ORIGINAL RESEARCH

Late Systolic Central Hypertension as a Predictor of Incident Heart Failure: The Multi-Ethnic Study of Atherosclerosis

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***Background*—**Experimental studies demonstrate that high aortic pressure in late systole relative to early systole causes greater myocardial remodeling and dysfunction, for any given absolute peak systolic pressure.

***Methods and Results*—**We tested the hypothesis that late systolic hypertension, defined as the ratio of late (last one third of systole) to early (first two thirds of systole) pressure–time integrals (PTI) of the aortic pressure waveform, independently predicts incident heart failure (HF) in the general population. Aortic pressure waveforms were derived from a generalized transfer function applied to the radial pressure waveform recorded noninvasively from 6124 adults. The late/early systolic PTI ratio (L/E_{SPTI}) was assessed as a predictor of incident HF during median 8.5 years of follow-up. The L/E_{SPTI} was predictive of incident HF (hazard ratio per 1% increase=1.22; 95% CI=1.15 to 1.29; $P<0.0001$) even after adjustment for established risk factors for HF (HR=1.23; 95% CI=1.14 to 1.32: $P<0.0001$). In a multivariate model that included brachial systolic and diastolic blood pressure and other standard risk factors of HF, L/E_{SPTI} was the modifiable factor associated with the greatest improvements in model performance. A high L/E_{SPTI} (>58.38%) was more predictive of HF than the presence of hypertension. After adjustment for each other and various predictors of HF, the HR associated with hypertension was 1.39 (95% CI=0.86 to 2.23; $P=0.18$), whereas the HR associated with a high L/E was 2.31 (95% CI=1.52 to 3.49; $P<0.0001$).

***Conclusions*—**Independently of the absolute level of peak pressure, late systolic hypertension is strongly associated with incident HF in the general population. **(*J Am Heart Assoc*. 2015;4:e001335 doi: 10.1161/JAHA.114.001335)**

Key Words: arterial hemodynamics • heart failure • late systolic load • left ventricular afterload

Heart failure (HF) affects ≈2.4% of the US population and 10% of individuals aged >75 years. The burden of HF has increased markedly over the last few years. Data from the American Heart Association[1,2] indicated that the number of new HF cases in the United States increased from 348 000 in 2000 to 670 000 in 2007, representing a 93% increase over this time period. A recent American Heart Association policy statement estimated that the number of people with HF in the United States may increase from 5 million in 2012 to >8 million in 2030.[3] Once HF ensues, mortality is high, with 50% of Medicare beneficiaries not surviving 3 years after an HF hospitalization.[4] Similarly, HF is associated with a markedly impaired quality of life[5–8] and high societal costs.[3] Therefore, characterizing the risk factors for the development of new-onset HF is an important goal, in order to design better preventive strategies.

A series of animal and human studies have linked late systolic load with myocardial remodeling and dysfunction.[9–21] Experimental data in rat models demonstrate that, for any given level of left ventricular (LV) peak systolic pressure, an afterload pattern that results in predominantly late-systolic hypertension, rather than early-systolic hypertension, causes greater LV remodeling and fibrosis.[13] Studies in healthy instrumented dogs have shown that balloon inflations in the ascending aorta during late systole impair diastolic relaxation more than early systolic inflation, for any given increase in

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peak systolic LV pressure.[9,19–21] More recently, it has been shown that late systolic hypertension assessed from a carotid pressure waveform[16] or an invasively measured aortic pressure waveform[18] is associated with impaired early diastolic relaxation in humans. This implicates the loading sequence (early versus late systolic) as a potential mechanistic determinant of myocardial dysfunction in humans, independent of the absolute systolic blood pressure level. However, whether late systolic hypertension predicts the risk of incident HF in the general population is unknown. In this study, we tested the hypothesis that a simple surrogate of the loading sequence, defined as the ratio of late systolic (last one third of systole) to early systolic (first two thirds of systole) pressure-time integrals (PTI) of the central pressure waveform, is independently associated with an increased risk of incident HF in a multiethnic sample from general population free of clinically manifest cardiovascular disease at baseline.

