# Hemodynamic Correlates of Blood Pressure Across the Adult Age Spectrum

## Noninvasive Evaluation in the Framingham Heart Study

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***Background***—Systolic blood pressure and pulse pressure are substantially higher in older adults. The relative contributions of increased forward versus reflected pressure wave amplitude or earlier arrival of the reflected wave to elevated pulse pressure remain controversial.

***Methods and Results***—We measured proximal aortic pressure and flow, forward pressure wave amplitude, global wave reflection, reflected wave timing, and pulse wave velocity noninvasively in 6417 (age range, 19 to 90 years; 53% women) Framingham Heart Study Third Generation and Offspring participants. Variation in forward wave amplitude paralleled pulse pressure throughout adulthood. In contrast, wave reflection and pulse pressure were divergent across adulthood: In younger participants, pulse pressure was lower and wave reflection was higher with advancing age, whereas in older participants, pulse pressure was higher and wave reflection was lower with age. Reflected wave timing differed modestly across age groups despite considerable differences in pulse wave velocity. Forward wave amplitude explained 80% (central) and 66% (peripheral) of the variance in pulse pressure in younger participants (<50 years) and 90% and 84% in the older participants (≥50 years; all $P<0.0001$). In a stepwise model that evaluated age–pulse pressure relations in the full sample, the late accelerated increases in central and peripheral pulse pressure were markedly attenuated when variation in forward wave amplitude was considered.

***Conclusions***—Higher pulse pressure at any age and higher pulse pressure with advancing age is associated predominantly with a larger forward pressure wave. The influence of wave reflection on age-related differences in pulse pressure was minor. **(*Circulation*. 2010;122:1379-1386.)**

**Key Words:** aorta ■ blood pressure ■ epidemiology ■ hemodynamics



Blood pressure increases substantially with advancing age across the full human lifespan; however, patterns of change in various blood pressure components (systolic, diastolic, mean, and pulse pressures) are complex and nonlinear.[1] The pathogenesis of nonlinear age trajectories of blood pressure components has been debated vigorously in recent years. There is general agreement that mean arterial pressure increases in young adulthood and then remains relatively stable in middle-aged and older adults.[2] The early increase in mean arterial pressure is a manifestation of greater cardiac output or peripheral resistance, possibly a result of activation of the sympathetic nervous system, hypervolemia, or small-vessel disease or dysfunction.[3] From midlife on, when hypertension is prevalent, systolic and pulse pressures increase substantially, mean arterial pressure plateaus, and diastolic pressure falls.[1,2] Thus, a considerable majority of the population burden of hypertension is associated with increasing pulse pressure with advancing age.

### Clinical Perspective on p 1386

The hemodynamic mechanisms underlying the increase in pulse pressure from midlife on remain unclear. A contemporary view asserts that increasing pulse pressure is attributable to increased amplitude and earlier return of a reflected

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pressure wave as a result of aortic wall stiffening and increased pulse wave velocity (PWV).[4] However, this notion is challenged by reports that relative wave reflection, as assessed by central augmentation index, increases until midlife and then plateaus or falls thereafter at a time when pulse pressure and PWV increase dramatically.[5,6] The discrepancy between changes in augmentation and pulse pressure suggests that an increase in forward wave amplitude may account for the age-related increase in pulse pressure.

The considerable burden of disease attributable to nonoptimal blood pressure levels and inadequate blood pressure control even when therapy is initiated[7] provide an impetus to better define mechanisms of blood pressure elevation throughout the human lifespan. Such pathophysiological knowledge is essential to facilitate the development and use of more effective management strategies. Therefore, we performed a comprehensive noninvasive assessment of hemodynamics across the adult human age spectrum to define hemodynamic correlates of blood pressure with advancing age in a community-based setting.

## Methods

### Study Participants

The designs of the Framingham Offspring and Third Generation studies have been presented.[8,9] The cohorts include predominantly white participants of European descent. Noninvasive hemodynamics were assessed routinely in participants undergoing their first examination for the Third Generation (2002 to 2005) and eighth examination for Offspring (2005 to 2008) study. The Boston University Medical Center Institutional Review Board approved the protocol, and all participants gave written informed consent.

