Components of Hemodynamic Load and Cardiovascular Events
The Framingham Heart Study

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Background—Elevated blood pressure is the leading modifiable risk factor for cardiovascular disease (CVD) and premature death. The blood pressure waveform consists of discrete hemodynamic components, derived from measured central pressure and flow, which may contribute separately to risk for an adverse outcome. However, pressure-flow measures have not been studied in a large, community-based sample.

Methods and Results—We used proportional hazards models to examine the association of incident CVD with forward pressure wave amplitude, mean arterial pressure, and global reflection coefficient derived from wave separation analysis and echocardiography in 2492 participants (mean age 66±9 years, 56% women) in the Framingham Heart Study. During follow-up (0.04–6.8 years), 149 participants (6%) had a CVD event. In multivariable models adjusting for age, sex, antihypertensive therapy, body mass index, heart rate, total and high-density lipoprotein cholesterol concentrations, smoking, and the presence of diabetes mellitus, forward pressure wave amplitude (hazard ratio, 1.40; 95% confidence interval, 1.16–1.67; P=0.0003) was associated with incident CVD, whereas mean arterial pressure (hazard ratio, 1.10; 95% confidence interval, 0.94–1.29; P=0.25) and global wave reflection (hazard ratio, 0.93; 95% confidence interval, 0.78–1.12; P=0.58) were not. After adding systolic blood pressure and carotid-femoral pulse wave velocity to the model, forward pressure wave amplitude persisted as a correlate of events (hazard ratio, 1.33; 95% confidence interval, 1.05–1.68; P=0.02).

Conclusions—Higher forward pressure wave amplitude (a measure of proximal aortic geometry and stiffness) was associated with increased risk for incident CVD, whereas mean arterial pressure and relative wave reflection (correlates of resistance vessel structure and function) were not associated with increased risk for incident CVD. (Circulation. 2015;131:354-361. DOI: 10.1161/CIRCULATIONAHA.114.011357.)

Key Words: cardiovascular diseases ■ hemodynamics ■ pulsatile flow

Blood pressure is a major risk factor for cardiovascular disease (CVD) that accounts for ~8 million premature deaths per year worldwide.1,2 Over the past decades, medications used to treat hypertension and prevent CVD events were designed to reduce mean arterial pressure (MAP). However, this MAP-focused approach may be suboptimal in light of the preponderance of predominant or isolated systolic hypertension, particularly among patients with persistently elevated blood pressure despite treatment.3-5 To assess residual CVD risk associated with persistently elevated blood pressure, investigators have evaluated novel measures of aortic stiffness and hemodynamic load, such as peripheral and central pulse pressure (PP) and aortic pulse wave velocity, which may be predictive of CVD progression and events.6-14 Indeed, we have shown previously that increased carotid-femoral pulse wave velocity is associated with increased risk for CVD events.6 Yet, little is known about the relative and incremental contributions to CVD risk of the mean and various pulsatile components of blood pressure.

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PP plays an important role in the pathogenesis of hypertension, particularly after midlife, and higher PP is related to clinical events. However, the components of PP that confer higher risk remain unclear. Some have argued that greater wave reflection, as indicated by augmentation index or augmented pressure, is associated with increased risk. Yet, augmentation index and augmented pressure are composite measures that may be affected by forward and backward waves. One must measure pressure and flow to separate forward and backward waves and compute the global reflection coefficient, which is the reference standard for assessing wave reflection. Systolic blood pressure (SBP) has been proposed as a primary guide to prognosis and therapy; however, SBP provides an aggregate measure of the effects of mean and pulsatile pressure that may potentially overlook components of each. Therefore, knowledge of SBP alone does not establish whether an individual has an abnormality of mean or pulsatile load, which is a distinction that may have treatment implications. Moreover, an earlier Framingham study showed that blood pressure models combining SBP with diastolic blood pressure (DBP) or PP with MAP were superior to any of the 4 single blood pressure components (SBP, DBP, MAP, or PP) considered alone at predicting CVD risk.

