

Systolic Blood Pressure, Diastolic Blood Pressure, and Pulse Pressure as Predictors of Risk for Congestive Heart Failure in the Framingham Heart Study

Agha W. Haider, MD, PhD; Martin G. Larson, ScD; Stanley S. Franklin, MD; and Daniel Levy, MD

Background: Although hypertension is a principal precursor of congestive heart failure (CHF), the separate relations of systolic, diastolic, and pulse pressure with risk for heart failure have not been fully elucidated.

Objective: To examine the value of blood pressure predictors of heart failure.

Design: Community-based inception cohort study.

Setting: Framingham, Massachusetts.

Patients: 2040 free-living Framingham Heart Study participants (mean age, 61 years [range, 50 to 79 years]).

Measurements: The association of baseline systolic, diastolic, and pulse pressure with risk for incident CHF was examined in 894 men and 1146 women. Framingham Heart Study participants free of CHF at the baseline examination (performed from 1968 to 1973) were monitored for up to 24 years (mean, 17.4 years) for new-onset heart failure. Cox proportional hazards models were used to adjust for age, sex, smoking, left ventricular hypertrophy, body mass index, diabetes mellitus, high-density lipoprotein cholesterol level, and heart rate; hazard ratios and 95% CIs for blood pressure variables were estimated.

Results: CHF developed in 234 participants (11.8%) during the follow-up period. All three blood pressure components were related to the risk for CHF, but the relation was strongest for systolic and pulse pressure. A 1-SD (20 mm Hg) increment in systolic pressure conferred a 56% increased risk for CHF (hazard ratio, 1.56 [95% CI, 1.37 to 1.77]); similarly, a 1-SD (16 mm Hg) increment in pulse pressure conferred a 55% increased risk for CHF (hazard ratio, 1.55 [CI, 1.37 to 1.75]). These associations were unrelated to age, duration of follow-up, and initiation of treatment for hypertension during follow-up; they were also observed in patients with systolic hypertension (systolic blood pressure \geq 140 mm Hg) at the baseline examination (hazard ratio, 1.41 [CI, 1.18 to 1.69] for pulse pressure and 1.42 [CI, 1.14 to 1.76] for systolic pressure).

Conclusions: Although each component of blood pressure was associated with risk for CHF, pulse and systolic pressure conferred greater risk than diastolic pressure. Increased pulse pressure may help identify hypertensive patients at high risk for overt CHF who are candidates for aggressive blood pressure control.

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For author affiliations, see end of text.

Hypertension is the most common risk factor for congestive heart failure (CHF). It confers a twofold risk for the occurrence of CHF and also carries the highest population attributable risk among all risk factors for CHF (1, 2). Placebo-controlled clinical trials in patients with hypertension have demonstrated a consistent reduction in risk for CHF attributable to the lowering of elevated blood pressure (3–6). The causal role of hypertension in the pathogenesis of CHF underscores the need to identify high-risk patients because early treatment may prevent or delay the occurrence of CHF (2, 7).

The prognostic significance of systolic and diastolic blood pressure in CHF has been reported. However, blood pressure may also be divided into two other components: steady (mean arterial pressure) and pulsatile (pulse arterial pressure) (8–10). Pulse pressure, a simple correlate of conduit vessel stiffness, is associated with left ventricular hypertrophy (11). Increased pulse pressure has also been implicated in the development and progression of large-vessel atherosclerosis and small-vessel disease (12–14). Accumulating evidence indicates that pulse pressure (defined as the difference between systolic and diastolic blood pressure) may be an important predictor of cardiovascular events (15–18). Pulse pressure predicts the risk for CHF in elderly persons (19, 20); however, the association of pulse pressure

with CHF in middle-aged men and women has not been examined.

The Framingham Heart Study provides an opportunity to examine the long-term associations of systolic, diastolic, and pulse pressure with the new onset of CHF in middle-aged and elderly men and women. Blood pressure and traditional risk factors have been measured repeatedly at serial examinations in this community-based cohort with long-term follow-up. We examined systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for CHF in the Framingham Heart Study.

METHODS

The Framingham Heart Study, which began in 1948, has followed 5209 participants (28 to 62 years of age at entry to the study) as part of a prospective epidemiologic study of cardiovascular disease. Enrollment criteria and study design have been published previously (21). Biennial follow-up visits included a medical history, physical examination, blood pressure measurements, 12-lead electrocardiography, and laboratory tests. Eligibility requirements for inclusion in our study were as follows: Participants had to be free of coronary heart disease and CHF and not be receiving antihypertensive therapy at Framingham Heart

Study clinic baseline examinations 10, 11, or 12 (1968 to 1973). Participants were followed for onset of CHF through mid-1994.