Methods

Study Population

The Multiethnic Study of Atherosclerosis enrolled 6814 men and women aged 45 to 84 years who identified themselves as white, African American, Hispanic, or Chinese and were free of clinically apparent cardiovascular disease, from 6 US communities between 2000 and 2002.[22] The study was approved by the institutional review boards of participating centers, and participants gave informed consent.

Data Collection

Standardized questionnaires were used to obtain information about cardiovascular risk factors and medication use. Resting blood pressure was measured 3 times with subjects in the seated position with a Dinamap-Pro100 oscillometric sphygmomanometer (GE Medical Systems, Waukesha, WI). The average of the last 2 measurements was used. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive medication use.[23] Serum total cholesterol, high-density-lipoprotein (HDL) cholesterol, and glucose were measured after a 12-hour fast. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL or hypoglycemic medication use.[24]

Hemodynamic Measurements

Radial arterial waveforms were recorded during 30 s at baseline, using the HDI/PulseWave-CR2000 tonometry device (Hypertension Diagnostics, Eagan, MN), digitized at 200 Hz and exported for offline processing using custom-designed software written in Matlab (The Mathworks, Natick, MA). All pressure waveforms were visually inspected by an investigator (J.A.C.) for quality and physiologic consistency. We excluded averaged waveforms that met any of the following criteria: (1) A nonphysiologic appearance (usually from bigeminy, trigeminy, or contamination of the signal average by aberrantly recorded complexes); (2) Cardiac cycle duration variation ≥10%; (3) Pulse height (beat-to-beat pulse pressure) variation ≥20%; and (4) Less than 10 adequately recorded cycles available for signal averaging.

A generalized transfer function[25] was applied to the radial pressure waveform to obtain a central pressure waveform, as previously described.[17] The aortic augmentation index was computed as the second/first systolic peak×100. Derived aortic pressure tracings were also analyzed by measuring the area under the central pressure curve (pressure–time integral) during the first (PTI_1), second (PTI_2) and last (PTI_3) one third of systole, as previously described.[16] We computed a dimensionless ratio of $PTI_3/(PTI_1+PTI_2)$ as a quantitative index of late

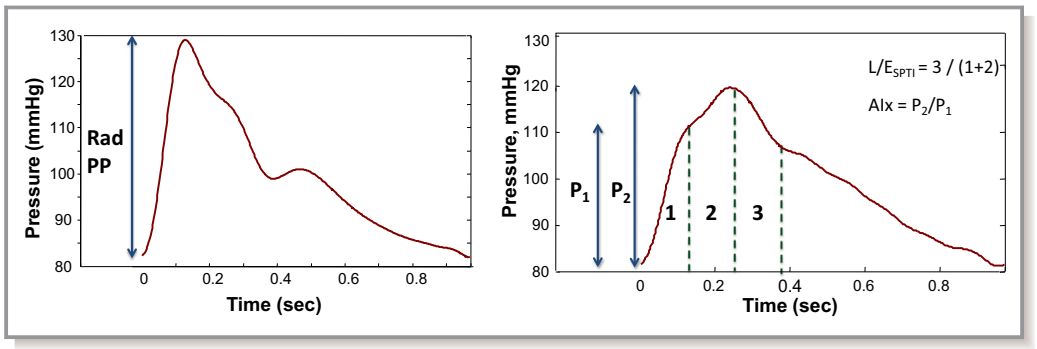

Figure 1. Assessment of early vs late aortic systolic pressure. The tonometric radial pressure waveform (left) is used to derive an aortic pressure waveform (right). The duration of the systolic portion of the aortic pressure waveform was then split in 3 equal tertiles to compute the area under the curve (pressure–time integral [PTI]) corresponding to each tertile (PTI_1, PTI_2, and PTI_3). The late/early systolic PTI (L/E_{SPTI}) was then computed as $PTI_3/(PTI_1+PTI_2)$. AIx indicates augmentation index; P1, first systolic peak; P2, second systolic peak; 1, 2 and 3, 1st, 2nd and 3rd pressure-time integrals of systole, respectively.

systolic hypertension (Figure 1). This ratio, which we call late/early systolic pressure–time-integral (L/E_{SPTI}) was multiplied by 100 and thus represents PTI_3 expressed as a percentage of PTI_1+PTI_2. Examples of central pressure waveforms demonstrating high and low L/E_{SPTI} are shown in Figure 2.