To our knowledge, no previous community-based study has compared the relations with incident CVD of a comprehensive panel of individual mean and pulsatile components of blood pressure derived from an analysis of measured central aortic pressure and flow. We hypothesized that true central forward pressure wave amplitude (FWA), the primary hemodynamic correlate of variability in central and peripheral PP in younger and older individuals, would be an important predictor of CVD risk in models that adjusted for standard risk factors, including SBP.

**Methods**

**Participants**

The design and selection criteria for the Framingham Offspring study have been detailed previously. Participants attending the eighth examination cycle of the Offspring cohort (n=3021; 2005–2008) were eligible for this analysis. Tonometry measurements were first implemented in February 1999 as described previously. A more comprehensive assessment of proximal aortic pressure-flow relations was implemented beginning with examination cycle 8 of the Offspring cohort. Participants were excluded for the following reasons: prior CVD (n=295), off-site examination with no laboratory data (n=79), incomplete hemodynamic data (n=110), no follow-up after examination cycle (n=12), and missing covariate data (n=33). Only 45 (1.5%) participants were missing data on covariates or follow-up. All protocols were approved by Boston University Medical Center’s Institutional Review Board, and participants provided written informed consent.

**Clinical Evaluation and Definitions**

Medical history, physical examination, and electrocardiography were performed routinely at each Framingham Heart Study examination. Physician-acquired blood pressures represent the mean of 2 auscultatory measurements obtained on seated participants at the time of the Framingham clinic examination. The physician blood pressures were acquired by using a mercury column sphygmomanometer and a standardized protocol with excellent measurement reproducibility. Peripheral PP was calculated as the difference between SBP and DBP. Body mass index was calculated by dividing weight in kilograms by the square of the height in meters. Criteria for diabetes mellitus were a fasting glucose level of ≥126 mg/dL (7.0 mmol/L), or the use of medications to treat diabetes mellitus. Smoking was defined as regular use of cigarettes in the previous year.

**Noninvasive Hemodynamics**

Hemodynamic data were acquired as previously described. Participants were studied in the supine position after a 5-minute rest. Supine auscultatory brachial SBP and DBP at the time of tonometry (referred to as tonometry blood pressures) were obtained by using a computer-controlled device. Arterial tonometry with simultaneous electrocardiography was obtained from brachial, radial, femoral, and carotid arteries by using a custom tonometer. Next, 2-dimensional echocardiographic images of the left ventricular outflow tract were obtained from a parasternal long-axis view followed by pulsed Doppler of the left ventricular outflow tract from an apical 5-chamber view. Tonometric, electrocardiographic, and echocardiographic data were digitized during the primary acquisition and transferred to the core laboratory (Cardiovascular Engineering, Inc, Norwood, MA) for analyses that were performed blinded to clinical data.

Tonometry waveforms were signal averaged with the use of the electrocardiographic R wave as a fiducial point. Cuff SBP and DBP obtained at the time of tonometry were used to calibrate the peak and trough of the signal-averaged brachial pressure waveform. DBP and integrated brachial MAP were used to calibrate carotid pressure tracings. Calibrated carotid pressure was used as a surrogate for central pressure. MAP was calculated by integration of the calibrated brachial pressure waveform. By using measured central pressure and flow, the forward and backward pressure waves were separated as described previously (Figure 1). The FWA was defined as the

![Figure 1. Central aortic wave separation analysis.](https://example.com/figure1.png)

