Among 1,433 men of Japanese ancestry living in Hawaii with blood pressure measured at four different physical examinations over a 10-year period, 110 events of definite coronary heart disease (CHD) occurred during 11.6 years of subsequent follow-up. Each subject's mean blood pressure, the slope of the regression of his blood pressure on age, and the variance of blood pressure about this regression line were tested for association with subsequent incident definite CHD. Adjusted for mean systolic blood pressure (SBP), the variance of SBP was significantly associated with CHD ($p < 0.001$); however, the slope was not significantly associated with CHD. Variation in body weight was an independent risk factor for CHD. The effect of variation in SBP was significantly higher among men not taking antihypertensive medication; among men taking antihypertension medication, the standardized relative risk was 1.00. Comparing men in the highest quintile of SBP variation with those in the lowest quintile, the relative risk of CHD was 2.0 among all subjects and 5.3 among the 1,007 men not taking antihypertensive medication (95% confidence interval 1.8–15.4). Some of the beneficial effect of taking antihypertensive medication may have been due to reducing the effect of SBP variance rather than simply lowering the average SBP. 

such a longitudinal study design with adjustment for confounding variables at baseline to test whether variability in blood pressure is a risk factor for coronary heart disease among middle-aged Japanese men participating in the Honolulu Heart Program.

MATERIALS AND METHODS

The Honolulu Heart Program is an ongoing longitudinal epidemiologic study of CHD and stroke among men of Japanese ancestry who were born between 1900 and 1919 and were living on the island of Oahu, Hawaii, in 1965. The study design and methodology have been described in detail elsewhere (5–7). In brief, of a target population of 11,148 men aged 45–65 years in 1965 with known addresses on Oahu, 8,006 agreed to participate in the first examination during 1965–1968. These men were reexamined on two more occasions, and a 30 percent random sample was invited to participate in an additional series of studies on lipoproteins. There has been continuous surveillance of the subjects by use of hospital and mortality records for CHD, stroke, and all-cause mortality. Follow-up has been exceptionally complete, due partly to the very low emigration rate. At the third cohort examination, it was found that 100 percent of the reported cases of stroke and CHD had already been identified through ongoing surveillance (6). After 23 years of follow-up, a survey showed that the Honolulu Heart Program knew the vital status of all but five members of the 8,006 studied men.

The study design divides time into two parts, the period when serial blood pressure measurements were taken and the subsequent follow-up period. The cohort examinations were spaced approximately 3 years apart, examinations 1, 2, and 3 being conducted from 1965–1968, 1968–1970, and 1971–1974, respectively. In addition, a 30 percent random sample (n = 2,249) of men who completed the second examination were invited into the Cooperative Lipoprotein Study (during 1970–1972). Of these men, 1,656 living subjects participated in the Lipoprotein Study 2, which was conducted during 1975–1978; this group of men formed the basis for this analysis. Follow-up was from the date of the Lipoprotein Study 2 through December 31, 1988, which averaged 11.6 years.

Of the original 1,656 men from the random sample, 191 men were excluded from the analysis because they had preexisting cardiovascular disease. An additional 32 subjects were excluded because they had not participated in at least two of the previous examinations or were missing information on some baseline variable. The remaining 1,433 men had blood pressure measurements from four consecutive examinations except for 25, who had only three measurements. The incidence of first events of definite CHD included CHD deaths and nonfatal myocardial infarction documented by electrocardiogram or cardiac enzyme changes. Diagnosis was made in conference by two or more regular study physicians and, when autopsy information was available, a pathologist (6). There were 111 incident cases of definite coronary heart disease during the follow-up period; one case was among the subjects not used in the analysis because of incomplete information on other variables.

“Blood pressure at an examination” here denotes the mean of all available measurements taken during a physical examination. There were three blood pressure measurements taken at examinations 1 and 2 (two by nurses and one by the examining physician), two at examination 3 (taken by a medical technologist and the examining physician), and two taken at the Lipoprotein Study 2 (taken by a nurse and the examining physician). Before having their blood pressure measurements taken, subjects responded to a lengthy questionnaire while sitting and then moved to an examining room where they sat for about 10 minutes; after this, the first of the blood pressure measurements was taken. Repeated blood pressure measurements were taken at least 15 minutes apart. Blood pressure was measured using a mercury manometer with a standard cuff applied to the seated subject’s left arm. Diastolic blood pressure was recorded at the fifth Korotkoff phase (disappearance of sound).

