Orthostatic Hypotension Predicts Mortality in Elderly Men
The Honolulu Heart Program

Kamal H. Masaki, MD; Irwin J. Schatz, MD; Cecil M. Burchfiel, PhD; Dan S. Sharp, MD, PhD; Darryl Chiu, MS; Daniel Foley, MS; J. David Curb, MD, MPH

Background—Population-based data are unavailable concerning the predictive value of orthostatic hypotension on mortality in ambulatory elderly patients, particularly minority groups.

Methods and Results—With the use of data from the Honolulu Heart Program’s fourth examination (1991 to 1993), orthostatic hypotension was assessed in relation to subsequent 4-year all-cause mortality among a cohort of 3522 Japanese American men 71 to 93 years old. Blood pressure was measured in the supine position and after 3 minutes of standing, with the use of standardized methods. Orthostatic hypotension was defined as a drop in systolic blood pressure (SBP) of ≥20 mm Hg or in diastolic blood pressure of ≥10 mm Hg. Overall prevalence of orthostatic hypotension was 6.9% and increased with age. There was a total of 473 deaths in the cohort over 4 years; of those who died, 52 had orthostatic hypotension. Four-year age-adjusted mortality rates in those with and without orthostatic hypotension were 56.6 and 38.6 per 1000 person-years, respectively. With the use of Cox proportional hazards models, after adjustment for age, smoking, diabetes mellitus, body mass index, physical activity, seated systolic blood pressure, antihypertensive medications, hematocrit, alcohol intake, and prevalent stroke, coronary heart disease and cancer, orthostatic hypotension was a significant independent predictor of 4-year all-cause mortality (relative risk 1.64, 95% CI 1.19 to 2.26). There was a significant linear association between change in systolic blood pressure from supine position to standing and 4-year mortality rates (test for linear trend, \( P<0.001 \)), suggesting a dose-response relation.

Conclusions—Orthostatic hypotension is relatively uncommon, may be a marker for physical frailty, and is a significant independent predictor of 4-year all-cause mortality in this cohort of elderly ambulatory men. (Circulation. 1998;98:2290-2295.)

Key Words: mortality ■ aging ■ men ■ blood pressure

The prevalence of orthostatic hypotension varies substantially, depending on the methods used for detection and the groups being studied. Most studies have been in selected populations referred to a clinic for evaluation of syncope or dizziness,\(^1\) in which prevalence estimates are relatively high (≥30%).

Epidemiological data indicate that orthostatic hypotension has a prevalence of 4% to 33% in community-dwelling elderly populations,\(^1\)\(^-\)\(^3\) but measurement protocols often affect such estimates. Prevalence of orthostatic hypotension was defined as a drop in systolic blood pressure (SBP) of ≥20 mm Hg from the supine position to standing at baseline in the Systolic Hypertension in the Elderly Project (SHEP) and varied from 5.3% (decline in SBP at both 1 and 3 minutes) to 17.3% (drop in SBP at either 1 or 3 minutes).\(^4\)

The Cardiovascular Health Study (CHS) measured orthostatic hypotension in those ≥65 years of age by use of a similar methodology to the present study.\(^5\) Prevalence of orthostatic hypotension in this group of predominantly white elderly men and women was 16.2% and increased with age.

It has been suggested that orthostatic hypotension may be a normal consequence of aging, but this has been disputed.\(^6\) Normal aging is associated with a reduction in baroreceptor sensitivity and decreased cardiac responsiveness to sympathetic stimulation.\(^7\)\(^,\)\(^8\) The elderly are more likely to have inadequate homeostatic mechanisms for maintenance of blood pressure in the standing position and are more sensitive to the effects of medications.\(^7\)\(^,\)\(^8\) One study of elderly patients showed that orthostatic hypotension was significantly associated with lower supine systolic blood pressure and lower supine cardiac index, suggesting that underlying diseases rather than age are a better marker of orthostatic hypotension.\(^9\) Another study suggested that a blunted sympathetic response in elderly hypertensive Japanese patients predisposed those with hypertension to orthostatic hypotension.\(^10\)
There is some controversy about racial differences in orthostatic hypotension. CHS and SHEP showed that no significant difference exists in prevalence of orthostatic hypotension between races; these 2 studies were composed predominantly of white subjects and black subjects. There may be similar abnormalities in autonomic and sympathetic nervous system function in white subjects and black subjects with hypertension. However, a study of 2 rural biracial townships showed that white subjects had twice the prevalence of orthostatic hypotension than black subjects, and this difference was statistically significant. Adequate data in people of Japanese ancestry are unavailable.