Diastolic blood pressure is subtracted from measured pressure (P'), leaving only the pulsatile component. Flow (Q) is rescaled by characteristic impedance, Zc, to transform units to equivalent mm Hg, and the upstrokes of pressure and flow are aligned. After rescaling and alignment, the forward pressure wave (P) is the average of Q and P, and backward wave (P') is the difference between P and P'.
Hemodynamics measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>True forward pressure wave amplitude, mm Hg</td>
<td>57±17</td>
</tr>
<tr>
<td>Primary pressure wave amplitude, mm Hg</td>
<td>50±15</td>
</tr>
<tr>
<td>Tonometry mean arterial pressure, mm Hg</td>
<td>98±12</td>
</tr>
<tr>
<td>Global reflection coefficient</td>
<td>0.36±0.07</td>
</tr>
<tr>
<td>Characteristic impedance, DSC</td>
<td>245±97</td>
</tr>
<tr>
<td>Peak aortic flow, mL/s</td>
<td>306±69</td>
</tr>
</tbody>
</table>

All values are mean±standard deviation except as noted. DSC indicates dyne × sec/cm²; and HDL, high-density lipoprotein.

Outcomes

Major CVD events were defined as fatal or nonfatal myocardial infarction, unstable angina (prolonged ischemic episode with documented reversible ST-segment changes), heart failure, and ischemic or hemorrhagic stroke. Medical records were obtained for all hospitalizations and physician visits related to CVD during follow-up and were reviewed by a committee of 3 investigators; events were adjudicated following written guidelines. Criteria for these CVD events have been described previously.32,33 Follow-up evaluations were performed on data acquired through December 31, 2011.

Statistical Analyses

The primary goal was to assess whether individual key components of hemodynamic load are associated with increased risk for a first major CVD event adjusting for standard CVD risk factors. Baseline characteristics for the study sample were tabulated. We examined the association between separate components of hemodynamic load (FWA, global reflection coefficient, and MAP) and the time to a first major CVD event by using Cox proportional hazards regression, after confirming that the assumption of proportionality was met. Covariates were selected a priori and included components of the Framingham risk score: age, sex, use of antihypertensive therapy, serum total and high-density lipoprotein cholesterol concentrations, smoking, body mass index, heart rate, and the presence of diabetes mellitus.

Clinically acquired physician SBP and the components of the pressure waveform (FWA, global reflection coefficient, primary pressure wave amplitude, and MAP) were added individually to the base model. Individual hemodynamic variables that were related to the incidence of CVD events in multivariable Cox models were evaluated further after accounting for physician SBP. In addition, to assess whether pulsatile load, input, or both were related to events, characteristic impedance and peak aortic flow, which are the major correlates of FWA, were entered together in a Cox model adjusting for the covariates defined above. Similarly, to assess whether FWA or backward wave amplitude or both were related to events, FWA and backward wave amplitude were entered together in a Cox model adjusting for the covariates defined above. For individual hemodynamic variables that showed statistically significant relations with incident CVD events, we examined effect modification. We tested interactions of 3 covariates—older age (defined as 65–90 versus 40–64), sex, and hypertension treatment status—with hemodynamic variables by incorporating corresponding interaction terms in the analysis. To illustrate relations between hemodynamic variables and events, continuous predictor variables were segregated by quartiles (Q1–Q4), and Kaplan-Meier curves of survival free of a CVD event were constructed. We performed cause-specific hazard analyses in the Cox models, where non-CVD death was a competing (censoring) event; Kaplan-Meier plots were not modified for competing events.

All analyses were performed with SAS version 9.3. For our primary analysis, we evaluated 4 components of blood pressure (FWA, reflection coefficient, primary pressure wave, and MAP); hence, a 2-sided \( P < 0.05/4 = 0.0125 \) was considered statistically significant.

Results

Study exclusion criteria resulted in a sample of 2492 participants (1402 [56%] women). Table I in the online-only Data Supplement presents a comparison of baseline characteristics of included and excluded participants. Baseline characteristics of the study sample are presented in Table 1. During follow-up (0.04–6.8; median, 5.4 years), 149 of 2492 participants (6%) had a first major CVD event. The most common events were myocardial infarctions (n=50), heart failure (n=46), and stroke (n=38); 13 episodes (9% of all events) were fatal. Figure 1 depicts a representative example of measured pressure and flow and separated forward and backward pressure waveforms. The amplitudes (maximum minus minimum) of these waveforms were used to define the hemodynamic components of blood pressure. Table II in the online-only Data Supplement provides a correlation matrix for standard blood pressure and component hemodynamic measures.