Event Adjudication

In addition to 4 on-site examinations, a telephone interviewer contacted participants every 9 to 12 months to inquire about incident cardiovascular events. Two physicians independently reviewed copies of medical records and death certificates for hospitalizations and outpatient cardiovascular diagnoses, for blinded end-point classification using prespecified criteria.[26] The diagnosis of HF was established by "definite" criteria, which required clinical symptoms (eg, dyspnea) or signs (eg, edema), a physician HF diagnosis, and medical treatment for HF in addition to (1) pulmonary edema/congestion by chest radiograph and/or (2) dilated ventricle or poor LV function by echocardiography or ventriculography, or evidence of LV diastolic dysfunction.

Statistical Analysis

We examined the association between hemodynamic measures and time to HF using the Kaplan–Meier method and Cox regression. Model goodness-of-fit was assessed with the Akaike's information criterion (AIC) and Bayesian information criterion.[27,28] Model discrimination was assessed with the Harrel's *c*-index (which is analogous to the area under the receiver-operator-characteristic curve).[27,29] Improvements in subject reclassification by L/E_{SPTI} were further assessed using the category-free net reclassification improvement,[27,29,30] which depends on the increased probability that a new model will categorize case subjects as higher risk and decreased probability that it will categorize control subjects as lower risk, compared to a base model. We also computed the integrated discrimination improvement, which expresses the improvement in discrimination slopes (mean difference in predicted probabilities between case and control participants) between the base model and new model.[27,29–31] Various indices of model performance were used to (1) assess the added predictive value of L/E_{SPTI}, and (2) compare the predictive value of L/E_{SPTI} to that of well-established risk factors.[27]

We also compared the risk associated with late systolic hypertension (as defined from the L/E_{SPTI}) versus the risk associated with hypertension, defined by standard criteria JNC-7 based on brachial systolic and diastolic blood pressure.[23] We therefore defined a "high" L/E_{SPTI} based on a cut point chosen to match the prevalence of "high L/E_{SPTI}" to the prevalence of hypertension (defined by standard