A satisfactory evaluation of central pressure-flow relations was obtained in 4028 (99%) of 4082 Third Generation participants and 2768 (96%) of 2889 Offspring participants. A satisfactory evaluation of carotid-brachial and carotid-femoral PWV (CFPWV) was obtained in 3858 (95%) Third Generation and 2704 (94%) Offspring participants, resulting in 3831 (94%) Third Generation and 2645 (92%) Offspring participants with complete hemodynamic data. Additional exclusions for missing covariate data gave a final sample size of 6417.

To assess reference hemodynamic values, we defined a reference sample of 1547 (24%) participants by excluding participants for 1 or more of the following nonexclusive reasons: age ≥50 years (n=3100), hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or drug treatment for hypertension; n=2086), diabetes mellitus (fasting blood glucose ≥126 mg/dL or treatment with insulin or oral hypoglycemic agent; n=535), dyslipidemia (total cholesterol ≥240 mg/dL, triglycerides ≥150 mg/dL, high-density lipoprotein ≤40 mg/dL, or treated for a lipid disorder; n=2842), cardiovascular disease (coronary heart disease, heart failure, stroke, transient ischemic attack, or intermittent claudication; n=405), current cigarette smoking (smoking within 12 months before the index examination; n=891), or obesity (body mass index ≥30 kg/m$^2$; n=1545).

### Noninvasive Hemodynamic Data Acquisition and Analysis

Details of the noninvasive hemodynamic protocol and analyses have been published and are summarized in the online-only Data Supplement.[10–15] As reported previously, reproducibility of central hemodynamic measures with our protocol is high, with intraclass correlation coefficients of 0.93 to 0.95 for repeated measures of central hemodynamic variables such as cardiac output and characteristic impedance.[13,16] Noninvasive central hemodynamic measures correlate closely with invasive measures.[10]

### Statistical Analysis

Sample characteristics were tabulated separately in the reference sample and the entire study sample (the broad sample). Using the median age of the broad sample (49 years), we defined 2 age subgroups (<50 or ≥50 years of age). Cut points for extreme values for hemodynamic variables were defined as the 95th percentile (5th percentile for total arterial compliance and reflected wave transit time) of the reference sample. Percentages of participants with values outside those limits were tabulated by age subgroup for key hemodynamic variables. Logistic regression was use to compare the prevalences of extreme values between age subgroups, with adjustment for sex, body mass index, heart rate, total cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting glucose, diabetes mellitus, prevalent cardiovascular disease, use of antihypertensive medication, use of lipid medications, and active smoking. To illustrate the association of hemodynamic variables with age, variables were summarized according to decades of age and plotted. To ensure adequate sample size at the lower and upper extremes of age, participants <30 or ≥80 years of age, respectively, were grouped together. We used bilinear curve fitting to estimate the slopes of hemodynamic variables relative to age, with an age transition point at 50 years.

We used stepwise linear regression to assess the proportion of variance in central and peripheral pulse pressures attributable to variability in forward wave amplitude, relative wave reflection, and reflected wave timing. The global reflection factor was used as a measure of relative wave reflection (see the Methods section in the online-only Data Supplement). Temporal overlap of the reflected wave with systole was used as a measure of relative timing. Models were constructed separately in median age subgroups. To assess the contribution of wave components to age-related differences in pulse pressure, we repeated the stepwise models in the full sample and included variables for age and for age if age was ≥50 years (which provides an estimate of the change in age slope after 50 years of age). Change in the age effects at each step was considered a measure of the contribution of the entered variable to differences in pulse pressure with increasing age. All models were adjusted for sex.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

### Sample Characteristics

Characteristics of the reference and broad samples are presented in Table 1. The reference sample was leaner and by definition had a healthier risk factor profile. Similarly, younger participants in the broad sample had a lower risk factor burden and prevalence of disease than older participants (Table 1).