Cox proportional hazards models for individual components of hemodynamic load are presented in Table 2. After adjusting for standard risk factors, several of the pulsatile blood pressure measures, including physician SBP, true FWA, backward wave, and primary pressure wave amplitude, were associated with increased risk for a first major CVD event (Table 2, left). In contrast, MAP and reflection coefficient were not significantly related to events in risk factor–adjusted models. In a dual model that considered both FWA and backward wave amplitude, FWA (hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.01–1.73; \( P = 0.04 \)) was associated with events, whereas backward wave amplitude (HR, 1.07; 95% CI, 0.84–1.37; \( P = 0.59 \)) was not. When the single hemodynamic...
component models were adjusted for physician SBP (Table 2, center) and further adjusted for carotid-femoral pulse wave velocity (Table 2, right), the relation between true FWA and CVD events persisted, whereas the relations for other variables were no longer significant.

In a dual model that evaluated whether risk associated with FWA was attributable to increased pulsatile load or flow, characteristic impedance (HR, 1.24; 95% CI, 1.09–1.71; \(P=0.008\)), but not peak aortic flow (HR, 1.36; 95% CI, 0.99–1.56; \(P=0.06\)), was related to events. We did not find significant effect modification of the FWA relation with events by sex \(P=0.06\), age \(P=0.39\), or hypertension treatment status \(P=0.59\). Because the cerebral circulation may be particularly sensitive to loss of wave reflection,\(^{35}\) we performed a sensitivity analysis that excluded stroke as an end point \(n=38\), resulting in 111 events (4.5%) with a median of 5.4 years of follow-up. Results of the primary outcome models for quartile groups of FWA were as follows: first quartile group, 16/618 (2.4%); second quartile group, 23/628 (3.7%); third quartile group, 40/623 (6.4%); and fourth quartile group, 71/623 (11.4%). CVD indicates cardiovascular disease; and FWA, forward pressure wave amplitude.

## Discussion

### Principal Findings

We investigated the relations of individual mean and pulsatile components of blood pressure with incidence of first-onset CVD events in middle-aged and older participants in the community-based Framingham Heart Study. In a model that included standard CVD risk factors, SBP, primary pressure wave, and FWA were associated with increased risk, whereas MAP was not, indicating that the pulsatile rather than the steady flow component of blood pressure was associated with increased risk for CVD. The global reflection coefficient was not associated with incident CVD events in the base risk factor model. Similarly, backward wave amplitude was not related to events in a dual model that included FWA, indicating that, after considering the effects of FWA, relative wave reflection was not associated with CVD risk. When the base model was further adjusted for physician SBP, the association between higher FWA and CVD risk persisted, indicating that clinic SBP alone does not fully capture blood pressure–related risk. We have demonstrated previously that higher carotid-femoral pulse wave velocity was associated with higher CVD risk.\(^{36}\) In the present study, after further adjusting for carotid-femoral pulse wave velocity, the relation between FWA and CVD remained, underscoring the complementary nature of these related but distinct measures of aortic function. Additionally, in the dual model, we showed that characteristic impedance, but not peak aortic flow, was associated with elevated risk for CVD events.

