ORIGINAL ARTICLE

Blood Pressure Hyperreactivity to Standing: a Predictor of Adverse Outcome in Young Hypertensive Patients

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ABSTRACT: The prognostic significance and the mechanisms of blood pressure (BP) hyperreactivity to standing remain controversial. This study aims to evaluate the association of orthostatic hyperreactivity with major adverse cardiovascular and renal events in a cohort of young hypertensive subjects. We studied 1207 untreated subjects screened for stage I hypertension with a mean age of 33.1±8.6 years. The orthostatic BP change was calculated as the difference between 6 standing and 6 supine BP readings obtained during 2 separate visits. Hyperreactivity to standing was defined as the standing-supine systolic BP difference in the top decile. The mean difference in the whole group was −2.5±7.3/4.6±5.4 mm Hg. Ambulatory hypertension evaluated with 24-hour recordings was more common in Hyperreactors than Normoreactors (90.8% versus 76.4%, P=0.001). In 630 participants in whom 24-hour urinary catecholamines were measured, epinephrine/creatinine ratio was higher in hyperreactors (118.4±185.6 versus 77.0±90.1 nmol/mol, P=0.005). During a 17.2-year follow-up, 105 major adverse cardiovascular and renal events were accrued. In a multivariate Cox model, hyperreactivity to standing was an independent predictor of major adverse cardiovascular and renal events with a hazard ratio of 1.97 (95% CI, 1.10–3.52). Hyperreactivity remained an independent predictor of adverse events even when ambulatory BP data and incident hypertension during follow-up were included in the Cox model (hazard ratio, 1.94 [95% CI, 1.10–3.44]). Our data indicate that in young-to-middle-age hypertensive subjects an exaggerated systolic BP response to standing is associated with sympatho-adrenergic hyperreactivity and is an independent predictor of major adverse cardiovascular and renal events. Orthostatic BP assessment gives the advantage of simple acquisition and provides prognostic information on top of ambulatory BP. (*Hypertension*. 2022;79:984–992. DOI: 10.1161/HYPERTENSIONAHA.121.18579.) • Supplemental Material

Key Words: blood pressure ▪ cardiovascular diseases ▪ catecholamines ▪ dyslipidemias ▪ hypertension

The decision whether to treat young hypertensive subjects with pharmacological therapy mainly depends on the level of blood pressure (BP) and the presence of concomitant risk factors.[1,2] Survival models for predicting risk of cardiovascular events in these patients usually include age, sex, BP measured in the lying or sitting position, smoking, dyslipidemia, diabetes, and parental history of premature cardiovascular disease.[3]

The BP response to change in body position as a measure of cardiovascular reactivity to standing has been rarely used in clinical practice as well as in epidemiological studies.[4,5] Even the most recent guidelines on BP measurement of the European Society of Hypertension recommend to measure standing BP only in

patients with treated hypertension when there are symptoms suggesting postural hypotension, especially in the elderly.[6] Indeed, several studies have found an association between positional BP changes and adverse health outcomes in persons whose BP decreases on standing.[7,8] However, some studies have found that the risk is highest in persons whose BP increases with changes in body position[9,10] and that an exaggerated BP response to standing is a predictor of future hypertension,[11] of cardiovascular events and mortality particularly in older patients.[12–15]

Only few prognostic data do exist in young to middle age people as the BP reaction to standing has never been included in predictive risk models in this age range.[16,17]

Novelty and Significance

What Is New?
- We investigated whether systolic blood pressure (BP) hyperreactivity to standing was associated with long-term adverse outcomes.

What Is Relevant?
- We showed that young-to-middle age hypertensive patients with a baseline systolic BP increase from lying to standing >6.5 mm Hg had an increased risk

of cardiovascular and renal events during a 17-year follow-up.

Summary
Our findings indicate that measuring BP in the upright posture may be important in young individuals and call for early pharmacological intervention in patients with exaggerated BP response to standing. Future hypertension guidelines should encourage measurement of BP on standing also in young individuals.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
BP	blood pressure
HDL	high-density lipoprotein
MACE	major adverse cardiovascular event

BP hyperreactivity to standing might be particularly deleterious in young individuals who will be exposed to its effect all along the life course.