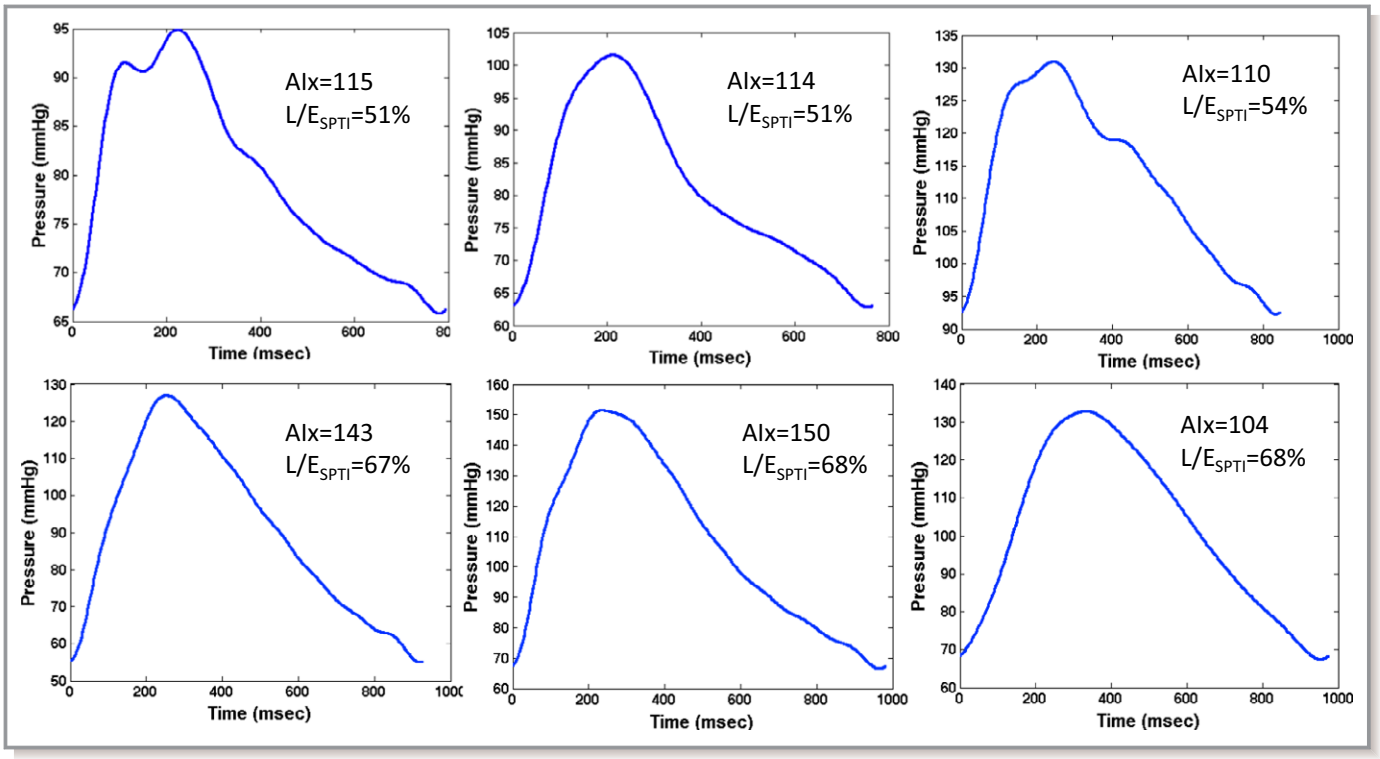

Figure 2. Examples of central pressure waveforms demonstrating a high (top row) and low (bottom row) late/early systolic pressure–time integral (L/E_{SPTI}). AIx indicates Augmentation index.

criteria) in the sample. Since the prevalence of hypertension in the sample at baseline was 45%, a "high L/E_{SPTI}" was defined as a value above the 55th percentile of L/E_{SPTI} (58.38%). Tests were 2-sided with α=0.05. Analyses were performed using SPSS v17 (SPSS Inc, Chicago, IL). Net reclassification improvement and integrated discrimination improvement were computed using the R package survIDINRI.[32]

Results

Of 6336 participants who underwent radial tonometry, 6152 (97.1%) had technically adequate data. Twenty-eight participants had no follow-up information, leaving 6124 participants in the analysis. Table 1 shows baseline characteristics of participants included in this study. The L/E_{SPTI} ratio was weakly correlated with systolic blood pressure (R^2=0.116; P<0.0001), heart rate (R^2=0.11; P<0.0001), age (R=0.15; P<0.0001), and was greater in women (59.9%; 95% CI=59.8 to 60) than men (58.3%; 95% CI=58.2 to 58.4; P<0.0001). A significant difference between men and women was present after adjustment for race, diabetes, blood pressure, body height and weight, smoking, glomerular filtration rate, antihypertensive medication use, total cholesterol and HDL cholesterol (adjusted mean for women=59.4%; 95% CI=59.3 to 59.5; adjusted mean for men=58.8; 95% CI=58.7 to 58.9; P<0.0001).

During the course of follow-up (median: 8.47 years, interquartile range: 7.74 to 8.64), 135 participants experienced a first episode of HF. Hazard ratios (HR) for incident HF associated with a 1% increase in L/E_{SPTI} in unadjusted analysis and various adjusted models are shown in Table 2. Standardized HR (ie, corresponding to 1 SD increase in L/E) are also shown. In unadjusted analyses (Model 1), a greater L/E ratio predicted a higher risk of incident HF (HR per 1% increase=1.22; 95% CI=1.15 to 1.29; P<0.0001). The HR per SD increase in the L/E ratio was 1.74 (95% CI=1.49 to 2.04; P<0.0001). These estimates were robust to multivariable adjustment for various confounders (Models 2 to 4, Table 2). In a model that included age, ethnicity, gender, diabetes mellitus, systolic and diastolic blood pressure, body mass index, antihypertensive medication use, total cholesterol, HDL cholesterol, current smoking, heart rate, estimated glomerular filtration rate, and traditional systolic indices derived from pulse-wave analysis (aortic augmentation index and pulse pressure amplification; Model 4, Table 2), the adjusted HR per 1% increase in the L/E_{SPTI} ratio was 1.24 (1.14 to 1.34:

Table 1. Baseline Characteristics of Study Participants (n=6124)

