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Normal systolic blood pressure and risk of heart failure in US male physicians

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Aims Heart failure (HF) is a major public health issue and hypertension is a major predictor of HF. Observational studies have demonstrated a continuous and graded relationship between 'normal' systolic blood pressure (SBP) and cardiovascular disease. However, limited data are available on the relationship between normotensive SBP and the risk of HF.

Methods and results To test the hypothesis that there is a graded relation between SBP and HF risk among subjects with normal SBP, we used data on 18 876 participants who were healthy and were free of HF at baseline. Incident HF cases were ascertained by annual follow-up questionnaires and validated through a review of medical records. Cox proportional hazard model was used to compute multivariable-adjusted hazard ratios with corresponding 95% confidence intervals. Between 1982 and 2008, 1098 cases of HF occurred. There was a 35% increased risk of HF among subjects with SBP 130–139 mmHg compared with people with optimal SBP (<120 mmHg). In addition, there was a linear trend in HF risk across the normal range of SBP.

Conclusion Our findings suggest a linear relationship between normotensive SBP and HF risk. Strategies to prevent HF, such as lifestyle modification, should be emphasized across all blood pressure ranges.

Keywords Epidemiology • Heart failure • Blood pressure • Risk factors

Introduction

Heart failure (HF) is a major public health issue in most of the world with 15 million cases in the 51 countries represented by the European Society of Cardiology.[1] With the growing prevalence of cardiovascular risk factors, its impact will only become more pronounced over time. Despite substantial therapeutic advancement for patients with HF, the prognosis after HF diagnosis generally remains poor.[2,3] Therefore, further understanding of those factors that predispose patients to HF is essential to guide strategies for prevention.

Elevated blood pressure confers a two-fold risk for the occurrence of HF and has a substantial population attributable risk.[4–6] Observational studies have demonstrated a continuous and graded relationship between blood pressure and cardiovascular disease[7] as well as an increase in the absolute and relative risk of cardiovascular disease between patients with high-normal systolic blood pressure [specified as a systolic blood pressure (SBP) of 130–139 mmHg] compared with optimal systolic blood pressure (specified as a SBP < 120 mmHg).[8] However, there is only limited information regarding the relationship between SBP within the normal range and HF. The current study prospectively assessed whether there is a graded and linear relationship between normotensive SBP and HF. We also investigated whether the SBP–HF relation differs between HF with and without antecedent myocardial infarction.

Methods

The present study analysed data from the Physicians Health Study I (PHS I), which was a randomized, double-blind, placebo-controlled trial in which a 2×2 factorial design was used to study low-dose aspirin and beta carotene for the primary prevention of cardiovascular disease and cancer among US male physicians. A detailed description

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of PHS I has been previously published.[9] For the present study, we excluded patients with a known diagnosis of HF at the baseline examination (0.3%), missing data on SBP at the baseline examination (14%), and missing covariate data (2.3%), leaving a final sample of 18 876 male physicians. Each participant gave written informed consent, and the study protocol was approved by the institutional review board at Brigham and Women's Hospital, Boston, MA, USA.

Systolic blood pressure was self-reported on a standard questionnaire, at baseline, 24 months, and 84 months after enrolment. Validation of self-reported blood pressure in the PHS has been previously reported.[10]

Ascertainment of outcomes, including HF, in the PHS has been obtained through yearly questionnaires, and has been previously described.[11] Specifically, a questionnaire was mailed to each participant every 6 months during the first year and annually thereafter. In a subset of these physicians, the HF diagnoses had been previously confirmed with the use of the Framingham criteria.[11,12] In addition, we also assessed the validity of self-reported incident HF by reviewing medical records of subjects with a diagnosis of HF that occurred up to 30 days before a hospitalization for myocardial infarction or stroke. Two physicians (one general internist and a cardiologist) independently reviewed 55 charts that met the above criteria. A diagnosis of HF was made if there was sufficient evidence in the chart; this included (i) a diagnosis of HF on the discharge summary, (ii) major signs and symptoms from the Framingham criteria for a HF diagnosis, (iiii) chest X-ray evidence for congestive HF, (iv) minor signs and symptoms with concomitant treatment for HF (use of diuretics, digoxin in the absence of atrial fibrillation, angiotensin converting-enzyme inhibitors, angiotensin receptor blockers, and beta-blockers). Using all of these criteria, HF was confirmed in 50 out of 55 cases (~91%). There was excellent agreement between the two examiners (kappa = 92.3%) in that only one case of self-reported HF was confirmed by one of the two physicians. The latter case was then re-reviewed by both physicians who concluded that there was sufficient evidence for the HF diagnosis (a discharge summary indicating prevalent HF).