It is assumed here that a 10- to 12-year period of observation during middle age is short enough that a subject’s systematic change in blood pressure, if any, is adequately measured by a straight line. For each subject, the mean of blood pressure measurements from each examination was regressed on the subject’s age at examination date; the variance of the residuals from the line was used to estimate random variation. The mean, slope of the regression line, and variance of the residuals were computed for systolic and diastolic blood pressures and also for body weight. For one additional analysis, the average short term (15–30 minutes) variance in SBP was estimated by averaging the variances of the replicate SBP measurements taken at examinations 1 and 2.

During the four physical examinations, subjects were asked whether they were using antihypertensive medication. For certain analyses, a variable was created that equaled 1 if use of antihypertensive medication was acknowledged at any examination and that equaled 0 otherwise. A total of 426 subjects used some form of antihypertensive medication. Including this variable and its cross products with the blood pressure variables allowed testing for the presence of interac-
tion of taking medication with the blood pressure variables.

Cox's proportional hazards regression model (8, 9) was used for analyses of the relative risk of incident definite coronary heart disease. The Cox regression coefficients are estimates of the natural logarithm of the relative risk associated with an increase of the independent variable by one unit. A likelihood ratio test for equality of relative risks from the most recent blood pressure and the most distant blood pressure was constructed (by comparing the difference in log likelihoods for the model in which both were fit simultaneously and the model using their average; −2 times the difference in log likelihood is distributed as chi-squared with one degree of freedom). Not all variables were measured at each examination. To adjust for potential confounding variables, the most recent measurement available of each covariate was used. Age and Quetelet's index (weight/height squared) were from the final physical examination (Lipoprotein Study 2), serum cholesterol and packs of cigarettes smoked per day were recorded from examination 3, and serum glucose was measured at examination 1. These five variables were used for covariate adjustment in each analysis except those involving fluctuations in body weight, a potential confounding variable; in these analyses, the subject's height and the mean, slope, and standard deviation of weight were used in place of Quetelet's index. (The standard deviation of body weight, instead of the variance, was used to keep the scale similar to an earlier analysis of body weight variation (2).)

RESULTS

The first blood pressure measurement (taken at examination 1) and the final measurement (taken at Lipoprotein Study 2) did not differ significantly in their ability to predict the risk of heart disease occurring during the follow-up period: For systolic blood pressure, the likelihood ratio test for a difference in relative risks was $\chi^2 = 0.02, p = 0.90$ and, for diastolic blood pressure, the result was $\chi^2 = 1.25, p = 0.26$. In other words, the blood pressure measurement taken 10 years earlier was as good a predictor of subsequent heart disease as the last measurement. The mean blood pressure was a better predictor of CHD than a single measurement. Adjustment was made for age, Quetelet's index, serum cholesterol, serum glucose, and packs of cigarettes smoked per day.

The results from proportional hazards regression of adjusted risk of definite coronary heart disease on systolic blood pressure variables are given in table 1. The mean blood pressure was very highly significant, as expected. The slope of the line describing systematic change in systolic blood pressure over time was not a significant predictor of subsequent heart disease, but the variance of the deviations about the line was very highly significant ($p < 0.0001$). With SBP measured in units of 10 mmHg, the relative risk for an increase of one unit of variance of blood pressure is 1.14 (standardized relative risk = 1.23).

To learn whether the effect of fluctuation in systolic blood pressure on heart disease risk was due simply to underlying variation in body weight, the mean, slope, and standard deviation of fluctuations in body weight, adjusted for height, were included in the analysis (table 2). The mean body weight, adjusted for height, and the standard deviation of body weight were both significant predictors of subsequent coronary heart disease; however, the slope of body weight was not significant. The estimate of the relative risk of CHD due to the variance in systolic blood pressure was virtually unchanged by adding the weight variables.