Characteristic	Median (IQR) or Count (%)
Number of HF events	135 (2.2)
Age, y	62 (53 to 70)
Sex	
Male	2918 (47.6)
Female	3207 (52.4)
Ethnicity	
White	2319 (37.9)
African American	1659 (27.1)
Chinese American	751 (12.23)
Hispanic American	1396 (22.8)
Body mass index, kg/m^2	27.5 (24.5 to 31.2)
Total cholesterol, mg/dL	192 (171 to 215)
LDL cholesterol, mg/dL	116 (96 to 136)
HDL cholesterol, mg/dL	48 (40 to 59)
Triglycerides, mg/dL	111 (78 to 160)
Diabetes mellitus	776 (12.7)
Current smoking	2222 (36.3)
Hypertension	2729 (44.6)
Estimated glomerular filtration rate, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	79.7 (69.6 to 92)
Hypertension medication use	2269 (37.0)
Brachial SBP, mm Hg	123.5 (111 to 139.5)
Brachial DBP, mm Hg	72 (65 to 78.5)
L/E_{SPTI}, %	59 (57.2 to 60.9)
Heart rate, bpm	63 (57 to 70)

DBP indicates diastolic blood pressure; HDL, high-density lipoprotein; HF, heart failure; IQR, interquartile range; L/E_{SPTI}, late/early systolic pressure–time integral; LDL, low-density lipoprotein; SBP, systolic blood pressure.

Table 2. Results of Cox Proportional Hazards Models Examining the Relationship Between the L/E_{SPTI} at Baseline and the Risk of Heart Failure During Follow-Up (Number of Events=135)

	Hazard Ratio Per 1% Increase in L/E_{SPTI} (95% CI)	Standardized Hazard Ratio (95% CI)*	P Value
Model 1	1.22 (1.15 to 1.29)	1.74 (1.49 to 2.04)	<0.0001
Model 2	1.27 (1.18 to 1.36)	1.95 (1.60 to 2.36)	<0.0001
Model 3	1.22 (1.14 to 1.32)	1.76 (1.44 to 2.16)	<0.0001
Model 4	1.24 (1.14 to 1.34)	1.82 (1.45 to 2.28)	<0.0001

Model 1 is unadjusted (n=6124). Model 2 (n=6124) is adjusted for age, ethnicity, gender, and heart rate. Model 3 (n=6107) is additionally adjusted for diabetes mellitus, systolic and diastolic blood pressure, and body mass index. Model 4 (n=6098) is additionally adjusted for antihypertensive medication use, total cholesterol, HDL cholesterol, current smoking, estimated glomerular filtration rate, aortic augmentation index, and aortic-to-radial pulse pressure amplification. HDL indicates high-density lipoprotein; L/E_{SPTI}, late/early systolic pressure–time integral.

*The standardized hazard ratio (HR) is the HR per 1-SD increase in L/E_{SPTI}. The SD for L/E_{SPTI} is 2.8%.

$P<0.0001$) and the standardized HR was 1.82 (95% CI=1.45 to 2.28). In this model, neither aortic augmentation index (standardized HR=0.94; 95% CI=0.76 to 1.15; $P=0.53$) nor pulse pressure amplification (standardized HR=0.94; 95% CI=0.73 to 1.33; $P=0.94$) were predictive of incident HF.

Table 3 shows the significant predictors of HF in model 4, along with standardized HR, Wald statistics, and other measures of improvements in model performance (Bayesian information criterion, Akaike's information criterion, and *c*-index) by each significant independent predictor of HF in this model. Of all the variables in this model, L/E_{SPTI} was the modifiable factor associated with the highest standardized HR, Wald statistic, the greatest reduction in Akaike's information criterion and Bayesian information criterion, and the greatest improvements in *c*-statistics. These improvements in model performance were also greater than those provided by both systolic and diastolic blood pressure together (bottom of Table 3). The addition of L/E_{SPTI} to a model containing all other variables shown in Table 3 resulted in a category-free net reclassification improvement of 0.24 (95% CI=0.05 to 0.45; $P=0.027$) and an integrated discrimination improvement of 0.015 (95% CI=0.003 to 0.04; $P<0.0001$).