Demographic data were collected at baseline. Information on co-morbid illness including type 2 diabetes mellitus, atrial fibrillation, and angina has been collected through annual follow-up questionnaires. Information on physical activity, smoking, alcohol use, egg consumption, breakfast cereal consumption, and body mass index were obtained at baseline.

We classified each subject into categories of SBP. For participants with normotensive SBP (SBP $<$ 140 and not receiving antihypertensive medications), categories included SBP of $<$120, 120–129, and 130–139 mmHg. For participants with hypertensive SBP (SBP $\geq$ 140 mmHg or receiving treatment for hypertension), categories included SBP of $<$130, 130–139, 140–149, 150–159, and $\geq$160 mmHg. Subjects that were not receiving blood pressure medications and whose SBP was below 120 mm Hg were used as the reference group for all analyses. We computed person-time of follow-up from baseline blood pressure to the first occurrence of HF, death, date of the receipt of the last follow-up questionnaire, or censoring date (March 2008). Within each SBP group, we computed the incidence rate of HF by dividing the number of cases by the corresponding person-time. We used Cox proportional hazards model to compute multivariable-adjusted hazard ratios with corresponding 95% confidence intervals. We assessed confounding by using a 10% change in hazard ratio. Assumptions for the proportional hazards models were tested by including main effects and product terms of covariates and time factor. These assumptions were met as all *P*-values were $>$0.05. The initial model adjusted only for age (categorical). The fully adjusted model also controlled for body mass index ($<$25, 25–29.9, and 30+ kg/m^2), smoking (never, former, or current smoker), alcohol use ($<$1 drink/week, 1–4 drinks/week, 5–7 drinks/week, and $\geq$8 drinks/week), physical activity ($<$1 time/week, 1–4 times/week, or $\geq$4 times/week), consumption of breakfast cereals (none, up to 1/week, 2–6/week, and $\geq$7/week), egg consumption (none, up to 1/week, 2–6/week, and $\geq$7/week), aspirin arm (yes/no), and history of atrial fibrillation or diabetes.

In secondary analyses, we examined the relationship between SBP and HF in patients with and without a history of antecedent myocardial infarction. We also repeated the main analysis using updated blood pressure measurements at 24 and 84 months in a time-dependent Cox model. In addition, we re-analysed the data by grouping subjects with hypertensive SBP according to whether they were receiving blood pressure medication or not (given the known increase in risk of overall cardiovascular disease in patients treated as opposed to untreated for hypertension). All analyses were completed with the use of SAS, version 9.1 (SAS Institute, Cary, NC, USA). The significance level was set at 0.05. All authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Among the 18 876 participants from the PHS I, the mean age at randomization was 53.8 $\pm$ 9.5 years. *Table 1* presents baseline characteristics of the study participants according to SBP category. Higher blood pressure was significantly associated with older age; higher body mass index; higher prevalence of diabetes; lower percentage of regular exercise; and lower percentage of breakfast cereal use. During an average follow-up of 20.7 years, 1098 new cases of HF occurred.

For normotensive SBP participants (SBP $<$ 140 mmHg and not receiving treatment for hypertension), the crude incidence rates for HF were 14.9, 18.5, and 29.5 per 10 000 person-years for the SBP categories of $<$120, 120–129, and 130–139 mmHg, respectively. In a multivariable Cox regression model adjusted for age, body mass index, smoking, alcohol use, physical activity, egg consumption, breakfast cereal intake, aspirin arm, diabetes, and atrial fibrillation, hazard ratios (95% CI) for HF were 1.0 (reference), 1.10 (0.89–1.37), and 1.35 (1.09–1.68) for the normotensive SBP categories of $<$120, 120–129, and 130–139 mmHg, respectively. In trend models, an increase in the risk of HF was seen across the normotensive SBP categories (*P* for linear trend = 0.009) (*Table 2*).