A variable for the subject’s use of antihypertensive medication at any examination was included in the regression along with its cross products to test for interaction with the blood pressure variables. The interactions of use of antihypertensive medication with mean blood pressure and slope of blood pressure were not significant ($p = 0.13, 0.70$, respectively), but use

<table>
<thead>
<tr>
<th>SBP variable</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
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<td>1.14**</td>
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<tr>
<td>Variance among men not using antihypertensive medication</td>
<td>1.23***</td>
<td>1.14–1.32</td>
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</table>

* $p = 0.005$; ** $p < 0.001$; ***$p < 0.0001$.

† SBP is in units of 10 mmHg. Adjustment was made for age, serum cholesterol, serum glucose, pack-years of cigarettes, and weight/(height squared).
CHD was computed for the different quintiles of both pressure variation as a risk factor, the relative risk of nonlinear effect of SBP. Since these values are slightly higher than the value of SBP among nonmedicated subjects, adjusted by a cubic polynomial of mean SBP, was 1.29; and the relative risk, adjusted by quintiles of mean SBP, was 1.27. The within-examination variance of replicate SBP measurements, averaged over examinations 1 and 2, was only slightly associated with the among-examinations variance (r = 0.078). Using all subjects who attended the first two examinations and starting follow-up from examination 2, there were 7,107 informative subjects and 795 cases of definite CHD. Adjusted for covariates the variance and mean of SBP. Adjusted for mean SBP and other covariates, the relative risk of CHD increased monotonically by quintile of SBP variance; the relative risks were 1, 1.2, 1.5, 1.7, and 2.0, relative to the lowest quintile (see figure 1). Among men not taking antihypertensive medication, the relative risks of CHD by quintile (with cutpoints defined from the entire sample) were 1, 1.6, 2.0, 2.7, and 5.3, with only the highest quintile being significantly different from the lowest quintile (p = 0.002, 95 percent confidence interval 1.8–15.4).

The effect of adjusting for SBP variance on the estimate of the effect of mean SBP is shown in figure 2 for three models. The top line is the relative risk of definite CHD, by quintile of mean SBP, without adjusting for SBP variance. The lowest quintile is the reference group. The middle line gives the estimates when corrected by quintile of SBP variance. The lowest line displays estimates from the model including interaction of SBP variance with taking antihypertension medication. The relative risk of CHD among men in the highest quintile of average SBP changes from about six to five to four as adjustment for SBP variance is made more elaborate.

The within-examination variance of replicate SBP measurements, averaged over examinations 1 and 2, was only slightly associated with the among-examinations variance (r = 0.078). Using all subjects who attended the first two examinations and starting follow-up from examination 2, there were 7,107 informative subjects and 795 cases of definite CHD. Adjusted for covariates

<table>
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<th>Variable</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
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<tr>
<td>Variance</td>
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<td>1.05–1.23</td>
</tr>
</tbody>
</table>

\* p = 0.05; ** p < 0.01; ***p < 0.002.

† For relative risks, SBP is in units of 10 mmHg, and body weight is in units of 5 kg. Adjustment was made for subject's height and all covariates listed in table 1 except for body mass index. The standard deviations for the body weight mean, slope, and standard deviation were 8.83 kg, 0.43 kg/year, and 1.13 kg, respectively.
and mean SBP, there was only suggestive evidence for association between within-examination variation and subsequent definite CHD (95 percent confidence interval for relative risk = 0.99–1.16, p = 0.08). The interaction of replicate SBP variance with taking antihypertensive medication was not significant (p = 0.48). The results for diastolic blood pressure (DBP) might be expected to be similar to systolic blood pressure. However, the variance of diastolic blood pressure was not a significant predictor of subsequent definite coronary heart disease (p = 0.23). Since this might be due in part to not using the right scale for DBP, several power transformations of the variance were tried. The log of the DBP variance was a significant predictor of subsequent coronary heart disease (p = 0.026), and the improvement in fit from using the log transformation of the variance, rather than the variance, was of borderline significance (likelihood ratio $\chi^2 = 3.47$, p = 0.06). The effect of the log variance of DBP was not significantly (p = 0.21) greater among men not taking antihypertensive medication. In a multivariate model, the relative risk of CHD among men in the highest quintile, compared with the lowest quintile, was 2.5 for both mean DBP and variance of DBP. As with SBP, the mean and variance of DBP were moderately correlated ($r = 0.22$), so the estimate of the effect of DBP was lowered by adjusting for DBP variance.