Figure 3 shows the HR associated with hypertension (prevalence=45%) or a high L/E_{SPTI} (ie, >0.594 or 59.4%; prevalence=45%) in various Cox models. All models include the presence of hypertension and a high L/E_{SPTI} as predictors of HF. In unadjusted analyses, both hypertension (HR=2.61; 95% CI=1.79 to 3.81; $P<0.0001$) and a high L/E_{SPTI} (HR=2.08; 95% CI=1.44 to 3.01; $P<0.0001$) were significant independent predictors of HF. A high L/E_{SPTI} was a robust independent predictor of HF with increasing adjustment for confounders. In contrast, hypertension did not significantly predict HF in a model that adjusted for a high L/E and various confounders (age, ethnicity, gender, heart rate, diabetes mellitus, body mass index, antihypertensive medication use, total cholesterol, HDL cholesterol, current smoking, and estimated glomerular filtration rate; Model 4 in Figure 3). In this model, the HR associated with hypertension was 1.39 (95% CI=0.86 to 2.23; $P=0.18$), whereas the HR associated with a high L/E was 2.31 (95% CI=1.52 to 3.49; $P<0.0001$). The cumulative hazard for HF among participants stratified according to the presence or absence of hypertension or a high L/E_{SPTI}, adjusted for age, ethnicity, gender, heart rate, diabetes mellitus, body mass index, antihypertensive medication use, total cholesterol, HDL cholesterol, current smoking, and estimated glomerular filtration rate is shown in Figure 4. It can be seen that participants with a high L/E demonstrated the highest hazard for HF, even in the absence of hypertension, whereas participants with a low L/E (both normotensive and hypertensive) comprised the strata with the lowest hazard for HF.

There was no evidence of effect modification by gender (P for interaction=0.26) or age (P for interaction=0.96) regarding the association between L/E_{SPTI} and incident HF.

Discussion

Our study demonstrates that late systolic central hypertension, assessed noninvasively via analysis of a central pressure waveform derived from radial tonometry, is an important independent risk factor for new-onset HF among adults in the

Table 3. Predictors of Incident Heart Failure in Multivariable Analysis (n=6098)

Full Model With Adjusted HR (*c*-Index=0.81)						
	Standardized HR*	Wald Statistic	*P* Value	Change in BIC†	Change in AIC†	Change in *c*-Index‡
Age	1.54 (1.22 to 1.95)	12.968	<0.0001	−8.4	−11.30	0.015
Male gender	2.05 (1.63 to 2.58)	37.234	<0.0001	−33.5	−36.40	0.031
Body mass index	1.29 (1.06 to 1.56)	6.618	0.01	−1.4	−4.30	0.01
Diabetes mellitus	1.20 (1.04 to 1.37)	6.442	0.011	−1.2	−4.10	0.01
Systolic blood pressure	1.28 (1.00 to 1.62)	3.961	0.047	1.0	−1.90	0.005
Diastolic blood pressure	0.77 (0.60 to 0.99)	4.264	0.039	0.6	−2.30	0.005
Heart rate	1.45 (1.20 to 1.75)	15.261	<0.0001	−9.7	−12.60	0.011
L/E_{SPTI}	1.78 (1.45 to 2.17)	30.948	<0.0001	−23.8	−26.70	0.016
Systolic and diastolic blood pressure added together§	—	—	—	0.10	−2.80	0.005

All models are adjusted for ethnicity, antihypertensive medication use, total cholesterol, high-density lipoprotein cholesterol, current smoking, and estimated glomerular filtration rate. Only significant predictors of heart failure are shown. HR indicates hazard ratio; L/E_{SPTI}, late/early systolic pressure–time integral.

*SDs are as follows: age, 10.2 years; body mass index, 5.5 kg/m^2; systolic blood pressure, 21.4 mm Hg; diastolic blood pressure, 10.3 mm Hg; heart rate, 10 bpm; L/E_{SPTI}, 2.8%.

†AIC, Akaike's information criterion; BIC, Bayesian information criterion. For both, larger decreases (changes with negative sign) indicate a larger improvement in model fit.

‡Larger increases indicate a larger improvement in model performance.

§This row presents improvements in model performance when both systolic and diastolic blood pressure are added to a model containing all other variables contained in the full model.