For patients with hypertensive SBP (SBP $\geq$ 140 or receiving treatment for hypertension), the crude incidence rates of HF were 34.0, 54.0, 48.2, 77.6, and 99.3 per 10 000 person-years for the SBP categories of $<$130,130–139, 140–149, 150–159, and $>$160 mmHg, respectively. Compared with the common reference group, multivariable adjusted hazard ratios (95% CI) were 1.91 (1.36–2.68), 2.61 (2.04–3.34), 2.04 (1.63–2.55), 2.66 (1.99–3.55), and 3.42 (2.33–5.04) for the hypertensive SBP categories of $<$130, 130–139, 140–149, 150–159, and 160 mm Hg, respectively (*P* for linear trend $<$ 0.0001).

In subjects with normotensive SBP, additional adjustment for SBP as a time-dependent covariate led to a hazard ratio of 1.17 (0.91–1.51) for subjects with SBP between 120 and 129 mmHg

Table 1 Baseline characteristics of the 18 876 US male physicians according to systolic blood pressure

	Systolic blood pressure						
	Normotensive and not on treatment			SBP ≥ 140 mmHg or treated for hypertension			
Characteristics	<120 (N = 3888)	120–129 (N = 6023)	130–139 (N = 3992)	<130 (N = 666)	130–139 (N = 1207)	140–149 (N = 2265)	150–159 (N = 591)	>160 (N = 244)
Age (years)	51.0. ± .8.3	51.9 ± 8.7	54.3 ± 9.5	53.8 ± 8.4	55.9 ± 9.2	58.5 ± 10.0	62.6 ± 9.2	65.7 ± 9.5
Body mass index (kg/m^2)	24.0 ± 2.4	24.5 ± 2.5	25.1 ± 2.8	25.1 ± 2.9	25.5 ± 2.9	25.6 ± 3.1	25.9 ± 3.3	26.1 ± 3.8
Systolic BP (mmHg)	111.0 ± 5.1	121.9 ± 2.8	131.6 ± 2.6	121.0 ± 5.0	132.3 ± 2.9	141.0 ± 2.2	151.1 ± 2.2	164.5 ± 7.5
Diastolic BP (mmHg)	71.3 ± 6.2	77.3 ± 5.2	80.3 ± 4.5	81.6 ± 6.9	85.8 ± 5.6	85.0 ± 6.1	87.7 ± 6.6	89.7 ± 9.9
Current drinkers (%)	71.1	74.4	74.9	72.5	74.0	75.4	77.0	71.7
Current smokers (%)	9.3	10.7	11.9	8.9	10.6	12.9	13.0	17.2
Exercise ≥1/week (%)	89.0	88.1	87.4	86.0	83.8	82.9	81.4	78.7
Diabetes (%)	1.0	1.9	3.0	3.9	3.8	6.1	9.3	11.9
Atrial fibrillation (%)	1.4	1.4	1.5	2.0	1.8	1.9	1.7	1.2
ASA arm (%)	50.2	49.7	49.9	49.9	50.2	49.0	50.1	57.0
Breakfast cereal (%)	75.6	72.6	70.8	69.7	67.5	69.3	70.0	68.9
Eggs ≥2 per week (%)	46.2	46.4	47.3	46.6	47.6	50.7	50.4	52.5

and 1.36 (1.05, 1.77) for subjects with SBP between 130 and 139 mmHg. Despite the slight increase in hazard ratios, the trend across the normotensive SBP categories remained unchanged.

Of the 1098 total cases of HF, 171 (15.6%) had antecedent myocardial infarction and 927 (84.4%) did not have antecedent myocardial infarction. Similar inference could be made for HF without and with antecedent myocardial infarction (*Table 3*). Our analysis using treatment status to reclassify subjects with hypertensive SBP showed a continuous increase in the risk of HF across categories of SBP as expected (P for trend < 0.0001, *Table 4*). Of note, 397 subjects were excluded from this analysis due to conflicting information on blood pressure medication and reported SBP.

Discussion

Although hypertension is a well-established risk factor for HF, limited information is available on the relationship between SBP within the normal range and the risk of HF. In this prospective study, we found evidence for a positive association between SBP and HF risk among normotensive subjects not receiving treatment for hypertension. Among subjects with a SBP between 130 and 139 mm Hg, there was a significantly increased risk of HF as well as a linear trend in HF risk across normotensive SBP categories. In both HF with and without antecedent myocardial infarction, we found suggestive evidence for an increased risk of HF (albeit non-statistically significant) in people with SBP between 130 and 139 mmHg with a similar positive trend in the hazard ratios across the normotensive SBP categories. In addition, our findings confirm the previously reported two-fold increased risk of HF in subjects with hypertensive SBP.