To our knowledge, the predictive capacity of positional BP changes for cardiovascular disease has never been investigated in young people with hypertension. Thus, the aim of the present study was to quantify the risk of major adverse cardiovascular events (MACE) associated with the BP response to standing in young subjects with stage 1 hypertension and low cardiovascular risk profile. This investigation was conducted in the participants of the Hypertension and Ambulatory Recording Venetia study (HARVEST), a prospective cohort study initiated in April 1990.[18,19]

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Subjects

We investigated 1207 subjects from the HARVEST, a multicenter long-term prospective cohort study, of 18 to 45-year-old individuals screened for stage 1 hypertension (systolic BP of 140 to 159 mm Hg and diastolic BP of 90 to 99 mm Hg) and never treated for hypertension.[18–20] The study is conducted in 17 hypertension units in Italy. Patients' selection and recruitment was obtained with the collaboration of the local general practitioners. Exclusion criteria included diabetes, renal impairment, and cardiovascular diseases. More information on recruitment criteria have been reported elsewhere.[18–20] Patient files, blood, and urine samples were periodically collected and taken to the coordinating center in Padova, Italy, where they were

processed. Only subjects who had at least 6 months of follow-up were included in the present analysis.

Procedures

The procedures followed were in accordance with institutional guidelines. At baseline, all subjects underwent physical examination, anthropometry, blood chemistry, and urine analysis.[18–20] Participants completed questionnaires about their medical history, family history of cardiovascular disease, and an interview about their physical activity habits and current use of cigarettes, alcoholic beverages, and coffee.[21] The study was approved by the HARVEST Ethics Committee and by the Ethics Committee of the University of Padova. A written informed consent was given by the participants.

BP Measurement

Brachial office BP was measured with a mercury sphygmomanometer with appropriately sized cuffs, during 2 visits performed 2 weeks apart. At the enrolment patients underwent also 24-hour ambulatory BP monitoring using the A&D TM-2420 model 7 (Tokyo, Japan), or the ICR Spacelabs 90207 (Redmond, WA). The procedures used for the validation and the application of the instrumentation have been reported elsewhere.[22] Measurements were taken every 10 minutes during the day (06.00–23.00 hours) and every 15 to 30 minutes during the night (23.00–06.00 hours) according to the previously published procedures.[22] Only recordings containing error measurements of 20% or less were considered acceptable for evaluation. The arithmetic average of the edited pressures was used as the ambulatory measurement for each recording period. Patients with average 24-hour systolic BP ≥130 mm Hg or 24-hour diastolic BP ≥80 mm Hg were said to have ambulatory hypertension. During the ambulatory BP recordings, urine was collected for catecholamine measurement in 630 participants (see Supplemental Material).