We obtained data for selected risk factors from the baseline examination. Methods for assessing risk factors have been published previously (21, 22). Risk factors, including age, sex, cigarette smoking, heart rate, antihypertensive medication use, and total and high-density lipoprotein cholesterol levels, were assessed. Sitting systolic and diastolic blood pressure were measured twice by the examining physician (using a mercury column sphygmomanometer) and averaged. We used body mass index (kg/m^2) as a measure of obesity. Participants were categorized as smokers if they smoked cigarettes regularly within the 1-year period before the baseline examination. Electrocardiography revealed left ventricular hypertrophy when increased voltage was associated with major ST-T repolarization changes ("strain" pattern) (22). Diabetes mellitus was defined on the basis of a fasting blood glucose level greater than 7.77 mmol/L (>140 mg/dL), two random nonfasting blood glucose levels greater than 11.10 mmol/L (>200 mg/dL), or the use of insulin or an oral hypoglycemic agent.

Diagnostic criteria for CHF have been described previously (21, 22). At each clinic examination, a history of interim hospitalizations and symptoms of CHF were obtained. Outside medical records of participants who did not attend an examination were evaluated for incident CHF. All suspected interim events were reviewed by a panel of three physicians who evaluated relevant Framingham Heart Study clinic notes, outside physician reports, and hospitalization records. Congestive heart failure was diagnosed when at least two major or one major and two minor criteria were present. Minor criteria were considered only if their presence could not be attributed to another disease process. Major criteria were paroxysmal nocturnal dyspnea, pulmonary rales, distended jugular veins, enlarging heart size on chest radiography, acute pulmonary edema, hepatojugular reflux, third heart sound, jugular venous pressure of 16 cm or greater, and weight loss of 4.5 kg or greater in response to diuresis. Major criteria also included pulmonary edema, visceral congestion, or cardiomegaly on autopsy. Minor criteria were bilateral ankle edema, nocturnal cough, shortness of breath on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by one third from the previous maximum recorded value, and heart rate of 120 beats/min or more.

Statistical Analysis

We used multivariable Cox proportional hazards regression models to examine the relations of systolic, diastolic, and pulse pressure with CHF. After accounting for age and sex and using a P value less than 0.15 as the selection criterion, we determined covariates by stepwise selection from the following list: body mass index, diabetes, smoking status, total cholesterol level, high-density li-

Context

Hypertension is a recognized risk factor for the development of congestive heart failure (CHF). By measuring blood pressure, however, we have not yet been able to understand the significance of pulse pressure as a contributor to CHF in middle-aged men and women.

Contribution

Using data from the Framingham Heart Study, the authors found that although elevations of systolic, diastolic, and pulse pressure were all related to the risk for CHF, the relation was strongest for systolic and pulse pressure.

Cautions

Understanding the relationships between systolic, diastolic, and pulse pressure and risk for CHF is helpful; however, they do not help determine the increased risk faced by a person with systolic hypertension who also has increased pulse pressure.

—The Editors

poprotein (HDL) cholesterol level, total-HDL cholesterol ratio, left ventricular hypertrophy, and heart rate. Only total cholesterol level and total-HDL cholesterol ratio did not enter the model. After accounting for relevant covariates, we used Cox proportional hazards models to obtain hazard ratio estimates with 95% CIs for standardized values of systolic, diastolic, and pulse pressure. These estimates were obtained individually and pairwise by using SAS software (SAS Institute, Inc., Cary, North Carolina) (23). We repeated analyses for participants stratified according to hypertension status and sex. Because blood pressure and age are correlated, we conducted separate analyses for participants younger than 60 years of age and 60 years of age and older. To examine constancy of effects over time, follow-up was divided into early and late periods (<10 years, ≥ 10 years), and hazard ratios were calculated separately for early and late follow-up. In addition, we analyzed blood pressure as a time-varying covariate and assessed the effect of antihypertensive treatment after the baseline blood pressure measurements. We used the Kaplan-Meier method to plot age- and sex-standardized cumulative incidence rates for CHF as a function of pulse pressure tertile at baseline. Descriptive data are presented as percentages or means (\pm SD). A P value less than 0.05 was considered statistically significant.

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The funding sources had no role in the design, conduct, analyses, and reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

A total of 894 men and 1146 women, age 50 to 79 years, fulfilled criteria for inclusion in our study. **Table 1** presents baseline clinical characteristics for these persons.

