groups were compared with each other after adjustment for attained age, the square of attained age, BMI, resting SBP, and DBP as a background risk. Assuming the risk of hypertension among normal reactors for both systolic and diastolic responses to be 1.0, the relative risk for the isolated systolic hyperreactors was 1.55, with a 95% confidence interval of 1.11 to 2.11; for isolated diastolic hyperreactors 1.52, with a 95% confidence interval of 1.07 to 2.13; and for both systolic and diastolic hyperreactors 1.43, with a 95% confidence interval of 1.09 to 1.88. There was no significant difference among these three relative risks ($\chi^2(2)=0.21$). This means that the high BP response to cold, whether systolic or diastolic, is significantly related to the development of hypertension and that there is no multiplicative effect of systolic and diastolic responses.

DISCUSSION

Of the 1198 participants in the cold pressor test program, 824 normotensives at baseline were included in the present study to examine the prognostic values of BP response to cold and resting BP for the development of hypertension. Several factors were found to be associated with BP response to cold, allowing for the condition that the study subjects were limited to those with normal resting BP at baseline. First, the BP response increased significantly with age, which is in agreement with Hines' work[24]. Secondly, a high BP response was observed in cold pressor tests performed in summer[44]. This, though seemingly natural, indicates an important point. That is, although the cold pressor test had been conducted by a standardized method in which the subjects rested for at least 20 min in the room maintained at 25–30°C in any month of examination, a significant correlation between the month of examination and the BP response suggests that the outdoor temperature and consequently the body functions might cause seasonal variation in BP response. Regulation of room temperature is one of the standardized procedures for the BP measurement. Likewise, the outdoor temperature cannot be ignored for the purpose of the cold pressor test. Thirdly, a negative association between BP response and resting BP was observed. However, this doesn't directly lead to any conclusive statement that BP response is inversely related to resting BP, because our study subjects were normotensive; i.e., limits had been placed upon blood pressure itself. The association between resting BP and response should be confirmed in a population with a wider range of BP levels not affected by antihypertensive therapy. Lastly, the BP response of males was higher than that of females, a finding supported by other studies[22,33]. No relationship was observed between BMI, a marker of obesity, and BP response. Although they were not considered in the present study, other possible factors involved in the development of hypertension, such as physical training[47], Type A behavior pattern[53], and dietary salt intake[11], have been reported not to influence BP response to cold.

The cold pressor test was conducted in 1960 on atomic bomb survivors in Nagasaki as part of the study of accelerated aging due to radiation exposure[44]. If radiation exposure were to accelerate the process of aging, a high BP response would be expected in a highly exposed survivor as observed in aged people. The present study did not produce such evidence. Furthermore, the possible association between acute radiation symptoms and high BP response to cold was also examined, but no significant relationship was observed. It is, therefore, difficult to believe that radiation exposure is related to a high BP response to cold.

A number of investigations have shown that heredity is involved in the development of hypertension[20,37,40,49]. Likewise, the possible involvement of heredity in BP response is an intriguing question. Bouchard et al reported familial similarity in BP response to cold[3]. Hines observed a positive relationship between the BP response of a child and the BP status of the parents[24]. Wood et al reported that a family history of hypertension was more prevalent among hyperreactors than among normoreactors[56]. In the present study, it was examined whether a family history of hypertension obtained on a self-reported basis was related to the BP response to cold as well as to the subsequent development of hypertension. Neither was significant. However, since our data did not include information on the ages of the examinee's parents which is essential when the family history of hypertension is ascertained, it is unclear whether the family history of hypertension is involved in BP response and in the development of hypertension.

An increased BP response to cold may be suspected to suggest left ventricular hypertrophy (LVH). In fact Ewing et al found, in hypertension cases, a positive relationship between increased peripheral resistance at time of isometric exercise and cardiac hypertrophy[18]. In our subjects, LVH (left high R wave and ST-T change) was detected by the resting electrocardiogram, which may not be a sensitive indicator. The number of LVH cases was small, and no relationship between BP response and LVH was observed. This may be natural, considering that all of our study subjects had normal BP.