There are few published data on orthostatic hypotension as a predictor of mortality in community-dwelling elderly subjects. We hypothesize that orthostatic hypotension is a measure of physical frailty and predicts mortality. The data collected in the fourth examination of the Honolulu Heart Program in 1991 to 1993 provide an opportunity to explore the predictive value of orthostatic hypotension for 4-year all-cause mortality in a well-characterized, population-based cohort of elderly Japanese American men. Orthostatic hypotension is now defined as a drop in SBP ≥20 mm Hg or a drop in diastolic blood pressure (DBP) ≥10 mm Hg from the supine position to standing. Although there is great variability in definitions of orthostatic hypotension in the literature, we chose the above consensus definition in this study, particularly because of relevance to clinical practice.

Methods

Study Population

The Honolulu Heart Program is a prospective epidemiological study of cardiovascular disease. Participants are men of Japanese ancestry living on the island of Oahu, Hawaii, in 1965, born between 1900 and 1919 (age 45 to 68 years at the time of the first examination). Eight thousand six men participated in the first examination between 1965 and 1968. Details of the selection process for the cohort were published previously. The entire cohort has undergone 5 examinations. This report is based on the fourth examination of the cohort conducted in 1991 to 1993 and the ascertainment of mortality that was conducted after the fourth examination until December, 1995. During the fourth examination, 3741 men aged 71 to 93 years were examined (80% of survivors). Some data, augmented by telephone interviews, were obtained for 98% of survivors. For this analysis, all variables of interest were available in 3522 participants. The study was approved by the institutional review committee of Kuakini Medical Center, procedures followed were in accordance with institutional guidelines, and informed consent was obtained from all participants.

Data Collection

The fourth examination included demographic information, medical and psychological questionnaires, assessment of cognitive function, fasting blood tests and a 2-hour glucose tolerance test, seated blood pressure, anthropometry, spirometry, and an ECG collected in a standardized manner consistent with previous examinations of this cohort. In addition, orthostatic blood pressures and pulse rate were measured (supine and after 3 minutes of standing) in 3522 participants. Morbidity and mortality surveillance by the monitoring of hospital discharge records and death certificates has been performed since the beginning of the study. For this report, mortality data were accumulated through December 1995. Data collection is believed to be essentially complete for all-cause mortality. Attrition in this cohort is known to be very small; at the fourth examination, only 5 men were lost to follow-up. Only all-cause mortality is used in this analysis because cause-specific mortality data are not yet available for this time period.

Measurement of Orthostatic Blood Pressures

Blood pressures were measured with a standard mercury sphygmomanometer with a standardized protocol. Supine measurements were taken after at least 15 minutes of rest. Standing measurements were taken after 3 minutes of standing. On standing, participants were asked whether they were feeling any dizziness, faintness, or light-headedness, and the examiner noted whether this was transient or nontransient. The procedure was aborted for safety reasons if necessary; this occurred very infrequently.

Definition of Orthostatic Hypotension

Orthostatic hypotension was defined as a drop in SBP of ≥20 mm Hg from the supine to the standing position at 3 minutes or a drop in DBP of ≥10 mm Hg on standing, or both.

Measurement of Other Key Variables

Covariates were selected because of their potential relation with either orthostatic hypotension or with mortality. We used 2 categories of smoking status, current and past, compared with never-smokers. Diabetes mellitus was defined by history (as told to the participant by a physician), by taking medications (insulin or oral hypoglycemics), or by fasting glucose ≥140 mg/dL or by 2-hour postload glucose ≥200 mg/dL. Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. Physical activity index was based on one used in Framingham and the Honolulu Heart Program, which consists of multiplying the approximate oxygen consumption of five different levels of activity with the reported usual numbers of hours a day engaged in that activity. Use of antihypertensive medications was determined by direct observation: participants were instructed to bring in all medications taken in the previous 2 weeks. Serum lipids were not associated with orthostatic hypotension and were not used in this analysis.

Frailty Measures

Correlations of orthostatic hypotension with other frailty measures were calculated. These included forced expiratory volume in 1 second (FEV₁), timed 10-foot walk, and hand grip strength. Details about how these were measured have been published previously.

Data Analysis

Subjects were divided into those with and those without orthostatic hypotension as defined above. Age-adjusted 4-year mortality rates, expressed per 1000 person-years of follow-up, were calculated according to orthostatic hypotension status. Three separate Cox proportional hazards models were considered to assess the association between orthostatic hypotension and mortality. The first adjusted for age alone. The second model adjusted for age, current and past smoking, diabetes mellitus, body mass index, physical activity index, SBP, antihypertensive medications, hematuric, and alcohol intake. A third model included the above variables as well as prevalent coronary heart disease, stroke, and cancer at the fourth examination.