<table>
<thead>
<tr>
<th>Hemodynamic Measure</th>
<th>Hazard Ratio Including Standard Risk Factors (\text{LCL, UCL}) (P)</th>
<th>Hazard Ratio Including Standard Risk Factors and Physician SBP (\text{LCL, UCL}) (P)</th>
<th>Hazard Ratio Including Standard Risk Factors, Physician SBP, and CFPWV (\text{LCL, UCL}) (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician SBP</td>
<td>1.26 (1.07, 1.48) (0.005)</td>
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</tr>
<tr>
<td>Tonometry mean arterial pressure</td>
<td>1.10 (0.94, 1.29) (0.25)</td>
<td>0.92 (0.75, 1.13) (0.45)</td>
<td>0.98 (0.79, 1.22) (0.88)</td>
</tr>
<tr>
<td>Forward pressure wave amplitude</td>
<td>1.40 (1.16, 1.67) (&lt;0.001)</td>
<td>1.32 (1.06, 1.64) (0.01)</td>
<td>1.33 (1.05, 1.68) (0.02)</td>
</tr>
<tr>
<td>Backward pressure wave amplitude</td>
<td>1.30 (1.10, 1.53) (0.002)</td>
<td>1.20 (0.98, 1.47) (0.08)</td>
<td>1.21 (0.97, 1.50) (0.09)</td>
</tr>
<tr>
<td>Primary pressure wave amplitude</td>
<td>1.28 (1.07, 1.52) (0.007)</td>
<td>1.17 (0.95, 1.44) (0.13)</td>
<td>1.16 (0.94, 1.45) (0.17)</td>
</tr>
<tr>
<td>Global reflection coefficient</td>
<td>0.95 (0.79, 1.14) (0.58)</td>
<td>0.93 (0.78, 1.12) (0.45)</td>
<td>0.94 (0.78, 1.13) (0.52)</td>
</tr>
</tbody>
</table>

Models add hemodynamic variables to the covariates individually, one at a time. In the center, all models also include physician SBP, and on the right, all models are additionally adjusted for CFPWV. Hazard ratios are expressed per 1 SD higher value, adjusted for standard risk factors; 149 events (6%) with median of 5.4 years of follow-up. CFPWV indicates carotid femoral pulse wave velocity; LCL, lower limit of the 95% confidence interval; SBP, systolic blood pressure; SD, standard deviation; and UCL, upper limit of the 95% confidence interval.

Figure 2. Kaplan–Meier plot of the probability of remaining free of first major CVD event during follow-up by quartiles of forward pressure wave amplitude. Participants are grouped according to quartiles of forward pressure wave amplitude: group I (<45.0 mmHg), group II (45.0 to <55.1 mmHg), group III (55.1 to <66.8 mmHg), and group IV (≥66.8 mmHg). CVD events per person for quartile groups of FWA were as follows: first quartile group, 16/618 (2.4%); second quartile group, 23/628 (3.7%); third quartile group, 40/623 (6.4%); and fourth quartile group, 71/623 (11.4%). CVD indicates cardiovascular disease; and FWA, forward pressure wave amplitude.
These data suggest that aortic wall stiffness or a mismatch between aortic diameter and pulsatile flow accounts for the increased risk associated with higher FWA. Thus, our results indicate that the forward pressure wave component of blood pressure and pulsatile load, rather than MAP, is the individual component of blood pressure that is most closely associated with first-onset major CVD events in our middle-aged and older community-based sample.

Relations of Components of Hemodynamic Load with Incident CVD Events
Several studies have evaluated relations between hemodynamic load and risk for CVD and disease-related events, including studies by Kannel et al., along with many others who have emphasized the prognostic value of SBP. Recent studies have shown that higher PP is associated with increased long-term CVD risk and progression, especially in advanced age, and in patients with heart failure, myocardial infarction, coronary artery disease, and hypertension. Although PP is a widely available measure of arterial stiffness and pressure pulsatility, the components of PP that account for increased CVD risk remain unknown. In this study, we adjusted our models for physician SBP, a well-accepted CVD risk factor; however, variable amplification between central and peripheral sites may offer variable relations of central and peripheral SBP and PP with CVD events. Yet, SBP and PP, whether central or brachial, represent composite hemodynamic measures. As a result, one cannot be certain which component of blood pressure confers risk when SBP or PP alone is examined.