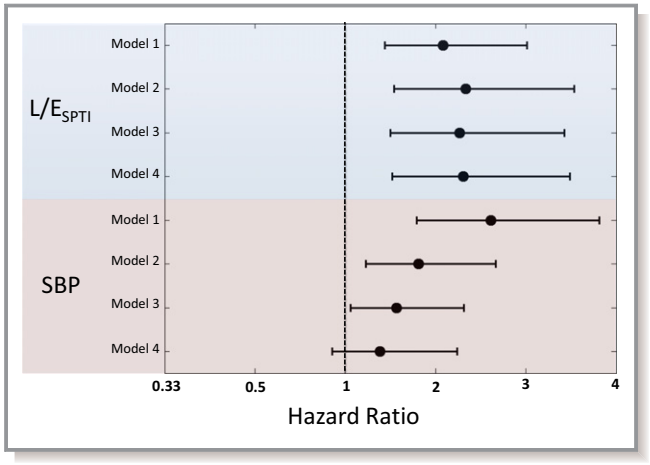

Figure 3. Hazard ratio associated with hypertension or a high L/E$_{SPTI}$ in various Cox models. All models include the presence of hypertension and a high L/E$_{SPTI}$ as predictors of HF. Model 1 (n=6124) includes no additional covariables. Model 2 (n=6124) is adjusted for age, ethnicity, gender, and heart rate. Model 3 (n=6107) is additionally adjusted for diabetes mellitus and body mass index. Model 4 (n=6098) is additionally adjusted for antihypertensive medication use, total cholesterol, HDL cholesterol, current smoking, estimated glomerular filtration rate, aortic augmentation index, and aortic-to-radial pulse pressure amplification. HDL indicates high-density lipoprotein; HF, heart failure; L/E$_{SPTI}$, late/early systolic pressure–time integral; SBP, systolic blood pressure.

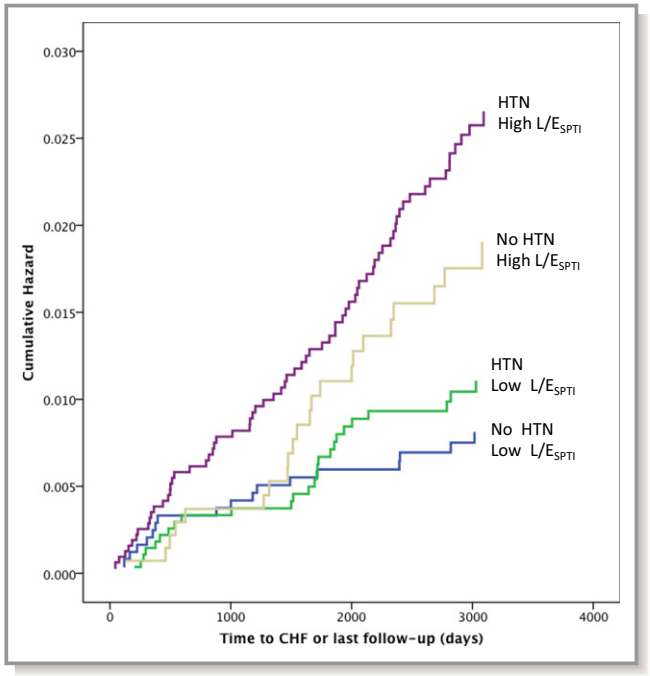

Figure 4. Cumulative hazard curves for HF among participants stratified according to the presence or absence of hypertension (prevalence=45%) or a high L/E$_{SPTI}$ (set empirically to an identical prevalence of 45% based on E/L$_{SPTI}$). Curves are adjusted for age, ethnicity, gender, heart rate, diabetes mellitus, body mass index, antihypertensive medication use, total cholesterol, HDL cholesterol, current smoking, and estimated glomerular filtration rate. The numbers of participants in each stratum are as follows: No HTN/Low L/E$_{SPTI}$=2214; HTN/Low L/E$_{SPTI}$=1155; No HTN/High L/E$_{SPTI}$=1182; HTN/High L/E$_{SPTI}$=1574. HDL indicates high-density lipoprotein; HF, heart failure; L/E$_{SPTI}$, late/early systolic pressure time integral; HTN, hypertension; CHF, congestive heart failure.

general population. In our large multiethnic sample of adults free of clinically apparent cardiovascular disease at baseline, a simple ratio of late versus early central pressure in systole (L/E$_{SPTI}$) was a strong predictor of incident HF independent of brachial systolic and diastolic blood pressure levels and other established predictors of HF, and was associated with important improvements in model performance and a significant population-attributable risk of HF.