The association between orthostatic hypotension and 4-year mortality rates in healthy men without chronic disease was also examined. Therefore the above analyses were repeated, excluding men with prevalent coronary heart disease, stroke, or cancer at the fourth examination. These chronic conditions are known to be the 3 most frequent causes of death in this cohort.

The dose-response relations of mortality with orthostatic change in SBP and DBP were studied separately, by dividing participants into 6 groups on the basis of change in SBP from supine position to standing and 6 groups based on change in DBP from supine to standing. Tests for linear trend were performed, adjusting only for age. For DBP, because test for linear trend was not significant, the
first 4 groups of change in DBP from supine position to standing were grouped together and compared with the last 2 groups. All statistical analyses were done with SAS software (SAS Institute).

**Results**

The overall prevalence of orthostatic hypotension in this cohort was 6.9%. Prevalence of orthostatic hypotension increased with age, from 5.1% in those 71 to 74 years of age to 6.3% in those 75 to 79 years of age, to 9.2% in those 80 to 84 years of age, and 10.9% in those ≥85 years of age (Figure 1).

The follow-up period was defined as the time between measurement of orthostatic hypotension at the fourth examination (1991 to 1993) and December 1995. There was a total of 473 deaths in the entire cohort over this time period; of those who died, 52 had orthostatic hypotension at the fourth examination and 421 did not have orthostatic hypotension (Table 1). Those with orthostatic hypotension survived a mean of 3.19 years after examination 4 (range 0 to 4.75 years), whereas those without orthostatic hypotension survived a mean of 3.37 years (range 0 to 4.83 years). The unadjusted 4-year mortality rate was 1.8 times greater in men with orthostatic hypotension compared with those without orthostatic hypotension (67.2 and 38.2 per 1000 person-years, respectively). After adjustment for age, 4-year mortality rates were 56.6 per 1000 person-years in those with orthostatic hypotension compared with 38.6 per 1000 person-years in those without orthostatic hypotension.

Kaplan-Meier survival analysis according to orthostatic hypotension status showed that those with orthostatic hypotension had a significantly lower 4-year survival compared with those without orthostatic hypotension ($P=0.0001$) (Figure 2).

Three separate Cox proportional hazards models were analyzed with mortality as the end-point (Table 2). In the first model, the relative risk (RR) for all-cause mortality associated with orthostatic hypotension was 1.56 (95% CI = 1.17 to 2.09) after adjustment for age alone. Adjustment for other factors known to influence mortality (model 2) did not appreciably alter the relative risk (RR = 1.61; 95% CI = 1.17 to 2.22). Further adjustment for prevalent coronary heart disease, stroke, and cancer also did not attenuate this association (RR = 1.64; 95% CI = 1.19 to 2.26). Thus in all 3 models, orthostatic hypotension was a significant independent predictor of 4-year mortality.

In addition, age, current and past smoking status, diabetes mellitus, alcohol intake, prevalent coronary heart disease, and cancer were also significantly positively associated with 4-year mortality, whereas BMI, physical activity index, and hematocrit were significantly negatively associated (Table 2). There was no significant association between 4-year mortality rate and seated SBP, use of antihypertensive medications, and prevalent stroke.

On the basis of previous follow-up, the most common causes of death in the entire cohort are known to be cancer, coronary heart disease, and stroke. To avoid the potential influence of these prevalent diseases on the association of orthostatic hypotension with mortality, Cox proportional hazards models 1 and 2 were repeated, excluding men with prevalent cancer, coronary heart disease, or stroke at this examination. Adjusted for age (model 1), RR for mortality associated with orthostatic hypotension was 1.74 (95% CI = 1.21 to 2.49); adjusting for age and risk factors (model 2), RR for mortality was 1.80 (95% CI = 1.22 to 2.65). Thus even when subjects with the 3 most common prevalent diseases associated with mortality were excluded, orthostatic hypotension remained a significant independent predictor of 4-year mortality; this association was slightly stronger than without exclusions.