Table 1. Baseline Clinical Characteristics of the Study Participants*

Variable	Total Participants (n = 2040)	Men (n = 894)	Women (n = 1146)
Age, y	61 ± 8	61 ± 8	61 ± 8
Smoking, %	33	36	32
Diabetes mellitus, %	7	7	7
Total cholesterol level, mmol/L (mg/dL)	5.98 ± 1.09 (231 ± 42)	5.70 ± 1.04 (220 ± 40)	6.22 ± 1.06 (240 ± 41)
High-density lipoprotein cholesterol level, mmol/L (mg/dL)	1.37 ± 0.41 (53 ± 16)	1.19 ± 0.34 (46 ± 13)	1.50 ± 0.41 (58 ± 16)
Body mass index, kg/m ²	26.1 ± 3.9	26.7 ± 3.6	25.6 ± 4.2
Left ventricular hypertrophy on ECG, %	3	3	3
Heart rate, beats/min	76 ± 13	73 ± 13	78 ± 13
Systolic blood pressure, mm Hg	136 ± 20	136 ± 19	135 ± 21
Diastolic blood pressure, mm Hg	79 ± 10	80 ± 10	78 ± 10
Pulse pressure, mm Hg	57 ± 16	56 ± 15	57 ± 16

* Values presented with plus/minus signs are the mean ± SD. ECG = electrocardiography.

During 35 497 person-years of follow-up (mean, 17.4 years [range, 0.06 to 24 years]), CHF developed in 234 (11.8%) persons. Myocardial infarction preceded CHF in 59 (25%) persons.

Increments of 1 SD in systolic pressure, pulse pressure, and diastolic pressure were associated with hazard ratios for congestive failure of 1.56, 1.55, and 1.24, respectively, after adjustment for age, sex, smoking, left ventricular hypertrophy, body mass index, diabetes mellitus, HDL cholesterol level, and heart rate (Table 2). When blood pressure tertiles were used, similar associations were observed among various components of blood pressure and CHF. No threshold effect or J-shaped association was documented (Table 2). The cumulative incidence of CHF according to tertiles of baseline pulse pressure is plotted in the Figure.

The joint influences of different blood pressure components were also examined, with adjustment for the covariates mentioned previously. Of note, correlations among the blood pressure variables ranged from modest to very

high ($r = 0.20$ for diastolic and pulse pressure, $r = 0.65$ for diastolic and systolic pressure, and $r = 0.88$ for systolic and pulse pressure). Diastolic pressure was not significant (hazard ratio, 1.12 [CI, 0.98 to 1.29]) in conjunction with pulse pressure (hazard ratio, 1.51 [CI, 1.33 to 1.72]). Likewise, diastolic pressure was not significant (hazard ratio, 0.86 [CI, 0.72 to 1.03]) in conjunction with systolic pressure (hazard ratio, 1.71 [CI, 1.45 to 2.01]), but joint estimates were less stable than those obtained for individual pressure variables. Finally, because of colinearity, joint estimation of coefficients for systolic and pulse pressures was highly unstable, resulting in unreliable parameter estimates and SEs (not shown).

When we stratified patients by age, 74 of 1007 patients younger than 60 years of age at baseline had CHF; 160 of 1033 patients 60 years of age or older at baseline had CHF. Hazard ratios were significantly greater than 1.0 in both age groups for all blood pressure components, except diastolic blood pressure for patients younger than 60 years of age (Table 3). Hazard ratios did not differ significantly between the two age groups for any blood pressure component (systolic pressure, $P = 0.13$; diastolic pressure, $P > 0.2$; pulse pressure, $P > 0.2$). During the first 10 years of follow-up, 70 of 2040 patients developed CHF; among 1700 patients who survived 10 years free of CHF, 164 developed CHF later. During each follow-up period, hazard ratios for each blood pressure component were significantly greater than 1.0, except for diastolic blood pressure during the first 10 years (Table 4). Hazard ratios did not differ significantly between early and late follow-up for any blood pressure component (systolic pressure, $P = 0.20$; diastolic pressure, $P > 0.2$; pulse pressure, $P = 0.07$).

When we stratified the study sample according to systolic hypertension status (≥ 140 mm Hg), systolic and pulse pressure remained predictive of risk for development of CHF among patients with systolic hypertension. In contrast, systolic, diastolic, and pulse pressures were not predictive of risk for CHF among patients with systolic blood pressure less than 140 mm Hg (Table 4). Nonetheless, hazard ratios did not differ significantly between systolic hypertension groups for any blood pressure component