Measurement of BP Response to Standing

The assessment of the BP reaction to standing was embedded in the larger clinical evaluation. Supine and standing BP and heart rate were measured during 2 visits performed 2 weeks apart (Figure 1). At each visit, 3 supine measurements were taken after the participant had lain on the examination bed
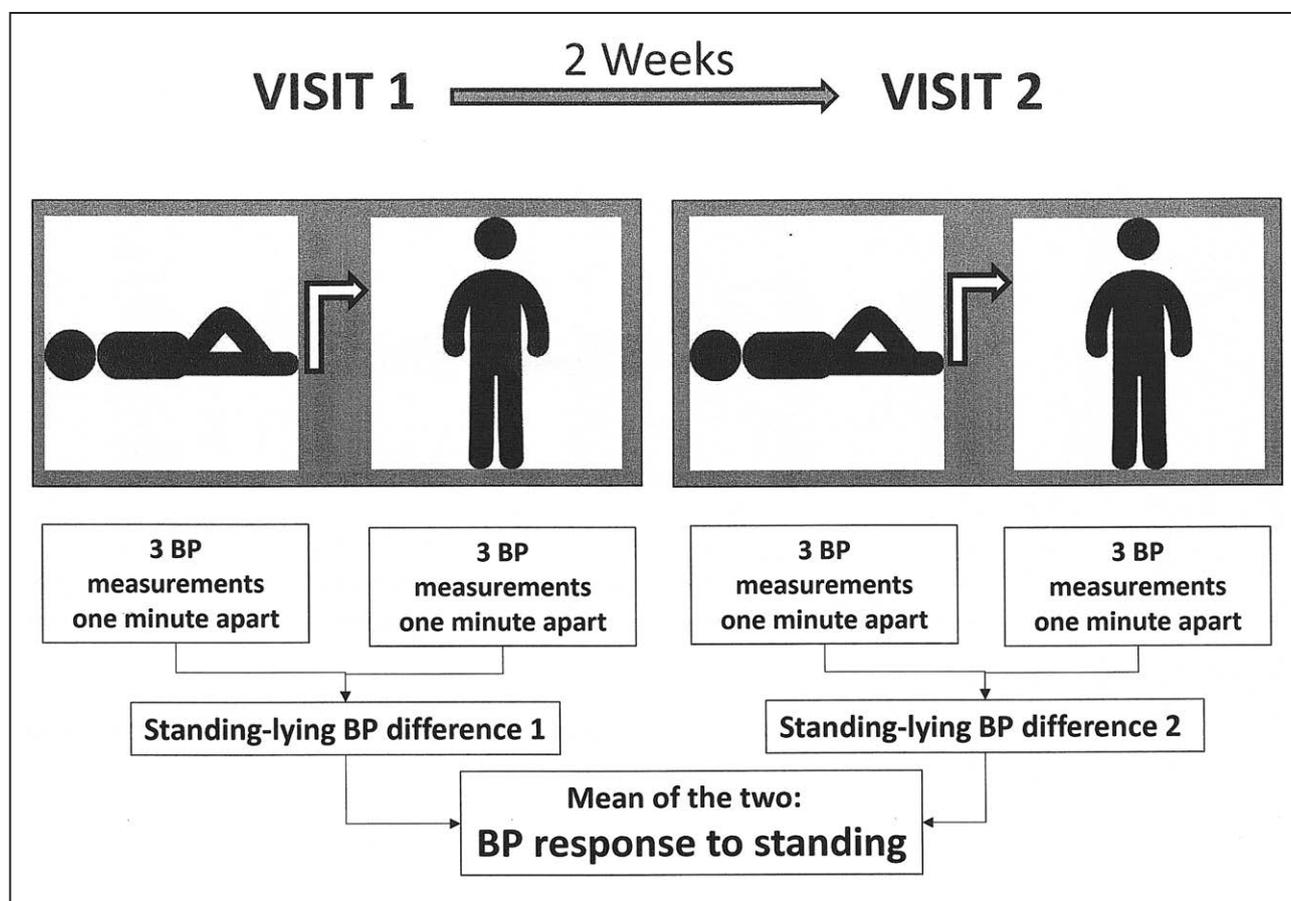
Figure 1. Protocol of the orthostatic blood pressure (BP) assessment.
At both visits, the first BP measurement was performed 1 minute after assuming the upright position followed by 2 BP measurements at 1 minute intervals. For each visit the difference between orthostatic and supine systolic BP readings was calculated. The overall BP response to standing was the mean of the BP differences during the 2 visits.

for a minimum of 5 minutes. After the supine data were collected, the participant assumed the upright position and three additional BP measurements were taken at 1-minute intervals. The difference between the 3 orthostatic and the 3 supine measurements was calculated. For purposes of this report, the orthostatic BP response to standing was defined as the average of the 2 standing-lying BP differences obtained during the 2 visits. As BP immediately after standing is subject to fluctuations, analyses using the mean of the first 2 standing measurements, the mean of the 2 second measurements and the mean of the two-third measurements were also made. In addition, the data obtained during each of the 2 visits were tested in the survival models.

Follow-Up

Office BP and lifestyle habits were assessed monthly during the first 3 months of follow-up, then after 6 months, and every 6 months thereafter. If after at least 6 months of implementation of nonpharmacological measures, the participant's BP was still above the operational threshold level, the patient was rescheduled for a visit within 2 to 4 weeks and the average BP was calculated. If BP was still above the limit, the patient was given antihypertensive drug treatment, otherwise he or she was checked at monthly intervals. The BP operational threshold level was established on the basis

of the criteria adopted by international guidelines at the time of patients' evaluation[23–26] (see Supplemental Material). Then treated and untreated subjects continued to be checked at 6-month intervals.