Other studies that sought to assess the relation between central arterial hemodynamics and CVD events did not directly measure central aortic flow. Instead, they used either a typical flow waveform or a pseudoflow waveform that was derived from the pressure data by using various modeling assumptions. Therefore, these studies were able to provide only an estimate of FWA and backward wave amplitude. In contrast, our study assessed the relative contributions to CVD risk of a comprehensive panel of individual components of mean and pulsatile hemodynamic load derived from directly measured central pressure and flow. The utility of absolute in comparison with relative measures of wave reflection as markers of CVD risk has been debated. However, the measures of absolute pressure wave reflection, such as augmentation pressure or backward wave amplitude, are highly correlated with FWA.

For example, in our cohort, absolute backward wave amplitude was more closely related to FWA (r=0.78, P<0.001) than to the global reflection coefficient (r=0.39, P<0.001). Additionally, pressure-only measures of wave reflection are confounded by ventricular function, which affects the balance between pressure augmentation and flow deceleration. In the present study, to assess whether CVD event risk was attributable to increased forward or backward waves, we used a dual model that considered both FWA and backward wave amplitude: FWA remained significant while backward wave amplitude did not, demonstrating that the association between the backward pressure wave and events was attributable to larger forward wave, not greater wave reflection, which is consistent with the findings for reflection coefficient alone.

The primary pressure wave amplitude, which is a pressure-only surrogate for FWA, was not associated with CVD risk after multivariable adjustment. The primary pressure wave amplitude, which is identified by an initial peak or inflection point in the central pressure waveform (Figure 1), may be confounded by variable overlap between forward and backward pressure waves. Depending on the timing and shape of the backward wave, the true forward wave may peak before or continue to rise after the inflection point that is used to identify the transition from forward to backward pressure wave in a central pressure waveform. Therefore, primary pressure wave amplitude misclassifies a variable and informative component of the true FWA.

The current study extends previous work and implicates the FWA by demonstrating its role in the adverse effects related to aortic stiffening and increased hemodynamic load with aging, which are not fully captured by SBP alone. SBP represents an aggregate measure of mean and pulsatile load that includes variable contributions from backward pressure waves and only a portion of the forward wave; consequently, SBP fails to capture the full measure of the risk associated with increased forward pressure wave pulsatility. Importantly, incident CVD events were not related to wave reflection or components of steady hemodynamic load, because they did not provide incremental CVD risk prediction after considering standard CVD risk factors in this community-based sample of middle-aged and older people. Although risk reclassification analysis using candidate hemodynamic measures is beyond the scope of this study, we believe a thorough investigation of the relative prognostic value for individual components of hemodynamic load is an important future direction, which could improve on current models and standard risk factors for incident CVD.

Potential Paradigm Shift in Hypertension Treatment
The World Health Organization has classified hypertension as the leading cause of preventable death throughout the world. A variety of pharmacological agents approved for treatment of hypertension are widely available, including low-cost generics. Yet, control of hypertension is less than ideal, with blood pressure reduced below hypertensive levels in about half of treated patients. Although current antihypertensive medications were systematically designed to reduce MAP, we have shown that MAP was not associated with CVD events in our cohort. In addition, drugs that reduce MAP, such as resistance vessel dilators, can increase cardiac output and peak flow, which could increase FWA and limit the reduction in CVD events even though SBP and MAP are reduced. These hypotheses will require testing in suitably designed intervention studies.

Recently, the Eighth Joint National Committee of the National Heart, Lung, and Blood Institute updated the US hypertension management guidelines, which set the target SBP for the population aged ≥60 years to <150 mmHg. The relaxed guidelines will presumably reduce the adverse effects of unnecessary antihypertensive medications. However,
focusing on the level of SBP alone may incompletely characterize risk. Based on our observations, we posit that a borderline-to-high SBP with normal FWA may not be as risky as a comparable SBP with markedly elevated FWA. Such a distinction may make it possible to ease the guidelines for SBP while still identifying cases that will benefit from more aggressive treatment.