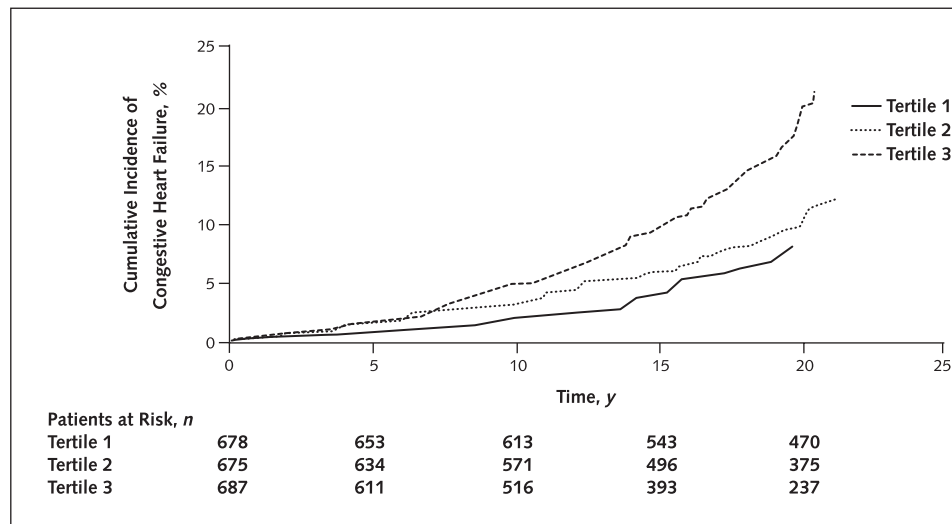
Table 2. Risk Factor–Adjusted Association of Blood Pressure with Congestive Heart Failure

Blood Pressure	Hazard Ratio (95% CI)*	P Value
Continuous variable†		
Pulse (1 SD)	1.55 (1.37–1.75)	<0.001
Systolic (1 SD)	1.56 (1.37–1.77)	<0.001
Diastolic (1 SD)	1.24 (1.08–1.42)	0.002
Categorical variable		
Pulse		
Tertile 1 (26–48 mm Hg)	1 (reference)	
Tertile 2 (49–60 mm Hg)	1.46 (0.98–2.16)	0.06
Tertile 3 (≥ 61 mm Hg)	2.56 (1.75–3.74)	<0.001
Systolic		
Tertile 1 (87–125 mm Hg)	1 (reference)	
Tertile 2 (126–141 mm Hg)	1.48 (0.99–2.21)	0.06
Tertile 3 (≥ 142 mm Hg)	3.07 (2.10–4.49)	<0.001
Diastolic		
Tertile 1 (49–74 mm Hg)	1 (reference)	
Tertile 2 (75–82 mm Hg)	1.33 (0.94–1.87)	0.11
Tertile 3 (≥ 83 mm Hg)	1.67 (1.18–2.37)	0.004

* Adjusted for age, sex, smoking, left ventricular hypertrophy, body mass index, diabetes mellitus, high-density lipoprotein cholesterol level, and heart rate.

† Values of 1 SD were 16 mm Hg for pulse pressure, 20 mm Hg for systolic pressure, and 10 mm Hg for diastolic pressure.

Figure. Cumulative incidence of congestive heart failure according to pulse pressure tertiles at the baseline examination.



Tertile 1 was defined as pulse pressure of 26 to 48 mm Hg, tertile 2 was defined as pulse pressure of 49 to 60 mm Hg, and tertile 3 was defined as pulse pressure of 61 to 150 mm Hg.

(systolic pressure, $P > 0.2$; diastolic pressure, $P > 0.2$; pulse pressure, $P > 0.2$).

In secondary analyses, hazard ratios and confidence limits were almost identical in separate analyses of men and of women (data not shown). In addition, interim myocardial infarction was highly significant as a time-dependent variable, but its inclusion did not materially affect the coefficients for the blood pressure variables. When time-dependent antihypertensive treatment after the baseline examination was included, time-dependent pulse pressure (hazard ratio, 1.27 [CI, 1.14 to 1.42]; $P < 0.001$) and time-dependent systolic pressure (hazard ratio, 1.23 [CI, 1.09 to 1.39]; $P < 0.001$) remained significant predictors of CHF, but time-dependent diastolic pressure was not (hazard ratio, 0.96 [CI, 0.85 to 1.10]; $P = 0.58$). Finally, among patients with systolic blood pressure of 140 mm Hg or higher, we jointly estimated coefficients for pairs of blood pressure variables. Coefficients for systolic and diastolic pressures were equal in magnitude but opposite in sign, indicative of a pulse pressure effect. When diastolic and pulse pressures were included, pulse pressure ($P < 0.001$) but not diastolic pressure ($P > 0.2$) was asso-

ciated with risk for CHF. When systolic and pulse pressures were included, resulting estimates were unstable.