### Arterial Properties in the Reference Group

The mean and 95% cut points for key hemodynamic variables in the reference group and the prevalences of extreme values in the broad sample are shown in Table 2. Prevalences of extreme values in the younger group (<50 years of age) were higher than the 5% expected by definition for a number of hemodynamic variables, including systolic, diastolic, and mean blood pressures; PWV; and cardiac output. In contrast, prevalences of abnormal characteristic impedance and peripheral resistance, key determinants of pulsatile and steady flow load, respectively, were not increased relative to the reference value (Table 2). Prevalences of extreme values for most hemodynamic variables (except cardiac output) were considerably higher than the expected 5% in the older group (Table 2). For example, more than half of the older partici-

**Table 1. Sample Characteristics**

| Variables | Reference Group* Age <50 y (n=1547) | Full Sample by Age Group Age <50 y (n=3317) | Age ≥50 y (n=3100) |
|---|---|---|---|
| Age, y | 37±7 | 38±7 | 64±9 |
| Women, n (%) | 1020 (66) | 1746 (53) | 1686 (54) |
| Height, cm | 170±9 | 171±9 | 167±10 |
| Weight, kg | 69±12 | 77±18 | 79±17 |
| Body mass index, kg/m$^2$ | 23.8±3.0 | 26.3±4.9 | 27.9±5.1 |
| Seated blood pressure, mm Hg | | | |
| Systolic | 110±10 | 115±13 | 128±17 |
| Diastolic | 71±8 | 75±10 | 74±10 |
| Heart rate, bpm | 60±9 | 62±10 | 62±10 |
| Total cholesterol, mg/dL | 177±27 | 187±35 | 189±38 |
| HDL cholesterol, mg/dL | 60±14 | 54±16 | 58±18 |
| Total/HDL cholesterol ratio | 3.1±0.8 | 3.7±1.4 | 3.5±1.1 |
| Triglycerides, mg/dL† | 70 (55, 93) | 89 (63, 133) | 101 (73, 141) |
| Glucose, mg/dL | 90±7 | 94±17 | 105±23 |
| Hypertension treatment, n (%) | 0 (0) | 189 (6) | 1356 (44) |
| Lipid treatment, n (%) | 0 (0) | 170 (5) | 1185 (38) |
| Cardiovascular disease, n (%) | 0 (0) | 12 (<1) | 393 (13) |
| Diabetes mellitus, n (%) | 0 (0) | 66 (2) | 469 (15) |
| Smoker, n (%) | 0 (0) | 583 (18) | 308 (10) |

HDL indicates high-density lipoprotein.

*The reference group further excluded participants with hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, current smoking, or obesity, as detailed in Methods.

†Median (25th, 75th percentiles).

pants had elevated supine brachial systolic and central pulse pressures and CFPWV, and ≥30% had elevated mean arterial pressure, characteristic impedance and forward wave amplitude, and reduced reflected wave transit time.

## Cross-Sectional Relations Between Age and Pulsatile Hemodynamics

Key pulsatile hemodynamic variables are summarized by decades of age in Figures 1 and 2 and separately by sex in Figures III and IV in the online-only Data Supplement. Slopes of the relations between age and hemodynamic variables for younger and older participants are presented in Table I in the online-only Data Supplement. Mean arterial pressure increased with age in the younger groups (<50 years of age); however, this age trend was attenuated by half after 50 years of age (Figure 1 and Table I in the online-only Data Supplement). Systolic blood pressure had a relatively flat age profile across younger decades and then increased in parallel with pulse pressure. Diastolic pressure increased in parallel with mean pressure across younger decades and then fell as pulse pressure increased in the older decades (Figures 1B, 1C, and 2A and Table I in the online-only Data Supplement). Augmentation index increased as pulse pressure fell in younger participants and then fell as pulse pressure increased in older participants (Figure 1B and Table I in the online-only Data Supplement). Differences in characteristic impedance across decades paralleled differences in pulse pressure (Figure 1C). CFPWV was higher with age, particularly after 50 years of age, when the age slope increased by 4-fold (Table I in the online-only Data Supplement). In contrast, differences in carotid-brachial PWV with age were modest (Figure 1D), particularly in older participants (≥50 years; Table I in the online-only Data Supplement). On average, the reflected wave arrived in midsystole in the youngest participants (<30 years of age, Figures 1C and 2B). The reflected wave arrived earlier with increasing age before 50 years of age and arrived later with increasing age thereafter (Table I in the online-only Data Supplement) despite major increments in CFPWV across the older decades (Figure 1D). Lower augmentation index with advancing age after 50 years of age contrasted with progressively higher pulse pressure, characteristic impedance, and CFPWV across these same age decades (Figure 1).