Furthermore, our data suggest a need to better define the effects of existing therapeutic agents on aortic function and FWA. For example, a previous study used a hemodynamic protocol analogous to the one used in the present study and demonstrated that relatively short-term therapy with omapatrilat reduced PP, characteristic impedance, and FWA in middle-aged and older patients with uncomplicated systolic hypertension.90 Similar evaluation of novel and existing therapies would better define the hemodynamic effects of antihypertensive drug therapy and would inform the design of clinical trials that could test the potential clinical value of a treatment strategy that targets modification of proximal aortic properties as a primary goal of therapy. Whether current or novel drugs with favorable effects on proximal aortic properties that produce preferential reduction in FWA will be more effective when used as monotherapy or in combination treatment needs further investigation.

Conclusion

In summary, we have shown that FWA is the key component of hemodynamic load that is associated with CVD events in a model that adjusts for standard risk factors. Current pharmacological strategies used to treat hypertension focus on reducing hemodynamic load by reducing MAP and may not adequately address a primary cause of blood pressure elevation,10 CVD progression, and associated excess morbidity and mortality. Our data suggest that further research on the hemodynamic mechanisms and clinical effects of interventions that focus on proximal aortic properties and pulsatile load is merited.

Acknowledgments

From the Framingham Heart Study of the National Heart, Lung, and Blood Institute of the National Institutes of Health and Boston University School of Medicine. This article is dedicated to the memory of Dr Joseph A. Vita, MD, an admired and respected friend, colleague, and mentor who will be greatly missed.

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Disclosures

Dr Mitchell is owner of Cardiovascular Engineering, Inc., a company that designs and manufactures devices that measure vascular stiffness. The company uses these devices in clinical trials that evaluate the effects of diseases and interventions on vascular stiffness. The other authors report no conflicts.

References


Hypertension is the leading modifiable risk factor for cardiovascular disease (CVD) and premature death. The blood pressure waveform consists of discrete hemodynamic components that can be assessed by measuring central pressure and flow; however, no community-based study has compared the relations of separate hemodynamic components with adverse CVD outcomes. In our study of 2492 Framingham Heart Study participants who experienced 149 CVD events, after adjusting for age, sex, routine systolic blood pressure, carotid-femoral pulse wave velocity, antihypertensive therapy, body mass index, heart rate, total and high-density lipoprotein cholesterol, smoking, and diabetes mellitus, 1 standard deviation higher forward pressure wave amplitude was associated with 33% higher risk for a first major CVD event. In contrast, mean arterial pressure, backward pressure wave amplitude, and global wave reflection were not associated with events in risk factor–adjusted models. Treatments for elevated blood pressure have focused on mean arterial pressure reduction to prevent CVD events; however, in our sample, forward wave amplitude is the component of blood pressure that is most closely associated with first-onset major CVD events. Our data suggest that current approaches to blood pressure management that are focused on mean arterial pressure do not adequately address a primary cause of systolic blood pressure elevation and CVD progression, consistent with the observation that a high proportion of hypertensive individuals have persistent isolated systolic hypertension and high residual CVD risk despite aggressive treatment. Thus, novel treatment approaches that target forward pressure wave amplitude may offer a more effective option to reduce blood pressure and excess morbidity and mortality.
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SUPPLEMENTAL MATERIAL


Supplemental Content:

Supplemental Table 1. Comparison of baseline characteristics of included and excluded participants.

Supplemental Table 2. Matrix of Pearson correlation coefficients for measures of individual hemodynamic components (N=2492).