Based on observations that BP response to cold is higher in hypertensives than in normotensives[24,25], it has been hypothesized that hyperreactivity in the BP response of normotensive subjects is indicative of a prehypertensive state, a latent phase of hypertension, suggesting potential abnormalities in blood pressure regulation[24]. In fact, individuals excluded from the present analysis due to hypertensive diseases and high resting BPs (≥140/90 mmHg) gave greater responses than normotensive subjects included in the present analysis, even after adjustment was made for confounding factors. Based on such "hyperreactivity hypothesis", several studies have been carried out on the effectiveness of the cold pressor test as a predictor of hypertension in apparently normotensive subjects.

Our results support the hypothesis that hyperreactivity is, more or less, a predictor of hypertension, in agreement with several previous studies[2,24,56]. However, some studies have failed to confirm the usefulness of the cold pressor test as a predictor of hypertension[15,23,50]. A study in the Netherlands[26] and the Bogalusa Heart Study[39], both of which examined an association between BP response to cold and the short-term variation of BP in children, gave different results. Thus, no definite conclusion has been reached concerning the usefulness of the cold pressor test. However, most of these follow-up studies were based on a simple comparison of the incidence rates of hypertension, and no adjustment was made for confounding factors associated with hypertension. In addition, consideration was not given to attained age, an important determinant for development of hypertension. Furthermore, the subjects in most studies have not been followed up until they reached old age, when hypertension is prevalent. Recently, Menkes et al reported on a study that demonstrated the effectiveness of the cold pressor test based on the results of a 20– to 36–yr follow-up of 910 medical students[35]. This study is comparable with ours in the number of study subjects, follow-up period, and the use of the survival analysis. Menkes et al applied Cox regression analysis in the adjustment for confounding factors such as age ATE, resting BPs, BMI, smoking history, and updated family history of hypertension, and reported that the systolic response was a significant and independent predictor of hypertension. This result is similar to ours. However, they observed no significance in the diastolic response. Our present study showed that the diastolic response was not a predictor by itself but became significant only after adjusted for resting DBP. Diastolic response might act as a predictor in supplementing resting DBP. Menkes et al stated further that the systolic response has a relative risk comparable to resting SBP. However, as suggested by the comparison of prognostic values between resting BP and BP response, it seems more reasonable to consider the BP response as an additional predictor to resting BP, rather than a strong predictor replacing resting BP.

Whether exposure to radiation contributes to the progression of hypertension is a problem peculiar to our sample. Sasaki et al reported that their cross-sectional study showed no evidence of a relationship between radiation exposure and BP level[43]. Our follow-up study, restricted to the individuals given cold pressor test, also gave no indication of such a relationship. However, these results do not necessarily imply the absence of a relationship between radiation exposure and the development of hypertension. The association between the two should be the subject of a follow-up study of the entire Adult Health Study sample.

Why can BP response in the cold pressor test be related to the development of hypertension? Elucidation of its mechanism is not the purpose of this study, but speculation is possible. Cold stimulus applied to one hand produces vascular constriction in the other hand[31)] and causes a great increase of peripheral resistance and a consequent rise in arterial BP[36,55)]. Many researchers have observed that cold stimulus not only increases arterial BP but also significantly increases the level of norepinephrine, the sympathetic neurotransmitter, in peripheral venous blood[4,8,9,30,45,51)]. Peripheral plasma norepinephrine is an indirect biochemical marker of the activity of the sympathetic nervous system[17,47,52)], and the above-mentioned result shows that this system is stimulated by the cold pressor test. This finding was confirmed by recent studies in which the activity of the sympathetic nervous system was directly determined and was found to be well correlated with arterial BP[19,46)]. This suggests that cold stimulus enhances the sympathetic nervous activity, which produces a vascular constriction and causes an increase in peripheral resistance and in arterial BP. BP response to cold stimulus is, therefore, considered to be a marker of sympathetic nervous activity. Elevated sympathetic nervous activity has been observed in hypertensives as compared with normotensives[1,14)], suggesting an abnormality in this nervous system[10,14,16,32,34)]. Thus, a high BP response to cold in normotensives, even though their resting BP is normal, reveals a sympathetic nervous activity similar to that of hypertensives. This is an indication of a prehypertensive state[24)], which suggests a high risk for progression to hypertension.

A major objection to using the cold pressor test to predict hypertension seems to lie in its reproducibility[38)]. Naturally, papers asserting the usefulness of the cold pressor test report that BP response is reproducible, whereas those asserting its uselessness report that it is not reproducible. Our current data do not permit comment on the reliability of BP response to cold. However, Jones et al indicated that acceptable reproducibility could be obtained with stress tests conducted under carefully controlled conditions[28)]. Few follow-up results are available concerning the cold pressor test. More studies should be done to allow a definite conclusion regarding the usefulness of the cold pressor test in predicting hypertension.