Definition of MACE

We ascertained vital status and the incidence of MACE from medical records and interviews with attending physicians and patient's families. As the definition of MACE is very heterogeneous,[27] in the present study, we decided to include all major complications of hypertension as individual outcomes including heart failure, renal events, and peripheral vascular disease. Renal events were defined as a chronic kidney disease stage 3 or higher (estimated glomerular filtration rate <60 mL/min per 1.73 m^2). Atrial fibrillation was also included because it is a major risk factor for stroke. However, as atrial fibrillation is not currently considered as a major cardiac event, all survival analyses were repeated after excluding this outcome. Thus, MACE included fatal and nonfatal ST-segment–elevation myocardial infarction, non–ST-segment–elevation acute coronary syndromes, any myocardial revascularization procedure, heart failure needing at least hospitalization, fatal and nonfatal strokes, any aortic or lower limb revascularization procedure, development of permanent atrial fibrillation, and chronic kidney disease.

Data Analysis

In agreement with previous reports,[28,29] an exaggerated BP reaction to standing was considered as the lower limit of the upper decile of the postural systolic BP change (>6.5 mm Hg). Also analyses on postural changes in diastolic BP were performed. However, diastolic BP changes were not associated with outcomes and thus only results for systolic BP are presented here.

Quantitative variables were reported as mean and SD, or as median and interquartile range, and differences in the distribution across groups were tested by ANCOVA and RM-ANCOVA tests adjusting for age and sex. Categorical variables were reported as percentage and differences in the distribution were tested by χ^2 test. Determinants of the BP response to standing were tested in multivariable linear and logistic regression analyses. Between-visit agreement was evaluated with correlation test and κ statistics (see Supplemental Material, Statistics). The risk of development of MACE related to the BP response to standing modeled as a categorical variable was evaluated by means of multivariable Cox proportional hazards analyses, adjusting for risk factors, and confounders (see Supplemental Material, Statistics). For the final model, a parsimonious set of covariates was selected using sequential backward elimination of the least significant variables, using $P<0.05$ to enter a variable into each step and $P<0.10$ to remove (final parsimonious model).[30] No violations to the proportional hazards assumption were detected by inspection of survival curves. Hazard ratios and corresponding 2-sided 95% CIs were derived from the regression coefficients in the Cox models. A 2-tailed probability value <0.05 was considered significant. All analyses were performed using Systat version 12 (SPAA Inc, Evanston, IL) and Medcalc version 15.8 (MedCalc Software, Ostend, Belgium).

RESULTS

Subjects' mean age was 33.1±8.6 years. Seventy-two point seven percent were male. Their mean office BP was 145.5±10.6/93.5±5.7 mm Hg in the lying posture and was 143.0±10.6/98.2±6.5 mm Hg on standing. The average standing-lying BP difference was −2.7±7.3/4.6±5.4 mm Hg. Figure 2 shows a frequency histogram of the standing-lying systolic BP difference for the entire sample. The distribution of the difference had a positive skewness with a coefficient of 0.25 ($P<0.001$), with similar values in males (0.24) and females (0.27). The lower limit of the upper decile was 6.5 mm Hg. The standing-lying systolic BP change was correlated with the diastolic change ($r=0.21$, $P<0.001$) but not with the heart rate change ($r=0.034$, $P=0.24$). A small nonsignificant decline in the response was observed from visit 1 to visit 2 (see Supplemental Material, Results and Figure S1). The agreement between the standing-lying BP differences during the 2 visits was fair according to κ statistics (see Supplemental Material, Results).

Hyperreactors Versus Normoreactors

The characteristics of the participants divided according to whether they had a normal or exaggerated (upper
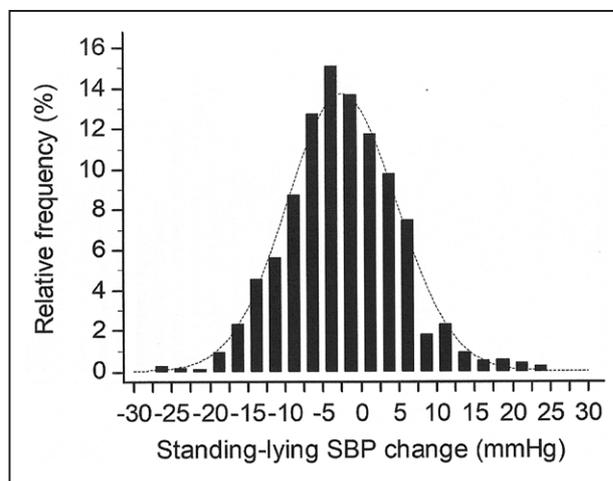

Figure 2. Frequency histogram of the standing-lying blood pressure difference in 1207 Hypertension and Ambulatory Recording Venetia study (HARVEST) participants with fitted normal distribution curve.