This supplementary material has been provided by the authors to give the readers additional information about their work.
**Supplemental Table 1. Comparison of baseline characteristics of included and excluded participants.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Included (N = 2492)</th>
<th>Excluded (N varies)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Measures</strong></td>
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<tr>
<td>Age, years</td>
<td>66 ± 9</td>
<td>72 ± 9</td>
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<tr>
<td>Women, N (%)</td>
<td>1402 (56)</td>
<td>261 (49)</td>
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<td>Height, cm</td>
<td>167 ± 10</td>
<td>167 ± 9</td>
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<td>Weight, kg</td>
<td>78 ± 17</td>
<td>81 ± 19</td>
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<td>Body mass index, kg/m²</td>
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<td>Physician blood pressure, mm Hg</td>
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<tr>
<td>Systolic</td>
<td>128 ± 17</td>
<td>131 ± 19</td>
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<tr>
<td>Diastolic</td>
<td>74 ± 10</td>
<td>70 ± 10</td>
</tr>
<tr>
<td>Pulse</td>
<td>54 ± 16</td>
<td>60 ± 18</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>62 ± 10</td>
<td>63 ± 11</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>189 ± 37</td>
<td>169 ± 36</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>58 ± 18</td>
<td>51 ± 16</td>
</tr>
<tr>
<td>Hypertension treatment, N (%)</td>
<td>1124 (45)</td>
<td>322 (63)</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>288 (12)</td>
<td>128 (30)</td>
</tr>
<tr>
<td>Current smoker, N (%)</td>
<td>219 (9)</td>
<td>54 (10)</td>
</tr>
<tr>
<td><strong>Hemodynamics measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True forward pressure wave amplitude, mm Hg</td>
<td>57 ± 17</td>
<td>60 ± 19</td>
</tr>
<tr>
<td>Tonometry mean arterial pressure, mm Hg</td>
<td>98 ± 12</td>
<td>100 ± 13</td>
</tr>
<tr>
<td>Global reflection coefficient</td>
<td>0.36 ± 0.07</td>
<td>0.35 ± 0.07</td>
</tr>
</tbody>
</table>

All values are mean ± standard deviation except as noted. Note that N varies (45 – 529) for excluded participants based on availability of data.
Supplemental Table 2. Matrix of Pearson correlation coefficients for measures of individual hemodynamic components (N=2492).

<table>
<thead>
<tr>
<th></th>
<th>Central SBP</th>
<th>SBP</th>
<th>MAP</th>
<th>DBP</th>
<th>Brachial PP</th>
<th>Forward wave</th>
<th>Backward wave</th>
<th>Reflection coefficient</th>
<th>Primary wave</th>
<th>Zc</th>
<th>Peak flow</th>
<th>CFPWV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician SBP</td>
<td>0.73</td>
<td>0.77</td>
<td>0.65</td>
<td>0.29</td>
<td>0.67</td>
<td>0.62</td>
<td>0.61</td>
<td>0.04</td>
<td>0.56</td>
<td>0.45</td>
<td>-0.01</td>
<td>0.50</td>
</tr>
<tr>
<td>Central SBP</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.59</td>
</tr>
<tr>
<td>DBP</td>
<td>0.85</td>
<td>0.36</td>
<td>0.35</td>
<td>0.81</td>
<td>0.80</td>
<td>0.85</td>
<td>0.08</td>
<td>0.05</td>
<td>0.76</td>
<td>0.60</td>
<td>-0.07</td>
<td>0.52</td>
</tr>
<tr>
<td>Forward wave</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Backward wave</td>
<td>0.76</td>
<td>0.53</td>
<td>0.52</td>
<td>0.58</td>
<td>0.58</td>
<td>0.12</td>
<td>0.47</td>
<td>0.40</td>
<td>0.02</td>
<td>0.05</td>
<td>0.01</td>
<td>0.45</td>
</tr>
<tr>
<td>Reflection coefficient</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary wave</td>
<td>0.90</td>
<td>0.86</td>
<td>-0.01</td>
<td>0.84</td>
<td>0.68</td>
<td>-0.05</td>
<td>0.54</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Zc</td>
<td>-0.39</td>
<td>-0.30</td>
<td>-0.02</td>
<td>0.51</td>
<td>-0.02</td>
<td>0.45</td>
<td>-0.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak flow</td>
<td>-0.09</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Top value is r, and bottom value is P in each cell. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; Zc, aortic characteristic impedance; CFPWV, carotid femoral pulse wave velocity. All values were obtained at the time of tonometry except physician.