**DISCUSSION**

We found fluctuations in systolic blood pressure to be predictive of subsequent definite coronary heart disease ($p < 0.0001$) after adjusting for average SBP. For comparison, the relative risk for the highest quintile, compared with the lowest quintile, was 4.0 for mean systolic blood pressure, 2.0 for the variance of SBP, and 3.5 for the variance of SBP among subjects not taking antihypertensive medication. These values are underestimated because the mean and variance could not be measured exactly for each subject (10, 11). Since the precision in the estimates of the variances is less than that of the means, the effect of blood pressure variation is probably underestimated more than the effect of average blood pressure.

Fluctuations in SBP were not associated with subsequent coronary heart disease among subjects taking antihypertensive medication, and the difference between users and nonusers was significantly different. Taking antihypertensive medication after the first examination could increase a subject’s SBP variance simply by dropping the subsequent SBP level, which would increase the among-examination variance without actually increasing spontaneous variability. Or, perhaps the benefit of taking antihypertensive medication was not due solely to lowering average blood pressure but also was due to removing the effect of SBP variance as a risk factor for CHD.

Body weight is correlated with blood pressure to some extent, and variability in body weight has been found to be associated with coronary heart disease and cardiovascular disease (2–4). Although variability in weight was a predictor of coronary heart disease in this study as well (p = 0.036), it was not the reason for the association of variability in systolic blood pressure and coronary heart disease: The relative risk associated with variation in systolic blood pressure was not affected by adjusting for variation in body weight.

Some of the excess risk that might have been attributed to average SBP apparently belonged to SBP variance, which is a confounder for average SBP. Among subjects not taking antihypertension medication, the relative risk of CHD among men in the highest quintile of SBP variance, compared with men in the lowest quintile, was of roughly the same size as the relative risk in the highest quintile of average SBP, suggesting that labile blood pressure has a significant impact on morbidity. The reason for the association between SBP fluctuations with CHD is not clear. Fluctuations in blood pressure might cause endothelial damage in arteries, which leads to formation of atherosclerosis. Instead, variation might be a marker for occasional spikes in blood pressure, with these temporary peaks
causing damage in much the same way as persistent high blood pressure.

The evidence for an effect of variation in DBP was more equivocal. The risk of CHD was not significantly associated with the variance in DBP, but the logarithm of DBP variance was associated with risk at the 0.05 level of significance. The risk associated with being in the highest quintile was 2.5 for both average DBP and variance of DBP.

There apparently has been little published research on the possibility of blood pressure variability as a risk factor. Hathaway and D'Agostino (1) found a barely significant association of SBP variance with subsequent CHD among a small group of Caucasian women. Their model corrected for average SBP and its slope but did not include use of antihypertension medication or changes in body weight. Prentice et al. (12) found no significant relation between cardiovascular disease and variance in blood pressure adjusted for the slope of blood pressure and the most recent value (rather than the mean blood pressure) in a Japanese cohort; information on use of antihypertensive medication had not been obtained. For the same cohort, Shimizu et al. (13) found no relation between stroke incidence and variance in blood pressure, adjusted for each subject's mean blood pressure and blood pressure slope.

The data used for this analysis included blood pressure measurements taken during four different examinations, roughly 3 years apart. Practicing physicians may not have such detailed information on many of their patients. Some indication of potentially elevated risk can come from blood pressure measurements taken at only two examinations. For the special case of two examinations, the variance is equal to $\frac{1}{2} (SBP_1 - SBP_2)^2$. A regression of log risk of CHD on one-half the squared difference of the SBP measurements from the first two examinations was highly significant using subjects not taking antihypertensive medication. Compared with men whose blood pressure remained constant and who had the same average blood pressure, a difference in SBP of 35 mmHg implied a relative risk of 2.0; a difference of 44 mmHg would give a relative risk of 3.0. These relative risks based on using two examinations are considerably underestimated because of the inaccuracy in estimating a variance based on only two observations. The Cox regression coefficient from using only the first two SBP measurements was only 61 percent of the value obtained by using all four examinations. Nevertheless, the results show that variation in SBP is a sufficiently strong predictor of definite CHD that it may ultimately be of value in a clinical setting. A longitudinal study with more blood pressure measurements should allow a more precise estimate of the real effect of SBP variation.

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REFERENCES