The distribution is skewed to the right with a coefficient of skewness of 0.25 ($P<0.001$). The coefficient of Kurtosis is 0.73 ($P<0.001$). The hypothesis of normal distribution was rejected by Shapiro-Wilk test with a P-value <0.001. SBP indicates systolic blood pressure.

decile) systolic BP response to standing are shown in Table 1. Age, sex distribution, and body mass index (BMI) were similar in the 2 groups. Hyperreactors to standing were more frequently smokers and coffee drinkers, had lower total cholesterol and higher HDL (high-density lipoprotein)-cholesterol. Norepinephrine and epinephrine were higher in the hyperreactors. However, after log-transformation, the difference was statistically significant only for epinephrine. The P value remained statistically significant also when epinephrine was adjusted for smoking, coffee drinking, and alcohol use ($P=0.007$).

In Table 2 and Table S1, the BP data for the 2 groups of subjects are reported. Hyperreactors to standing had a lower supine office systolic BP and higher 24-hour, daytime and night-time systolic BPs than normoreactors. Office heart rate was lower in hyperreactors but ambulatory heart rates did not differ between the 2 groups. Hyperreactors also had a greater orthostatic response of diastolic BP and a slightly greater orthostatic increase in heart rate. BP variability, the nocturnal BP dip, and the frequency of extreme dippers did not differ between the 2 groups. Ambulatory hypertension was more common in hyperreactors than normoreactors (90.8% versus 76.4%, $P=0.001$).

In a multivariable linear regression analysis, urinary epinephrine, smoking, and alcohol use were independent predictors of the BP response to standing (Table S2). The same variables and BMI were independently associated with BP hyperreactivity as categorical variable (Table S3).

During the follow-up, BMI increased from 25.4±3.4 to 26.2±3.6 kg/m². In an age-and-sex-adjusted RM ANCOVA, the P value was <0.001 for the global BMI change without significant interaction between BMI change and reactivity group ($P=0.73$). Due to the higher

Table 1. Clinical Characteristics of the Study Subjects Divided According to Whether They Had a Normal (Normoreactors) or an Exaggerated Systolic BP Response (Top Decile, Hyperreactors) to Standing

Variable	Normoreactors, n=1087	Hyperreactors, n=120	P value
Age, y	33.0±8.5	33.7±8.6	0.59
Body mass index, kg/m²	25.4±3.4	25.8±3.1	0.17
Sex (m/f, %)	72.8/27.2	72.5/27.5	0.96
Smoking (yes, %)	19.9	32.1	0.003
Alcohol use (yes, %)	46.4	55.0	0.086
Coffee consumption (yes, %)	73.0	81.7	0.051
Physically active (yes, %)	38.7	40.4	0.73
Family history for CV events (yes, %)	12.1	9.2	0.36
Glucose, mmol/L	5.17±0.67	5.16±0.51	0.79
Total cholesterol, mmol/L	5.13±0.98	4.93±1.04	0.013
HDL-cholesterol, mmol/L	1.35±0.33	1.42±0.36	0.033
Triglycerides, mmol/L	1.29±0.87	1.20±0.62	0.38
Creatinine, mmol/L	0.081±0.002	0.078±0.002	0.087
Epinephrine/creatinine, nmol/mol*	77.0±90.1	118.4±185.6	0.005†
Norepinephrine/creatinine, nmol/mol*	333.9±297.9	431.4±809.7	0.97†
Treated for HT during F.U (yes)	81.7%	69.7%	0.003

Values are given as mean±SD or proportions. *P* values were obtained from ANOVA or χ² analysis. Continuous data are adjusted for age and sex. BP indicates blood pressure; CV, coefficient of variation; F.U., follow-up; HDL, high-density lipoprotein; and HT, hypertension.

*From 24-hour urinary collections.

†*P* for log-transformed data.