The association between hypertension and HF was persuasively demonstrated in the Framingham Heart Study.[5] Hypertension (SBP > 140 mmHg) as opposed to 'normal' blood pressure (SBP < 140 mmHg) was associated with a two-fold increased risk of HF in men. Furthermore, a gradient of risk was seen between those patients with stage I hypertension (SBP 140–149 or diastolic blood pressure 90–99 mmHg in patients not receiving treatment) vs. stage II hypertension (SBP > 160 mmHg or diastolic blood pressure > 100 mmHg or the current use of antihypertensive medications). In another study, the Framingham investigators examined the risk of HF due to SBP, pulse pressure, and diastolic blood pressure, and as opposed to their prior study, they included normotensive individuals[13] SBP was divided into the following tertiles with tertile 1 as the reference: 87–125 mmHg, 126–141 mmHg, and ≥142 mmHg. In age-adjusted analysis, there was a suggestive trend towards an increased risk of HF within the normotensive group (although it did not reach statistical significance). Our study expands upon these findings. The significant larger size of the PHS cohort may have allowed us to see a statistically significant increase in risk among subjects with a SBP between 130 and 139 mmHg as the second tertile of SBP in the Framingham study covers a large range of SBP from 126 to 141 mmHg. Although this range is similar to the JNC VII category of prehypertension (SBP 120–139 mmHg), our findings demonstrate that there is likely a gradient of risk even within this JNC categorization. Further advantages of our study over the previous findings

Table 2 Incidence rates and hazard ratios (95% CI) of heart failure according to systolic blood pressure category

Systolic blood pressure (mmHg)	Cases	Crude incidence rate (cases /10 000 PY)	Hazard ratio (95% CI)	
			Age adjusted	Model 1[a]
Normotensive and no treatment for hypertension				
<120	128	14.9	1.0	1.0
120–129	240	18.5	1.16 (0.94–1.44)	1.10 (0.89–1.37)
130–139	243	29.5	1.55 (1.25–1.92)	1.35 (1.09–1.68)
SBP ≥ 140 mmHg or treated for hypertension				
<130	46	34.0	1.91 (1.36–2.68)	1.71 (1.22–2.40)
130–139	127	54.0	2.61 (2.04–3.34)	2.30 (1.79–2.95)
140–149	204	48.2	2.04 (1.63–2.55)	1.66 (1.32–2.09)
150–159	76	77.6	2.66 (1.99–3.55)	2.02 (1.51–2.71)
>160	34	99.3	3.42 (2.33–5.04)	2.46 (1.67–3.63)

[a]Adjusted for age, smoking, body mass index, alcohol consumption, history of diabetes, history of atrial fibrillation, physical activity, egg intake, aspirin arm, and breakfast cereal intake.

Table 3 Incidence rates and hazard ratios (95% CI) of heart failure in the presence or absence of antecedent myocardial infarction

Systolic blood pressure (mmHg)	Hazard ratio (95% CI)	
	HF without antecedent MI[a] (*N* = 927)	HF with antecedent MI[a] (*N* = 171)
Normotensive and no treatment for hypertension		
<120	1.0	1.0
120–129	1.11 (0.88–1.40)	1.02 (0.57–1.83)
130–139	1.34 (1.06–1.69)	1.48 (0.84–2.62)
SBP ≥ 140 or treated for hypertension		
<130	1.36 (0.91–2.03)	4.09 (2.05–8.16)
130–139	2.16 (1.64–2.83)	3.08 (1.65–5.77)
140–149	1.61 (1.26–2.06)	1.93 (1.07–3.50)
150–159	2.06 (1.50–2.82.)	1.79 (0.79–4.07)
>160	2.31 (1.50–3.56)	3.79 (1.54–9.35)

[a]Adjusted for age, smoking, body mass index, history of diabetes, and history of atrial fibrillation.

include the adjustment for multiple covariates known to be confounders of the relationship between SBP and HF. Finally, information in our study on antecedent myocardial infarction allows further insight into the mechanisms behind the development of HF among initially normotensive individuals.

Although our observational data can only demonstrate an association between systolic pre-hypertension and HF, the following biological mechanisms provide a potential mechanism by which increasing blood pressure might act as a causal agent in the development of HF. Pre-hypertension is known to have an increased risk of cardiovascular morbidity and mortality compared with optimal blood pressure[14] and the mechanism of this risk is assumed to be the same as that of hypertension. In patients with hypertension, both coronary artery disease and abnormal myocardial compliance are known to be in the causal pathway between hypertension and the development of HF. Mirroring this, there is evidence to suggest similar mechanisms to explain our findings of an increased risk of HF among patients with systolic pre-hypertension.