DISCUSSION

This large population-based study demonstrates that pulse pressure, a simple measure of pulsatile hemodynamic stress and arterial stiffness, is a robust predictor of risk for CHF. This association was independent of age, duration of follow-up, and initiation of treatment for hypertension during follow-up. Pulse pressure was a valuable measure in patients with elevated systolic blood pressure, in whom the magnitude of this association was greater than that of systolic blood pressure and far greater than that of diastolic blood pressure. Our findings suggest that pulse pressure may help identify hypertensive patients at high risk for overt CHF who are candidates for aggressive blood pressure control.

Blood Pressure and CHF

Hypertension is a principal precursor of CHF (1). Although myocardial infarction, diabetes mellitus, valvular heart disease, left ventricular hypertrophy, and cardiomy-

Table 3. Risk Factor–Adjusted Association of Blood Pressure with Congestive Heart Failure, by Age and Follow-up Period

Blood Pressure*	Age, y	Hazard Ratio (95% CI)†	P Value	Follow-up Period, y	Hazard Ratio (95% CI)†	P Value
Pulse (1 SD)	<60	1.40 (1.08–1.83)	0.01	<10	1.31 (1.07–1.60)	0.008
Pulse (1 SD)	≥60	1.60 (1.39–1.85)	<0.001	≥10	1.65 (1.42–1.92)	<0.001
Systolic (1 SD)	<60	1.33 (1.03–1.71)	0.03	<10	1.36 (1.10–1.70)	0.005
Systolic (1 SD)	≥60	1.66 (1.43–1.94)	<0.001	≥10	1.62 (1.39–1.89)	<0.001
Diastolic (1 SD)	<60	1.11 (0.86–1.44)	>0.2	<10	1.21 (0.94–1.55)	0.14
Diastolic (1 SD)	≥60	1.31 (1.11–1.55)	0.002	≥10	1.26 (1.07–1.48)	0.006

* Values of 1 SD were 16 mm Hg for pulse pressure, 20 mm Hg for systolic pressure, and 10 mm Hg for diastolic pressure.

† Adjusted for age, sex, smoking, left ventricular hypertrophy, body mass index, diabetes mellitus, high-density lipoprotein cholesterol level, and heart rate.

Table 4. Risk Factor–Adjusted Association of Blood Pressure with Congestive Heart Failure, by Systolic Hypertension Status*

Systolic Hypertension Status†	Hazard Ratio (95% CI)‡	P Value
Systolic blood pressure ≥ 140 mm Hg§		
Pulse (1 SD)	1.41 (1.18–1.69)	<0.001
Systolic (1 SD)	1.42 (1.14–1.76)	0.002
Diastolic (1 SD)	0.95 (0.78–1.16)	>0.2
Systolic blood pressure < 140 mm Hg		
Pulse (1 SD)	1.15 (0.78–1.71)	>0.2
Systolic (1 SD)	1.26 (0.81–1.95)	>0.2
Diastolic (1 SD)	1.09 (0.81–1.48)	>0.2

* Blood pressure variables were studied individually in separate models.

† Values of 1 SD were 16 mm Hg for pulse pressure, 20 mm Hg for systolic pressure, and 10 mm Hg for diastolic pressure.

‡ Adjusted for age, sex, smoking, left ventricular hypertrophy, body mass index, diabetes mellitus, high-density lipoprotein cholesterol level, and heart rate.

§ 137 events; 774 persons.

|| 97 events; 1266 persons.

opathies also predispose to CHF, the contribution of elevated blood pressure to the risk for developing heart failure in the general population and among persons with hypertension is substantial (1, 2). Several clinical trials have demonstrated that treatment of hypertension decreases the risk for CHF (3–6, 24). A meta-analysis of 12 randomized, placebo-controlled clinical trials reported a 52% reduction in the occurrence of CHF in hypertensive patients who received medication compared with those who received placebo (25). These findings are compatible with the results of a separate meta-analysis of hypertension trials in elderly persons that reported a 47% reduction in the incidence of CHF with the treatment of hypertension (26). Understanding the mechanisms that contribute to the risk for CHF in hypertensive patients may lead to approaches for its prevention and improvements in therapy.

Increasing evidence suggests a link between stiffness of conduit vessels and cardiovascular disease morbidity and mortality (16). Measures of aortic stiffness and pulse pressure have been demonstrated to be associated with left ventricular hypertrophy, myocardial infarction, and stroke in normotensive and hypertensive persons (11, 16, 17, 27, 28). The long-term association between conduit artery stiffness and risk for CHF in the community has not been elucidated despite many studies that suggest an association (15, 18, 19). Age (29), diabetes mellitus (30), hypertension (31, 32), and left ventricular hypertrophy (11) are associated with conduit artery stiffness, and they also are risk factors for CHF (8). Thus, there are several potential explanations for the association between elevated pulse pressure and risk for CHF.