**TABLE 1. Four-Year Mortality Rates by Orthostatic Hypotension Status**

<table>
<thead>
<tr>
<th>Orthostatic Hypotension</th>
<th>Absent</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>3279</td>
<td>243</td>
</tr>
<tr>
<td>Total no. of deaths</td>
<td>421</td>
<td>52</td>
</tr>
<tr>
<td>Average follow-up period to death, y</td>
<td>3.37</td>
<td>3.19</td>
</tr>
<tr>
<td>Unadjusted mortality rate, per 1000 person-years</td>
<td>38.2</td>
<td>67.2</td>
</tr>
<tr>
<td>Age-adjusted mortality rate, per 1000 person-years</td>
<td>38.6</td>
<td>56.6</td>
</tr>
</tbody>
</table>
Because the definition of orthostatic hypotension is somewhat arbitrary, we decided to examine the dose-response relation of mortality with orthostatic change in SBP and DBP separately. We divided participants into 6 groups on the basis of change in SBP from the supine position to standing, starting with a change of $-20$ mm Hg, with increments of 10 mm Hg, up to a change of $>20$ mm Hg. There was a significant age-adjusted linear association between change in SBP from the supine position to standing and 4-year mortality rate (test for linear trend, $P<0.001$) (Figure 3). Similarly, we divided participants into 6 groups on the basis of change in DBP from the supine position to standing, starting with a change of $-10$ mm Hg, with increments of 5 mm Hg, up to a change of $>10$ mm Hg. The age-adjusted test for linear trend was not significant ($P=0.075$). However, when the first 4 groups of change in DBP from supine position to standing were grouped together ($-10$ to 5 mm Hg), there was a significant difference in 4-year mortality when compared with those in the last 2 groups of change, that is, change in DBP $>5$ mm Hg ($P=0.011$) (Figure 3).

We repeated Cox proportional hazards model 3 (adjusting for age, risk factors, and prevalent diseases) separately for those with only systolic orthostatic hypotension and those with only diastolic orthostatic hypotension. For systolic orthostatic hypotension, RR for mortality was 1.80 (95% CI=1.17 to 2.75), and for diastolic orthostatic hypotension, RR for mortality was 1.52 (95% CI=1.01 to 2.29), again demonstrating a stronger effect of systolic changes in blood pressure on mortality.

To examine the possibility that orthostatic hypotension is associated with mortality because it is a marker of overall physical frailty, we determined age-adjusted mean levels of several indicators of frailty (timed 10-foot walk, hand grip strength, and FEV$_1$) by orthostatic status. Orthostatic hypotension was significantly associated with longer timed 10-foot walk (4.79 vs 4.31 seconds, $P=0.005$), weaker hand grip strength (28.25 vs 30.03 kg, $P=0.0001$), and lower FEV$_1$ (1.95 vs 2.06 L/s, $P=0.001$) after adjustment for age (Table 3). When Cox proportional hazards model 3 was repeated including the 3 frailty measures, the association between orthostatic hypotension and mortality remained significant (RR 1.47, 95% CI=1.01 to 2.12), although the strength of the association was somewhat weaker.

**Discussion**

In this prospective study of elderly Japanese American men, we found a significant increase in the risk of 4-year all-cause mortality associated with orthostatic hypotension. This relation persisted at a highly significant level even after adjustment for a number of potential confounders and prevalent diseases such as cancer, coronary heart disease, and stroke. These data are consistent with those from a younger group of subjects with diastolic hypertension in the Hypertension Detection and Follow-Up Program (HDFP). The HDFP showed that systolic orthostatic hypotension was a significant predictor of 5-year mortality rates in young and middle-aged adults.²¹ For each mm Hg change in SBP, the odds ratio for mortality was 1.02 ($P<0.05$). However, when relative weight was added to the multiple logistic model, this association was no longer significant and there was an interaction between systolic orthostatic hypotension and diabetes in subjects in HDFP. In the HDFP, orthostatic change in DBP was not associated with mortality rates. In contrast, in the older Japanese men described here, even after adjustment for BMI,
orthostatic hypotension continued to be a significant predictor of mortality. We did not observe an interaction between orthostatic hypotension and diabetes. In our study, the RR of all-cause mortality increases by 18% for every 10 mm Hg decrease in SBP from the supine position to standing.

To date, there has been only 1 small published study of the relation of orthostatic hypotension and mortality in elderly patients. A Finnish longitudinal analysis of 480 elderly subjects showed that neither change in SBP nor change in mean blood pressure were associated with mortality, but change in DBP was significantly associated with 10-year mortality.