Central and peripheral pulse pressures and pressure amplification are summarized by decades of age in Figure 2. Pulse pressure fell with age before 50 years of age and increased thereafter. Apparent amplification was maximal before 30 years of age, when central augmentation was minimal. Central augmentation was higher and apparent amplification was lower across age decades through 60 years of age (Figure 2C). In contrast, true amplification differed relatively little across age decades.

## Forward and Reflected Waves and Pulse Pressure

The contributions of waveform components to variability in central and peripheral pulse pressure in the younger and older participants are presented in Table 3. In the younger group, forward wave amplitude accounted for 80% of the variance in central pulse pressure and 66% of the variance in peripheral pulse pressure. In the older group, forward wave amplitude accounted for 90% of the variance in central pulse pressure and 84% of the variance in peripheral pulse pressure. Overall, the global reflection factor accounted for an additional 4% to 11% of variance, whereas overlap between forward and reflected waves accounted for 1% or less of the variance in pulse pressures (Table 3).

The statistical contribution of forward and reflected pressure waves to pulse pressure–age relations is presented in Table 4. A base model including only age variables and sex (model 1) demonstrates the accelerated increase in pulse pressure with age in the older subgroup (Table 4). When forward wave amplitude entered the model (model 2), late acceleration of the pulse pressure–age slope (age if ≥50 years) was markedly attenuated and model $R^2$ increased. When the global reflection factor (model 3) and reflected wave overlap (model 4) entered the model, further changes in residual pulse pressure–age relations and increments to model $R^2$ were modest.

# Discussion

The present study is a comprehensive noninvasive assessment of aortic input impedance and pulsatile hemodynamics in a

**Table 2. Hemodynamic Variables for the Reference Group and Prevalence of Abnormal Values by Age Group**

| Variables | Reference Group* (n=1547) Mean±SD | Reference Group* (n=1547) Cutoff Values† | Prevalence of Abnormal Values in the Broad Sample by Age, % Age <50 y (n=3317) | Age ≥ 50 y (n=3100) | P‡ |
|---|---|---|---|---|---|
| Supine blood pressure, mm Hg | | | | | |
| Systolic | 115±11 | 134 | 13 | 57 | <0.0001 |
| Diastolic | 64±8 | 76 | 14 | 21 | <0.0001 |
| Mean | 84±9 | 98 | 16 | 45 | <0.0001 |
| Brachial pulse pressure | 51±9 | 68 | 7 | 47 | <0.0001 |
| Central pulse pressure | 47±10 | 64 | 9 | 51 | <0.0001 |
| Peripheral resistance, dynes · s/cm$^5$ | 1669±323 | 2230 | 5 | 28 | <0.0001 |
| Characteristic impedance, dynes · s/cm$^5$ | 172±45 | 259 | 5 | 31 | <0.0001 |
| CFPWV, m/s | 6.4±0.9 | 8.1 | 12 | 69 | <0.0001 |
| Carotid-brachial PWV, m/s | 7.7±1.4 | 10.0 | 9 | 23 | <0.0001 |
| Total arterial compliance, mL/mm Hg | 1.71±0.53 | 0.99 | 6 | 29 | <0.0001 |
| Forward wave, mm Hg | 42±9 | 59 | 8 | 37 | <0.0001 |
| Reflection factor, ratio | 0.34±0.06 | 0.44 | 4 | 11 | <0.0001 |
| Augmentation index, % | 6.3±12.1 | 23.9 | 8 | 21 | <0.0001 |
| Reflected wave transit time, ms | 143±19 | 115 | 8 | 31 | <0.0001 |
| Cardiac output, L/min | 4.1±0.8 | 5.6 | 10 | 7 | <0.0001 |

*The reference group was defined as in Table 1 and Methods.

†All values represent the 95th percentile of the reference group, except those for total arterial compliance and reflected wave transit time, which represent the 5th percentile.