Stiffening of the conduit vessels increases pulse wave velocity, which results in premature return of the reflected pressure wave to the heart during systole (33). The early reflected pressure wave adds to the forward wave and increases load on the heart, whereas the reflected flow wave diminishes forward flow and stroke volume (33). In hypertensive patients, the left ventricle with reduced end-systolic

elastance (7) may be sensitized to this incremental late-systolic load (34), resulting in a reduction in stroke volume (35). Movement of the reflected wave from diastole into systole diminishes coronary perfusion pressure and has been shown to produce ischemia in animal models both with and without epicardial coronary stenoses (36–38). Increased aortic and left ventricular systolic pressures are manifestations of increased left ventricular hemodynamic load; both of these generate increased metabolic demands. Chronic, increased left ventricular pressure may predispose to ventricular hypertrophy, impaired diastolic relaxation, and, ultimately, CHF (39). However, on the basis of our observations, the possibility that pulse pressure is only a marker rather than a link between hypertension and CHF cannot be entirely excluded.

Comparison with Previous Studies

Earlier studies have reported an association of pulse pressure with cardiovascular disease morbidity and mortality (10, 16, 17). Pulse pressure also predicted death after myocardial infarction and recurrent myocardial infarction in an analysis of 2231 patients from the Survival and Ventricular Enlargement (SAVE) study (15) and 6781 patients randomly assigned into the Studies of Left Ventricular Dysfunction (SOLVD) trials (40). Pulse pressure predicted all-cause, cardiovascular, and coronary mortality in 19 083 middle-aged and elderly healthy French men enrolled in a screening program (17). Madhavan and colleagues found that pulse pressure, but not systolic or diastolic blood pressure, was an independent predictor of cardiovascular outcomes in 2207 untreated hypertensive patients who were followed for almost 5 years (28). Similarly, others have demonstrated an independent predictive role of pulse pressure in cardiovascular disease (16, 18, 20, 41, 42).

A recent Framingham investigation found that pulse pressure increases steeply with age, especially after the sixth decade of life, a time when diastolic pressure tends to decline (43). If left untreated, hypertension may accelerate the rate of development of large-artery stiffness (10), which can perpetuate a cycle of increasing systolic hypertension and increased arterial stiffness. These changes could worsen asymptomatic left ventricular dysfunction, culminating in overt CHF when a threshold is exceeded or when other precipitating factors occur concurrently (7). A report from the East Boston Senior Health Project demonstrated an association between increased pulse pressure and CHF in 1621 elderly (mean age, 78 years) men and women (19). Multivariate models adjusted for age, sex, mean blood pressure, history of coronary artery disease, diabetes mellitus, atrial fibrillation, and treatment for hypertension. The East Boston Senior Health Project (19) had a shorter follow-up (3.8 years) and used the diagnosis from the Medicare Provider Analysis and Review file (from the Centers for Medicare & Medicaid Services [formerly the Health Care Financing Administration]) to identify 221 CHF events (International Classification of Diseases,

Ninth Revision, Clinical Modification); nonhospitalized patients with milder CHF may have been missed (44). Similarly, among 2152 participants in the Established Populations for Epidemiologic Study of the Elderly program who were free of coronary disease and CHF at the baseline examination, pulse pressure showed a strong and linear relationship with risk for development of CHF. After adjustment for demographic characteristics, comorbid factors, and risk factors, a 10-mm Hg increment in pulse pressure was associated with a 14% increase in risk for CHF (20).

In our study cohort, pulse pressure emerged as a predictor of risk for CHF in patients with systolic hypertension (≥ 140 mm Hg). In previous reports from Framingham (45) and the East Boston Senior Health Project (19), pulse pressure was found to be a dominant predictor of coronary artery disease and CHF. Unlike the East Boston Senior Health Project (19), we did not document a J-shaped association of diastolic pressure with risk for CHF. Our study confirms a recent study that found a graded and independent association between pulse pressure and incidence of CHF (20).

Strengths and Limitations

The Framingham Heart Study provides a large, population-based sample in which risk factors are routinely assessed and the follow-up is extensive. In this cohort, referral bias is inherently low and the effect of pulse pressure on the development of CHF can be assessed more extensively than through an intervention trial or clinical series. Our study clarifies the independent association of pulse pressure with risk for CHF, especially in participants with systolic hypertension. The CHF criteria used by the Framingham Heart Study are clinical; therefore, the diagnosis of CHF may be subject to misclassification. This fact may have implications for our study because objective criteria for echocardiographic and radiologic imaging were not used to document CHF in this sample. However, throughout the 17 years of follow-up, the same criteria were used to establish the diagnosis of CHF. Our study sample was primarily white; thus, our findings may not apply to other racial and ethnic groups who may have an even greater risk for CHF. However, previous reports from other prospective studies have shown a similar association of pulse pressure with CHF.