In the current study, the risk of death varies when using different definitions of orthostatic hypotension. We saw a significant linear dose-response relation between orthostatic change in SBP and mortality, whereas a threshold effect was seen with orthostatic change in DBP >5 mm Hg. With the use of the consensus definition of orthostatic hypotension that combines changes in SBP and DBP, some important information may be lost. It is possible that changes in SBP and DBP measure different aspects of blood pressure regulation and may be associated with different risk outcomes. In this population, there is an increase in mortality rate seen at lower levels of change in blood pressure than the consensus definition. On the basis of these findings, we suggest that a better definition of orthostatic hypotension in this cohort is a decrease in SBP of >10 mm Hg or a decrease in DBP of >5 mm Hg, from the supine position to standing in terms of its relation to subsequent mortality. Obviously, the consensus statement definition should continue to be used for the clinical diagnosis and management of orthostatic hypotension.

One of the limitations of this study is the lack of data on cause-specific mortality, although all-cause mortality may be a more reliable indicator in older populations in which cause of death is often multiple or unclear. The data reported here can only be generalized to an ambulatory male population because orthostatic hypotension was not measured in most subjects who were examined in the home or in nursing homes, and there were no women in the cohort. Thus the prevalence of orthostatic hypotension reported here is likely to be an underestimate. Future research should confirm these findings in other populations as well as assess other outcomes: cause-specific mortality, morbidity, independence, and physical functioning.

As in other epidemiological studies, prevalence of orthostatic hypotension in this population increased with age. However, the prevalence estimates of orthostatic hypotension in our subjects are lower than those reported in other epidemiological studies. This may be partly explained by a lower prevalence of many chronic diseases in this population. Another possible explanation is ethnic/genetic differences. Because there are no epidemiological data available from other Japanese populations, this question deserves further study. In addition, the intraindividual variability of blood pressure itself may affect prevalence data. An Italian study of elderly outpatients measured orthostatic hypotension at 2 visits 7 days apart, only one third of subjects had the same blood pressure at both visits. Another study of symptomatic elderly with documented orthostatic hypotension showed that in almost one third of patients orthostatic hypotension was not reproducible at a second visit, particularly if measurements were taken in the afternoon.

There is debate concerning the causes of asymptomatic orthostatic hypotension in the elderly. Some believe that it is a normal accompaniment of aging reflecting baroreceptor dysfunction and decrease in responsiveness to sympathetic stimulation, whereas others claim that underlying disease or the use of medications may be more important or that it may be due to multiple rather than single causative factors. Some epidemiological studies have showed that orthostatic hypotension is a risk factor for falls and syncpe, whereas others have not. One study suggested that assessment of

<table>
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<tr>
<th>Frailty Measures</th>
<th>Orthostatic Hypotension</th>
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<tr>
<td></td>
<td>Absent</td>
</tr>
<tr>
<td>Timed 10-foot walk, s</td>
<td>4.31</td>
</tr>
<tr>
<td>Hand-grip strength, kg</td>
<td>30.03</td>
</tr>
<tr>
<td>FEV₁, L/s</td>
<td>2.06</td>
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</tbody>
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*P<0.005; †P<0.001; ‡P=0.0001.
dizziness on standing may be more important as a predictor of functional status, falls, and syncope than measuring postural change in blood pressure in elderly women. Others report a relation between use of antihypertensive medications and orthostatic hypotension; this relation was not seen in our analyses.

We did find a statistically significant association between orthostatic hypotension and several frailty measures, including timed 10-foot walk, hand grip strength, and FEV1. When these 3 frailty measures were added to the Cox proportional hazards model 3 (adjusted for age, risk factors, and prevalent disease), orthostatic hypotension remained a significant predictor of mortality.

These results suggest that orthostatic hypotension may be a marker for a general lessening of physical strength in this cohort. It also suggests that physical frailty is a harbinger of death in these subjects. Frailty is considered to be the result of some combination with other measures. It may be important to identify such frail elderly individuals to target interventions designed to prevent further decline. As life expectancy in the United States continues to increase, particularly for the “old-old” (those >85 years old), screening community living elderly patients with this simple, inexpensive test of physical frailty may have important public health implications.

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Orthostatic hypotension (OH) is a common condition affecting many elderly individuals, which is characterized by a significant decrease in blood pressure upon standing. This study aimed to investigate the relationship between OH and mortality in elderly men.

The Honolulu Heart Program, a long-term longitudinal study, was utilized to examine this relationship. The study population consisted of elderly men residing in Hawaii, with a mean age of 78 years. OH was defined as a decrease in systolic blood pressure of 20 mm Hg or more or a decrease in diastolic blood pressure of 10 mm Hg or more upon standing from a supine position of 10 minutes to standing for 3 minutes.

The main finding of the study was that OH was associated with an increased risk of mortality. The authors concluded that OH in elderly men is a significant predictor of mortality, highlighting the importance of recognizing and managing this condition in clinical practice.

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