For any given level of systolic blood pressure, a pattern characterized by prominent late-systolic load has been unequivocally demonstrated to exert deleterious effects on LV structure and function in animal models,[9,13,33] observations that have been supported by human studies.[15,16] Consistent with these mechanistic data, our study indicates that late systolic hypertension is an independent predictor of HF risk.

The aortic pressure profile is determined by the interactions between the left ventricle and the load imposed by the arterial tree.[33] The hemodynamic determinants of late systolic versus early systolic hypertension are different. Early systolic pressure is a function of the pulsatile increase in pressure as a result of the interaction between the LV and the proximal aortic characteristic impedance, whereas late systolic pressure is more dependent on the total compliance of the arterial tree and wave reflections.[14] Wave reflections arise at multiple sites of impedance mismatch along the arterial tree (such as points of branching or change in wall diameter or material properties)[33,34] and merge into a net reflected wave, which increases late systolic pressure and reduces late systolic flow in the aorta. These arterial phenomena in turn relate differentially to the LV wall stress at different time points during ejection.[35] During early ejection, active development of fiber cross-bridges occurs in the electrically activated myocardium and peak myocardial wall stress occurs,[36] at a time when systolic pressure coexists with quasidiastolic geometry. Myocardial fiber shortening and ejection of blood determine a progressive change in LV geometry, which causes a drop in myocardial stress during mid-to-late systole. This phenomenon, which appears to be favorable for the myocardium to reduce the late systolic load imposed by wave reflections, is, however, of variable magnitude and may be insufficient and/or compromised in the setting of low or low-normal LV ejection fraction or in the presence of pronounced late systolic arterial load.[35–38] Indeed, an elevation of late systolic

LV wall stress relative to early wall stress has been shown to be independently associated with diastolic dysfunction in middle-aged adults.[39]

We have previously shown than reflection magnitude estimated with a physiologic flow approach independently predicts the risk of incident HF in this cohort.[17] Such an approach is based on the relatively low variability of the flow waveform between individuals. It represents an approximation, which depends on the assumption of a physiologic flow waveform (rather than relying on measured flow). Furthermore, it does not directly assess the timing of arterial pressure during systole. In contrast, the approach undertaken in the current study does not require the use of any assumptions about flow waveform morphology and provides a direct quantification of early versus late systolic central hypertension. Furthermore, in contrast to augmentation index, this index does not rely heavily on the high-frequency components of the pulse wave contour, which tend to be more susceptible to noise and which relate less consistently between the radial and aortic locations.

Our study should be interpreted in the context of its strengths and limitations. To our knowledge, this is the first study to demonstrate an association between late systolic central hypertension and incident HF. Other strengths of our investigation include the multiethnic community-based sample, standardized assessments, and careful event adjudication using definitive criteria for HF. However, it is important to acknowledge several limitations. Our observational study cannot prove a causal link between late systolic hypertension and HF, although our observational data should be interpreted in the context of previous experimental studies, which demonstrate a cause–effect relationship between late systolic load and myocardial remodeling and dysfunction.[9–11,13,18–21] We did not measure aortic pressure directly, but rather derived it from a generalized transfer function, designed to reproduce the features of the central pressure waveform. This approach has limitations, because it assumes a fixed relationship between the harmonic components of pressure between the aorta and the radial artery. However, this relationship is actually variable, particularly for the higher harmonics of pressure. Since participants had no known cardiovascular disease at baseline, this cohort represents a particularly healthy sample of the population at large which is, however, ideal for examining early vascular changes predisposing to new-onset HF. Finally, our study did not assess how the L/E_{SPTI} relates to incident HF with preserved ejection fraction versus HF with reduced ejection fraction. This should be the focus of future research.

In summary, in an ethnically diverse population free of cardiovascular disease at baseline, late systolic hypertension was independently associated with incident HF. The systolic LV loading sequence may represent an important novel risk factor for HF and a potential therapeutic target for primary HF prevention.

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