Conclusion

In our study sample, although each component of blood pressure was associated with risk for CHF, pulse and systolic pressures conferred the greatest risk. Pulse pressure may help identify hypertensive patients at high risk for overt CHF who are candidates for aggressive blood pressure control. Therapies that improve arterial compliance may have value in the prevention and treatment of CHF in patients with elevated pulse pressure. However, evidence from randomized clinical trials is needed to determine

whether reduction of pulse pressure should be a specific target for the prevention of CHF.

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Requests for Single Reprints: Daniel Levy, MD, Framingham Heart Study, 73 Mount Wayte Avenue, Suite 2, Framingham, MA 01702-5827.

Current author addresses and author contributions are available at www.annals.org.

References

1. Kannel WB, Castelli WP, McNamara PM, McKee PA, Feinleib M. Role of blood pressure in the development of congestive heart failure. The Framingham study. *N Engl J Med*. 1972;287:781-7. [PMID: 4262573]
2. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275:1557-62. [PMID: 8622246]
3. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA*. 1991; 265:3255-64. [PMID: 2046107]
4. Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension. II. Results of long-term therapy. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA*. 1982;248:2004-11. [PMID: 6750167]
5. Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension. I. Results of short-term titration with emphasis on racial differences in response. Veterans Administration Cooperative Study Group on Antihypertensive agents. *JAMA*. 1982;248:1996-2003. [PMID: 6750166]
6. Kostis JB, Davis BR, Cutler J, Grimm RH Jr, Berge KG, Cohen JD, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. *JAMA*. 1997;278:212-6. [PMID: 9218667]
7. Vasan RS, Levy D. The role of hypertension in the pathogenesis of heart failure. A clinical mechanistic overview. *Arch Intern Med*. 1996;156:1789-96. [PMID: 8790072]
8. Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries. 3rd ed. Philadelphia: Lea & Febiger; 1990:216-50.
9. Smulyan H, Safar ME. The diastolic blood pressure in systolic hypertension. *Ann Intern Med*. 2000;132:233-7. [PMID: 10651605]
10. Franklin SS, Weber MA. Measuring hypertensive cardiovascular risk: the vascular overload concept. *Am Heart J*. 1994;128:793-803. [PMID: 7942450]
11. Girerd X, Laurent S, Pannier B, Asmar R, Safar M. Arterial distensibility and left ventricular hypertrophy in patients with sustained essential hypertension. *Am Heart J*. 1991;122:1210-4. [PMID: 1833966]
12. Lyon RT, Runyon-Hass A, Davis HR, Glagov S, Zarins CK. Protection from atherosclerotic lesion formation by reduction of artery wall motion. *J Vasc Surg*. 1987;5:59-67. [PMID: 3795393]
13. Baumbach GL, Siems JE, Heistad DD. Effects of local reduction in pressure on distensibility and composition of cerebral arterioles. *Circ Res*. 1991;68:338-51. [PMID: 1991342]