ACKNOWLEDGEMENTS

This publication is based on a manuscript (MS 09–94) resulting from research performed at the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan. RERF is a private foundation funded equally by the Japanese Minister of Health and Welfare and the US Department of Energy through the National Academy of Sciences.

(Received May 6, 1994)
(Accepted September 14, 1994)

REFERENCES

1. **Anderson, E.A., Sinkey, C.A., Lawton, W.J. and Mark, A.L.** 1989. Elevated sympathetic nerve activity in borderline hypertension humans. Hypertension **14:** 177–183.
2. **Barnett, P.H., Hines, E.A. Jr., Schirger, A. and Gage, R.P.** 1963. Blood pressure and vascular reactivity to the cold pressor test. J.A.M.A. **183:** 845–848.
3. **Bouchard, C., Leblanc, J., Cote, J., Jobin, J., Jobin, M., Labrie, A. and Leblanc, C.** 1983. Familial resemblance in catecholamine changes to cold stress and maximal exercise. Hum. Hered. **33:** 170–178.
4. **Bouloux, P.M., Grossman, A., Al-Damluji, S., Bailey, T. and Besser, M.** 1985. Enhancement of the sympathoadrenal response to the cold-pressor test by naloxone in man. Clin. Sci. **69:** 365–368.
5. **Chaney, R.H. and Arndt, S.** 1983. Predictability of blood pressure response to isometric stress. Am. J. Cardiol. **51:** 787–790.
6. **Chaney, R.H. and Eyman, R.K.** 1988. Blood pressure at rest and during maximal dynamic and isometric exercise as predictors of systemic hypertension. Am. J. Cardiol. **62:** 1058–1061.
7. **Cinciripini, P.M.** 1986. Cognitive stress and cardiovascular reactivity. I. Relationship to hypertension. Am. Heart J. **12:** 1044–1050.
8. **Cuddy, R.P., Smulyan, H., Keighley, J.F., Markason, C.R. and Eich, R.H.** 1966. Hemodynamic and catecholamine changes during a standard cold pressor test. Am. Heart J. **71:** 446–454.
9. **Cummings, M.F., Steele, P.M., Mahar, L.J., Frewine, D.B. and Russell, W.J.** 1983. The role of adrenal medullary catecholamine release in the response to a cold pressor test. Cardiovasc. Res. **17:** 189–191.
10. **de Champlain, J., Petrovich, M., Gonzalez, M., Lebeau, R. and Nadeau, R.** 1991. Abnormal cardiovascular reactivity in borderline and mild hypertension. Hypertension **17 (Suppl III):** 22–28.
11. **Dimsdale, J.E., Ziegler, M., Mills, P., Delehanty, S.G. and Berry, C.** 1990. Effects of salt, race, and hypertension on reactivity to stressors. Hypertension **16:** 573–580.
12. **Dlin, R.A., Hanne, N., Silverberg, D.S. and Bar-Or, O.** 1983. Follow-up of normotensive men with exaggerated blood pressure response to exercise. Am. Heart J. **106:** 316–320.
13. **Dock, D.S. and Fukushima, K.** 1976. A longitudinal study of arterial blood pressure in the Japanese, 1958–1972. RERF Technical Report 8–76.
14. **Egan, B., Panis, R., Hinderliter, A., Schork, N. and Julius, S.** 1987. Mechanism of increased alpha adrenergic vasoconstriction in human essential hypertension. J. Clin. Invest. **80:** 812–817.
15. **Eich, R.H. and Jacobsen, E.C.** 1967. Vascular

reactivity in medical students followed for 10 years. J. Chronic Dis. **20:** 583–592.