Increased vascular resistance is known to be an important haemodynamic component of elevated blood pressure and over time leads to the development of myocardial hypertrophy. Although myocardial hypertrophy can initially be a compensatory response to the increased wall stress associated with elevated vascular resistance, this process eventually leads to abnormal left ventricular diastolic filling,[15] ultimately culminating in the clinical manifestation of HF. This link is substantiated by the significantly increased risk of HF in patients with LVH.[5] However, these maladaptive changes in the vasculature and myocardium likely begin before the SBP defined as hypertension. In the Framingham population, a continuous association was found between SBP and left ventricular hypertrophy even within SBP ranges traditionally considered 'normal'.[16] This association suggests that LVH is a potential intermediary in the pathway to HF in pre-hypertension as well as hypertension. However, not all patients with elevated blood pressure who develop HF have LVH. Studies have demonstrated that increased vascular stiffness and resistance can lead to abnormal left ventricular wall stress even in the absence of left ventricular hypertrophy.[17,18] These abnormalities in myocardial compliance may be important early steps in the progression from pre-hypertension to the development of HF. Another important link between elevated blood pressure and the development of HF is coronary artery disease. Prior studies have demonstrated an association between pre-hypertension and an increased risk of myocardial infarction,[8,19] a known determinant of future HF. In addition, elevated blood pressure is known to be associated with a worse prognosis after a myocardial infarction likely by contributing to poor ventricular remodelling.[20]

The major strength of this study lies in the large sample size allowing sufficient power to detect a clinically meaningful effect and the 20+ years of follow-up time. In addition, the available data on the important confounders strengthened the multivariate

Table 4 Incidence rates and hazard ratios (95% CI) of heart failure according to systolic blood pressure categorized by hypertensive treatment status (*N* = 18 479)

Systolic blood pressure (mmHg)	Cases	Crude incidence rate (cases/ 10 000 PY)	Hazard ratio (95% CI) age adjusted	Hazard ratio (95% CI) model 1*
Normotensive				
<120	128	14.9	1.0	1.0
120–129	240	18.5	1.16 (0.94–1.44)	1.10 (0.89–1.37)
130–139	243	29.5	1.55 (1.25–1.92)	1.35 (1.09–1.68)
Hypertensive				
Untreated				
140–149	105	39.1	1.74 (1.34–2.25)	1.44 (1.12–1.88)
>150	36	56.3	1.93 (1.33–2.81)	1.47 (1.01–2.14)
Treated				
<140	154	53.7	2.65 (2.10–3.36)	2.33 (1.83–2.95)
140–149	99	64.2	2.52 (1.93–3.29)	1.98 (1.51–2.60)
≥150	74	108.3	3.74 (2.79–5.02)	2.77 (2.06–3.73)

*P for trend <0.0001, adjusted for age, smoking, body mass index, alcohol consumption, history of diabetes, history of atrial fibrillation, physical activity, egg intake, aspirin arm, and breakfast cereal intake.

analysis. However, our study has some limitations. The population of the PHS is limited to US male physicians who may have somewhat different lifestyles and behaviours than the general population as supported by a lower prevalence of smoking, diabetes, and obesity and a higher percentage of regular exercise. This, and the lack of adjustment for lifestyle change over time, limits the generalizability of our study. Another potential limitation is the lack of echocardiography data that could have provided further information on ejection fraction and valvular heart disease. Misclassification bias is also possible given the self-reporting of the exposure and outcome measure. However, such bias is less likely to have played a major role in our data for the following reasons: first, we validated self-reported HF with a very good accuracy. Second, blood pressure assessment was obtained prior to the development of HF, suggesting that any bias in reporting blood pressure is more likely to be non-differential and thus bias the results towards the null. Third, other investigators have reported a good accuracy of self-reported BP among physicians.[9] Finally, it is possible that residual confounding may be present due to changes in SBP over the course of follow-up. Of note, our time-dependent Cox model, using updated SBP measurements at 24 and 84 months, did not significantly change the hazard ratios for HF.

In conclusion, our findings are suggestive of a gradient of HF risk within the normal SBP range. Further research is needed to determine whether lowering of SBP within the normal range would prevent HF. However, lifestyle modifications to prevent HF should be emphasized across the entire range of blood pressure.

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