‡Represents *P* values for comparison of prevalence in age groups adjusted for variables noted in Methods.



large unselected community-based sample with participants spanning the adult age spectrum. The analyses document the known accelerated increase in systolic and pulse pressures with advancing age after midlife. Using a combined assessment of central aortic pressure and flow, which is required to separate and quantify forward and reflected waves, we demonstrate that the overwhelming majority of the late-life acceleration in the pulse pressure–age relation is attributable to differences in forward pressure wave amplitude. Furthermore, variability in forward wave amplitude accounts for the majority of the variability in central (80% to 90%) and peripheral (66% to 84%) pulse pressure within each age range when younger (<50 years) and older (≥50 years) participants are considered separately. As a result, the age profiles of forward wave amplitude, characteristic impedance, and pulse pressure are concordant throughout the adult age spectrum (Figure 1B and 1C). In contrast, the age profiles of wave reflection (global reflection factor or augmentation index) and pulse pressure are divergent throughout most of adulthood, with pulse pressure falling and wave reflection rising with age decade in younger participants and pulse pressure rising markedly as wave reflection falls after 50 years of age (Figure 1B and Table I in the online-only Data Supplement). Thus, across the adult age spectrum, forward pressure wave amplitude, which is closely related to characteristic impedance of the aorta, is by far the predominant correlate of central and peripheral pulse pressures at any age and the predominant correlate of the late increase in pulse pressure after midlife in our cross-sectional analysis of noninvasive hemodynamics in this large community-based sample.

## Pressure Wave Reflection and Amplification

Our findings on the contribution of wave reflection to pulse pressure differences with age contrast with prior studies that measured pressure only and considered augmented pressure amplitude rather than relative wave reflection, as assessed by the global reflection factor or augmentation index.[6,17,18] Augmented pressure represents the product of forward wave amplitude and relative wave reflection. If forward wave amplitude increases and relative wave reflection remains the same or even falls, as we have shown after 50 years of age, reflected wave amplitude will increase as long as the increase in forward wave amplitude exceeds the reduction in relative wave reflection. We avoided the confounding effect of forward wave amplitude on the amplitude of the reflected wave by evaluating the global reflection factor. Using this approach, we have shown that in younger and older participants, differences in relative wave reflection account for a modest proportion of the variance in pulse pressure.

To assess the contribution of wave reflection to differences between central and peripheral pulse pressure, we evaluated true and apparent pressure amplification. True amplification quantifies the increase in amplitude of the pressure waveform relative to the initial forward wave, whereas apparent amplification quantifies the net difference between central and peripheral pulse pressures. True amplification increases with increasing wave reflection, whereas apparent amplification decreases because augmentation of the central pressure waveform by a late pressure peak obscures true amplification. The reciprocal relation between apparent amplification and augmentation was present before 50 years of age, when the