16. **Esler, M., Ferrier, C., Lambert, G., Eisenhofer, G., Cox, H. and Jennings, G.** 1991. Biochemical evidence of sympathetic hyperactivity in human hypertension. Hypertension **17(Suppl III):** 29–35.
17. **Esler, M., Jenning, G., Korner, P., Willett, I., Dudley, F., Hasking, G., Anderson, W. and Lambert, G.** 1988. Assessment of human sympathetic nervous system activity from measurement of norepinephrine turnover. Hypertension **11:** 3–20.
18. **Ewing, D.J., Irving, J.B., Kerr, F. and Kirby, B. J.** 1973. Static exercise in untreated systemic hypertension. Br. Heart J. **35:** 413–421.
19. **Fagius, J., Karhuvaara, S. and Sundlof, G.** 1989. The cold pressure test: effects on sympathetic nerve activity in human muscle and skin nerve fascicles. Acta Physiol. Scand. **137:** 325–334.
20. **Falkner, B., Kushner, H., Onesti, G. and Angelakos, E.T.** 1981. Cardiovascular characteristics in adolescents who develop essential hypertension. Hypertension **3:** 521–527.
21. **Gordon, T. and Kannel, W.B.** 1972. Preposition to atherosclerosis in the head, heart, and legs. The Framingham Study. J.A.M.A. **221:** 661–666.
22. **Graham, T.E.** 1988. Thermal, metabolic, and cardiovascular changes in men and women during cold stress. Med. Sci. Sports Exerc. **20(Suppl):** 185–192.
23. **Harlan, W.R. Jr., Osborne, R.K. and Graybiel, C.A.** 1964. Prognostic value of the cold pressor test and the basal blood pressure based on an eighteen-year follow-up study. Am. J. Cardiol. **13:** 683–687.
24. **Hines, E.A. Jr.** 1940. The significance of vascular hyperreaction as measured by the cold-pressor test. Am. Heart J. **19:** 408–416.
25. **Hines, E.A. Jr. and Brown, G.E.** 1933. A standard test for measuring the variability of blood pressure: Its significance as an index of the prehypertensive state. Ann. Intern. Med. **7:** 209–217.
26. **Hofman, A. and Valkenburg, H.A.** 1983. Determinants of change in blood pressure during childhood. Am. J. Epidemiol. **117:** 735–743.
27. **Johnson, K.G., Yano, K. and Kato, H.** 1967. Cerebral vascular disease in Hiroshima, Japan. J. Chronic Dis. **20:** 545–559.
28. **Jones, R.I., Lahiri, A., Cashman, P.M., Dore, C. and Raftery, E.B.** 1986. Left ventricular function during isometric hand grip and cold stress in normal subjects. Br. Heart J. **55:** 246–252.
29. **Kannel, W.B.** 1976. Some lessons in cardiovascular epidemiology from Framingham. Am. J. Cardiol. **37:** 269–282.
30. **Kawahara, J., Sano, H., Fukuzaki, H., Saito, K. and Hirouchi, H.** 1989. Acute effects of exposure to cold on blood pressure, platelet function and sympathetic nervous activity in humans. Am. J. Hypertens. **2:** 724–726.
31. **Marriott, I., Marshall, J.M. and Johns, E.J.** 1990. Cutaneous vascular responses evoked in the hand by the cold pressor test and by mental arithmetic. Clin. Sci. **79:** 43–50.
32. **Matsukawa, T., Gotoh, E., Uneda, S., Miyajima, E., Shionoiri, H., Tochikubo, O. and Ishii, M.** 1991. Augmented sympathetic nerve activity in response to stressors in young borderline hypertensive men. Acta Physiol. Scand. **141:** 157–165.
33. **McAdoo, W.G., Weinberger, M.H., Miller, J.Z., Fineberg, N.S. and Grim, C.E.** 1990. Race and gender influence hemodynamic responses to psychological and physical stimuli. J. Hypertens. **8:** 961–967.
34. **McCrory, W.W., Klein, A.A. and Rosenthal, R.A.** 1982. Blood pressure, Heart rate, and plasma catecholamines in normal and hypertensive children and their siblings at rest and after standing. Hypertension **4:** 507–513.
35. **Menkes, M.S., Matthews, K.A., Krantz, D.S., Lundberg, U., Mead, L.A., Qaqish, B., Liang, K.Y., Thomas, C.B. and Pearson, T.A.** 1989. Cardiovascular reactivity to the cold pressor test as a predictor of hypertension. Hypertension **14:** 524–530.
36. **Murakami, E., Hiwada, K. and Kokubo, T.** 1980. Pathophysiologcal characteristics of labile hypertension patients determined by the cold pressor test. Jpn. Circ. J. **44:** 438–442.
37. **Paffenbarger, R.S. Jr., Thorne, M.C. and Wing, A.L.** 1968. Chronic disease in former college students. VIII. Characteristics in youth predisposing to hypertension in later years. Am. J. Epidemiol. **88:** 25–32.
38. **Parati, G., Trazzi, S., Ravogli, A., Casadei, R., Omboni, S. and Mancia, G.** 1991. Methodological problems in evaluation of cardiovascular effects of stress in humans. Hypertension **17(Suppl III):** 50–55.
39. **Parker, F.C., Croft, J.B., Cresanta, J.L., Freedman, D.S., Burke, G.L., Webber, L.S. and Berenson, G.S.** 1987. The association between cardiovascular response tasks and future blood pressure levels in children: Bogalusa Heart Study. Am. Heart J. **113:** 1174–1179.
40. **Perera, G.A., Gearing, F.R. and Schweitzer, H.D.** 1972. A family study of primary hypertension, Final Report. J. Chron. Dis. **25:** 127–132.
41. **Pooling Project Research Group.** 1978. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. J. Chronic Dis. **31:** 201–270.
42. **Preston, D.L., Lubin, J.H. and Pierce, D.A.** 1990. EPICURE command Summary. HiroSoft International Corporation, Seattle.
43. **Sasaki, H., Kodama, K., Kitano, K., Yamada, M., Fujiwara, S., Neriishi, K., Hosoda, Y., Sawada, H., Shimizu, Y. and Kata, H.** 1986. Secular trends of blood pressure in A-bomb survivors. Nagasaki Medical J. **61:** 442–448.
44. **Sasaki, T., Sweedler, D.R. and Okamoto, A.** 1964. Cold pressor test on atomic bomb survivors. RERF Technical Report 03–64.
45. **Scriven, A.J., Brown, M.J., Murphy, M.B. and Dollery, C.T.** 1984. Changes in blood pressure and plasm catecholamines caused by tyramine and cold