Table 2. Office Blood Pressure and Heart Rate Data of the Study Subjects Divided According to Whether They Had a Normal (Normoreactors) or an Exaggerated (Top Decile, Hyperreactors) Systolic BP Response to Standing

Variable	Normoreactors, n=1087	Hyperreactors, n=120	P value
Supine systolic BP	146.0±10.3	140.5±12.0	<0.001
Supine diastolic BP	93.6±5.7	92.8±5.6	0.084
Standing systolic BP	142.1±10.2	151.8±11.3	<0.001
Standing diastolic BP	98.0±6.4	99.9±6.8	0.004
Supine heart rate, bpm	74.9±9.5	71.8±9.2	0.001
Standing heart rate, bpm	80.6±9.8	78.5±9.4	0.032
Standing-lying systolic BP difference	−3.8±5.9	11.4±4.6	<0.001
Standing-lying diastolic BP difference	4.4±5.4	7.1±5.2	<0.001
Standing-lying heart rate difference, bpm	5.7±5.2	6.7±5.0	0.049

Values are given as mean±SD. *P* values were obtained from ANOVA and were adjusted for age and sex. BP indicates blood pressure.

baseline office BP levels in the Normoreactors, incident hypertension needing antihypertensive treatment during the follow-up was developed more frequently by normoreactors than hyperreactors (Table 1).

Cardiovascular Events

During a median follow-up of 17.3 (interquartile range, 8.7–20.5) years, there were 105 fatal and nonfatal MACE. The most common events were acute coronary syndromes (n=48) including 12 coronary revascularizations. The incidence of fatal and nonfatal stroke amounted to 13 cases. Other MACE included 3 cases of heart failure requiring hospitalization, 3 cases of aortic aneurism, 6 cases of peripheral vascular disease, 20 cases with atrial fibrillation, and 12 cases with renal events. Atrial fibrillation was present in 7 other patients with cardiovascular events.

Hyperreactivity to Standing as Predictor of MACE

In multivariate Cox analysis adjusted for age, gender, parental history of cardiovascular disease, smoking,

alcohol drinking, coffee use, physical activity habits, BMI, office systolic and diastolic BP, postural diastolic BP change, office heart rate, serum glucose, and total cholesterol (model 1), participants with hyperreactivity to standing had an almost doubled risk of MACE compared with those with normal reactivity with a hazard ratio of 1.97 (95% CI, 1.10–3.52). Inclusion in the model of 24-hour ambulatory systolic BP data (model 2) did not virtually change the strength of this relationship (hazard ratio, 1.90 [95% CI, 1.06–3.42]) nor did it the inclusion of incident hypertension during the follow-up (Table S4). Exclusion of atrial fibrillation from MACE (N=85) provided similar results (hazard ratio, 2.01 [95% CI, 1.06–3.82], for the final model). In Figure 3, the adjusted survival curves for the 2 outcomes are shown. When the first, second, and third orthostatic BP measurements were considered separately, only the third measurement was an independent predictor of MACE (Table S5), but the association with outcome was slightly attenuated compared with the mean of the 3 measurements. When the data obtained during the 2 visits were tested separately, only orthostatic hyperreactivity assessed during the second visit was a significant predictor of outcome (Table S6). The risk of MACE was greatest for the subjects hyperreactive at both visits (Table S6).