14. Christensen KL. Reducing pulse pressure in hypertension may normalize small artery structure. *Hypertension*. 1991;18:722-7. [PMID: 1835958]
15. Mitchell GF, Moyé LA, Braunwald E, Rouleau JL, Bernstein V, Geltman EM, et al. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. SAVE investigators. Survival and Ventricular Enlargement. *Circulation*. 1997;96:4254-60. [PMID: 9416890]
16. Darne B, Girerd X, Safar M, Cambien F, Guize L. Pulsatile versus steady component of blood pressure: a cross-sectional analysis and a prospective analysis on cardiovascular mortality. *Hypertension*. 1989;13:392-400. [PMID: 2522417]
17. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetière P, et al. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. *Hypertension*. 1997;30:1410-5. [PMID: 9403561]
18. Lee ML, Rosner BA, Weiss ST. Relationship of blood pressure to cardiovascular death: the effects of pulse pressure in the elderly. *Ann Epidemiol*. 1999;9:101-7. [PMID: 10037553]
19. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. *JAMA*. 1999;281:634-9. [PMID: 10029125]
20. Vaccarino V, Holford TR, Krumholz HM. Pulse pressure and risk for myocardial infarction and heart failure in the elderly. *J Am Coll Cardiol*. 2000;36:130-8. [PMID: 10898424]
21. Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: The Framingham Study. *Am J Public Health*. 1951;41:279-86.
22. Cupples LA, D'Agostino RB, Kannel WB, Wolf P, Garrison RJ, eds. The Framingham Study: An epidemiological investigation of cardiovascular disease. Section 34: Some risk factors related to the annual incidence of cardiovascular disease and death using follow-up repeated biennial measurements. Framingham Heart Study, 30 year follow-up. Publication PB87-177499. Bethesda: National Institutes of Health; 1988.
23. SAS/STAT Software: Changes and Enhancements through Release 6.11. Cary, NC: SAS Institute; 1996:381-490.
24. Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekblom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet*. 1991;338:1281-5. [PMID: 1682683]
25. Moser M, Hebert PR. Prevention of disease progression, left ventricular hypertrophy and congestive heart failure in hypertension treatment trials. *J Am Coll Cardiol*. 1996;27:1214-8. [PMID: 8609345]
26. Cutler J, Psaty BM, MacMahon S, Furberg CD. Public health issues in hypertension control: what has been learned from clinical trials. In: Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis and Treatment*. New York: Raven Pr; 1995:253-70.
27. Kannel WB, Wolf PA, McGee DL, Dawber TR, McNamara P, Castelli WP. Systolic blood pressure, arterial rigidity, and risk of stroke. The Framingham study. *JAMA*. 1981;245:1225-9. [PMID: 7206111]
28. Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension*. 1994;23:395-401. [PMID: 8125567]
29. Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O'Rourke MF. Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. *Circulation*. 1983;68:50-8. [PMID: 6851054]
30. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. *Circulation*. 1995;91:1432-43. [PMID: 7867184]
31. Benetos A, Laurent S, Hoeks AP, Boutouyrie PH, Safar ME. Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral arteries. *Arterioscler Thromb*. 1993;13:90-7. [PMID: 8422344]
32. Bouthier JD, De Luca N, Safar ME, Simon AC. Cardiac hypertrophy and arterial distensibility in essential hypertension. *Am Heart J*. 1985;109:1345-52. [PMID: 3159248]
33. O'Rourke MF, Kelly RP, Avolio AP, Hayward C. Effects of arterial dilator agents on central aortic systolic pressure and on left ventricular hydraulic load. *Am J Cardiol*. 1989;63:381-441. [PMID: 2658528]
34. Kass DA, Saeki A, Tunin RS, Recchia FA. Adverse influence of systemic vascular stiffening on cardiac dysfunction and adaptation to acute coronary occlusion. *Circulation*. 1996;93:1533-41. [PMID: 8608622]
35. Kelly RP, Tunin R, Kass DA. Effect of reduced aortic compliance on cardiac efficiency and contractile function of in situ canine left ventricle. *Circ Res*. 1992;71:490-502. [PMID: 1386792]
36. Watanabe H, Ohtsuka S, Kakihana M, Sugishita Y. Decreased aortic compliance aggravates subendocardial ischaemia in dogs with stenosed coronary artery. *Cardiovasc Res*. 1992;26:1212-8. [PMID: 1288867]
37. Watanabe H, Ohtsuka S, Kakihana M, Sugishita Y. Coronary circulation in dogs with an experimental decrease in aortic compliance. *J Am Coll Cardiol*. 1993;21:1497-506. [PMID: 8473662]
38. Buckberg GD, Fixler DE, Archie JP, Hoffman JI. Experimental subendocardial ischemia in dogs with normal coronary arteries. *Circ Res*. 1972;30:67-81. [PMID: 5007529]
39. O'Rourke MF, Kelly R, Avolio A. *The Arterial Pulse*. Philadelphia: Lea & Febiger; 1992:201-4.
40. Domanski MJ, Mitchell GF, Norman JE, Exner DV, Pitt B, Pfeffer MA. Independent prognostic information provided by sphygmomanometrically determined pulse pressure and mean arterial pressure in patients with left ventricular dysfunction. *J Am Coll Cardiol*. 1999;33:951-8. [PMID: 10091821]
41. Abernethy J, Borhani NO, Hawkins CM, Crow R, Entwisle G, Jones JW, et al. Systolic blood pressure as an independent predictor of mortality in the Hypertension Detection and Follow-up Program. *Am J Prev Med*. 1986;2:123-32. [PMID: 3453169]
42. Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet*. 2000;355:865-72. [PMID: 10752701]
43. Franklin SS, Gustin W 4th, Wong ND, Larson MG, Weber MA, Kannel WB, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation*. 1997;96:308-15. [PMID: 9236450]
44. Lloyd-Jones DM, Martin DO, Larson MG, Levy D. Accuracy of death certificates for coding coronary heart disease as the cause of death. *Ann Intern Med*. 1998;129:1020-6. [PMID: 9867756]
45. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study. *Circulation*. 1999;100:354-60. [PMID: 10421594]