exposure. J. Cardiovasc. Pharmacol. **6:** 954–960.
46. **Seals, D.R.** 1990. Sympathetic activation during the cold pressor test: influence of stimulus area. Clin. Physiol. **10:** 123–129.
47. **Seals, D.R.** 1991. Sympathetic neural adjustments to stress in physically trained and untrained humans. Hypertension **17:** 36–43.
48. **Tanji, J.L., Champlin, J.J., Wong, G.Y., Lew, E.Y., Brown, T.C. and Amsterdam, E.A.** 1989. Blood pressure recovery curves after submaximal exercise. A predictor of hypertension at ten-year follow-up. Am. J. Hypertens. **2:** 135–138.
49. **Thomas, C.B. and Cohen, B.H.** 1955. The familial occurrence of hypertension and coronary artery disease, with observations concerning obesity and diabetes. Ann. Intern. Med. **42:** 90–127.
50. **Thomas, J., Semenya, K.A., Neser, W.B., Thomas, D.J., Green, D.R. and Gillum, R.F.** 1985. Risk factors and the incidence of hypertension in black physicians: the Meharry Cohort Study. Am. Heart J. **110:** 637–645.
51. **Victor, R.G., Leimbach, W.N. Jr., Seals, D.R., Wallin, B.G. and Mark, A.L.** 1987. Effects of the cold pressor test on muscle sympathetic nerve activity in humans. Hypertension **9:** 429–436.
52. **Wallin, B.G., Sundlof, G., Eriksson, B.M., Dominiak, P., Grobecker, H. and Lindblad, L.E.** 1981. Plasma noradrenaline correlates to sympathetic muscle nerve activity in normotensive man. Acta Physiol. Scand. **111:** 69–73.
53. **Ward, M.M., Chesney, M.A., Swan, G.E., Black, G.W., Parker, S.D. and Rosenman, R.H.** 1986. Cardiovascular responses in type A and type B men to a series of stressors. J. Behav. Med. **9:** 43–49.
54. **Wilhelmsen, L., Wedel, H. and Tibblin, G.** 1973. Multivariate analysis of risk factors for coronary heart disease. Circulation **48:** 950–958.
55. **Wilson, B.L., Albright, G.L., Steiner, S.S. and Andreassi, J.L.** 1991. Cardiodynamic response to psychological and cold pressor stress: further evidence for stimulus response specificity and directional fractionation. Biofeedback Self Regul. **16:** 45–53.
56. **Wood, D.L., Sheps, S.G., Elveback, L.R. and Schirger, A.** 1984. Cold pressor test as a predictor of hypertension. Hypertension **6:** 301–306.