DISCUSSION

In this prospective cohort study of young-to-middle-age subjects screened for stage 1 hypertension, we observed an independent association between BP hyperreactivity to standing and risk of MACE even when accounting for traditional risk factors and several potential confounders. The risk associated with an exaggerated orthostatic BP response was almost
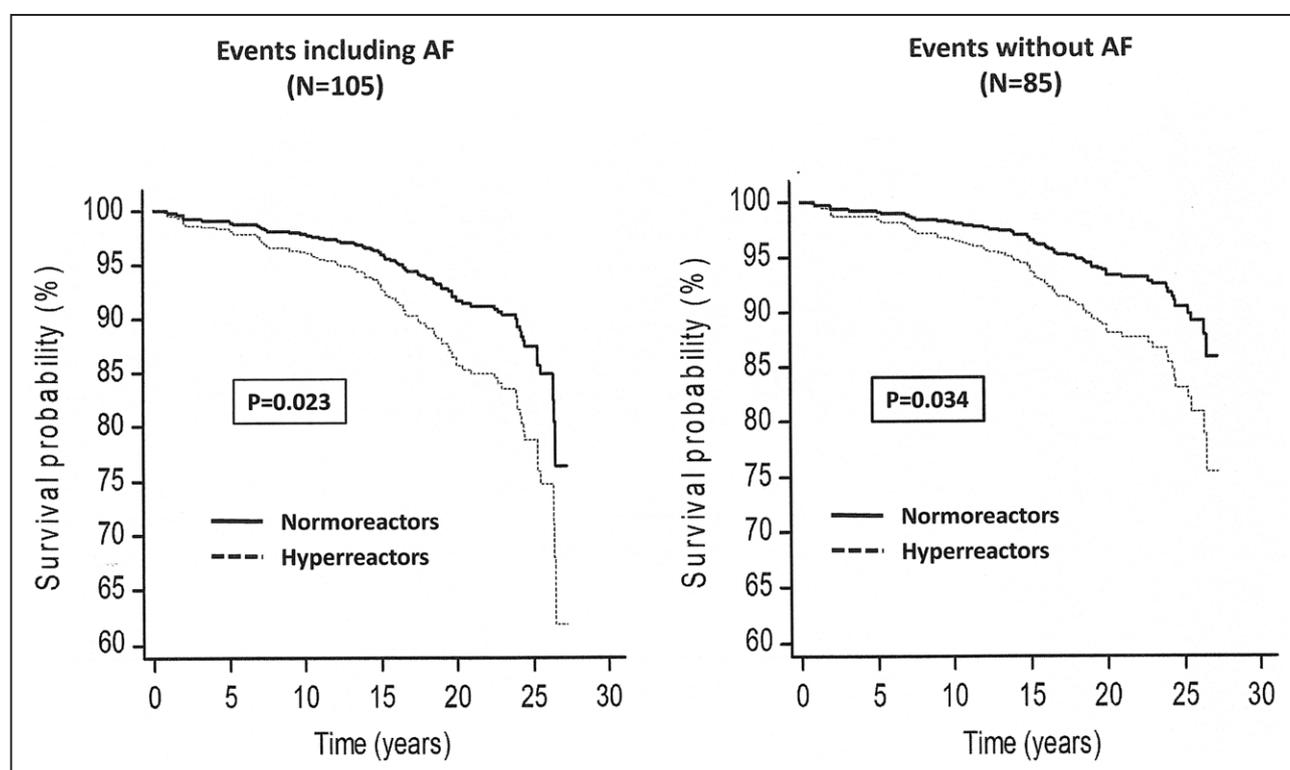
Figure 3. Adjusted survival curves from the Cox final model for the normoreactors and the hyperreactors to standing.
Major adverse cardiovascular and renal events including or excluding atrial fibrillation were considered as the outcome variable. AF indicates atrial fibrillation.

doubled irrespective of whether atrial fibrillation was included or not among the adverse outcomes. To our knowledge, no previous study has explored such a relationship in hypertensive young adults.

The postural change from the supine to standing position causes a decrease in venous return and a drop in cardiac output.[31] As a consequence, BP falls causing a baroreceptor-mediated sympathetic stimulation which promotes an increase in heart rate and vasoconstriction. In healthy individuals, the hemodynamic response to standing translates into a slight reduction of systolic BP and a slight elevation of diastolic BP[32,33] as shown by the present results. However, the systolic BP change from lying to standing in our participants was not normally distributed but was skewed toward higher values suggesting the possibility of a subpopulation characterized by hyperreactivity to standing. Thus, in agreement with previous studies,[28,29] we defined as hyperreactors to standing the participants in the top decile of the distribution.

At least part of the presumed effect of orthostatic hyperreactivity on cardiovascular disease may be due to its influence on 24-hour BP level which, in keeping with previous results,[33,34] was much higher among the hyperreactors than the normoreactors in spite of a lower supine office BP. However, adjustment for average 24-hour BP and other ambulatory BP parameters did not virtually change the association with risk of adverse outcomes, suggesting that hyperreactivity per se may be a causal

factor in the pathogenesis of MACE. Also, when incident hypertension was accounted for in the Cox model no attenuation of risk was noted ruling out the possibility that the increase in risk was due to hyperreactivity being a mere precursor of hypertension.

Possible Mechanisms

Mechanistic studies on neurohumoral contribution to orthostatic BP hyperreactivity are scanty and often performed in small samples. In agreement with the results of the Coronary Artery Risk Development in Young Adults study (CARDIA),[11] resting heart rate was lower in the hyperreactors suggesting that in these subjects sympathetic activity was not increased in resting conditions. However, the heart rate increase on standing was greater among the hyperreactors and 24-hour heart rate did not differ between the 2 groups. It is noteworthy to observe that patients with increased reactivity to standing had a higher level of 24-hour urinary epinephrine than the rest of the group. Pooled daytime and nocturnal samples were used in the present study to measure catecholamine output to assess the global effect of stressful stimuli over the 24 hours. In agreement with previous results the present data indicate that hyperreactors to standing are characterized by a normal sympathetic activity at rest but an increased sympathetic response to stressors. Indeed, previous studies have shown that plasma catecholamine

concentrations are within the normal range in patients with orthostatic hypertension but increase dramatically after standing up.[10,31] This neurohumoral overshoot seems to be peculiar to young adults whereas a vascular stiffness type seems to be the driving mechanism of orthostatic hypertension in older subjects.[31,33,35] An important role in this context can be played also by unhealthy lifestyle behaviours. Smoking, heavy coffee drinking, and alcohol intake cause an increase in catecholamine excretion,[36,37] and this effect might be detrimental particularly in young hypertensive subjects with increased sympatho-adrenergic reactivity to stressors.[38]

METHODOLOGICAL ISSUES

Hypertension guidelines have never focused on the BP response to standing and orthostatic hypertension has neither been included nor defined in consensus documents. In the absence of standardized accepted definition of BP hyperreactivity to standing, in the present study the 6.5 mm Hg cut point between normoreactors and hyperreactors was identified corresponding to the lower limit of the top systolic BP decile. This cutoff is similar to that used in the CARDIA and other studies (5 mm Hg)[11,32,39] but lower than that adopted in other studies especially in older people.[13,35] Some studies used arbitrary combinations of systolic and diastolic BP cutoffs.[40]

Another important issue with orthostatic BP assessment is for how long standing BP should be measured after the positional change. BP soon after standing is subject to wide fluctuations due to the immediate withdrawal of cardiac vagal activity and subsequent sympathetic activation.[4,31,33] Most previous studies have used the mean of 2 measurements[11,13,29] or even a single measurement[40] immediately after standing up. The present results indicate that from a prognostic standpoint 3 standing BP measurements are needed to estimate orthostatic BP and that the third measurement (3 minutes after the positional change) provides the best prognostic information. As the between-visit reproducibility was only fair according to κ statistics, we recommend that the BP response to standing be assessed on at least 2 visits.

Limitations

We acknowledge that the present study has several limitations. First, we enrolled only Whites and could not evaluate whether there was an interaction between the BP response to standing and racial background. Therefore, the present results may not be applicable to other ethnic groups. Second, due to the much lower prevalence of women in the young, stage 1 segment of the hypertensive population we could not estimate differences in the orthostatic hyperreactivity-MACE association between

men and women. A further limitation may be the relatively small number of MACE due to the young age of our participants. However, to avoid having an overfitted or unstable model a parsimonious multivariable Cox model was developed ensuring that there were >10 events for each variable. Also, we had no updated information on the lifestyle. However, previous long-term analyses of the HARVEST showed that only minor changes in participants' lifestyle habits occurred during the follow-up.[41]

One strength of the present study is the quality of the BP assessment during the positional changes which included 6 BP measurements in the supine and standing positions obtained during 2 visits. In addition, in all participants, BP was measured also with 24-hour ambulatory monitoring.

Perspectives

Among young-to-middle age people, stage 1 hypertension accounts for over 60% of patients with hypertension.[42] It is thus of paramount importance to identify the risk factors implicated in the early development of MACE. The present findings indicate that besides traditional risk factors, including ambulatory BP level and variability, a systolic BP response to standing >6.5 mm Hg is associated with an increased risk of MACE in young hypertensive people. These data expand on previous evidence of the patho-physiological links between sympathetic hyperreactivity and the cardiovascular risk. As orthostatic hyperreactivity is often associated with smoking, alcohol use, and heavy coffee drinking, our efforts should be focused primarily on management of unhealthy lifestyle behaviors. These measures can reduce the risk of developing MACE not only directly but also through a reduction of the BP response to standing. Our results also call for early pharmacological intervention in young hypertensive patients with elevated BP response to standing a condition in which ambulatory hypertension is almost always present. Future hypertension guidelines should encourage measurement of BP on standing also in young individuals and provide a uniform definition of BP hyperreactivity to standing possibly based on risk estimates.

Supplemental Materials

Expanded Materials and Methods
Expanded Results
Tables S1–S6
Figure S1

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