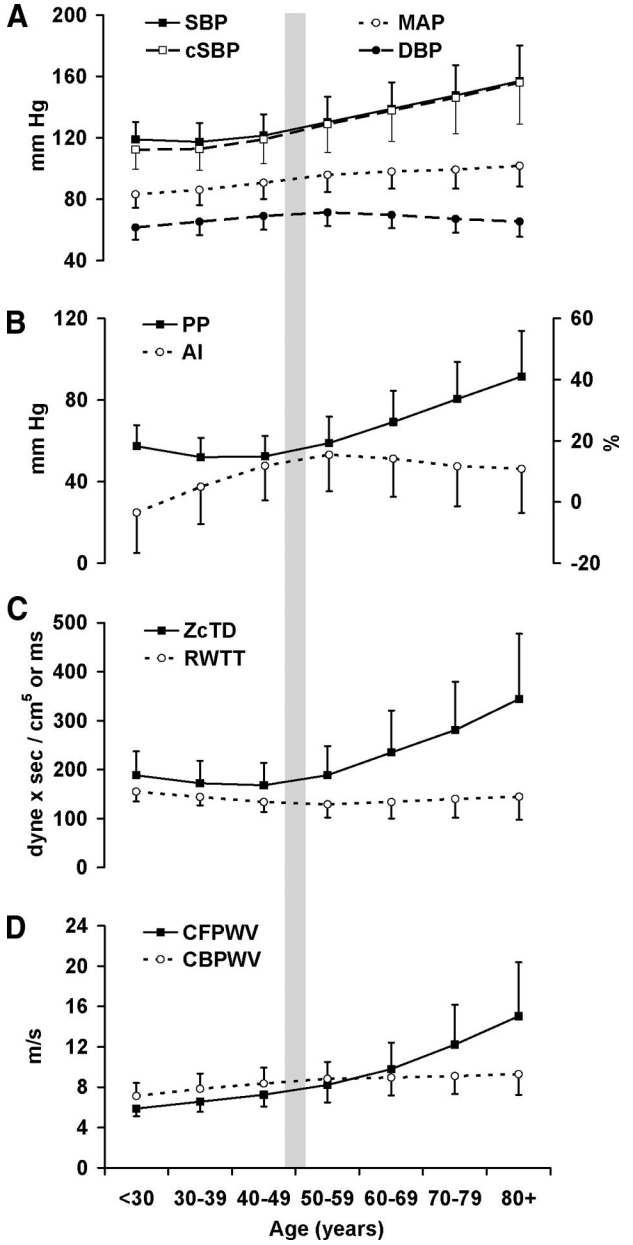


**Figure 1.** Key hemodynamic variables summarized by decades of age. A, Blood pressure components: brachial systolic (SBP), central systolic (cSBP), diastolic (DBP), and mean arterial (MAP) pressures. B, Peripheral pulse pressure (PP) and central augmentation index (AI). C, Characteristic impedance of the aorta computed in the time domain (ZcTD) and reflected wave transit time (RWTT). D, CFPWV and carotid-brachial PWV (CBPWV). The sample size per decade was 463 (<30 years of age), 1334 (30 to 39 years of age), 1521(40 to 49 years of age), 1096 (50 to 59 years of age), 1103 (60 to 69 years of age), 689 (70 to 79 years of age), and 213 (≥80 years of age).

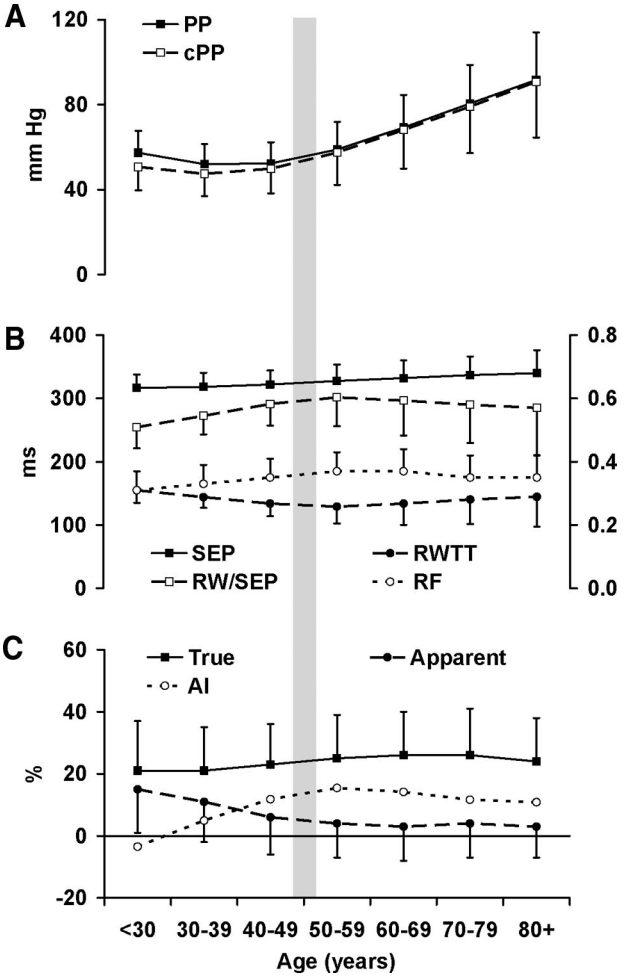


**Figure 2.** Pressure amplification and measures of wave reflection by decades of age. A, Brachial (PP) and central (cPP) pulse pressures. B, Systolic ejection period (SEP), reflected wave transit time (RWTT), overlap between reflected wave arrival and the systolic ejection period (RW/SEP), and the global reflection factor (RF). C, True and apparent amplification and augmentation index (AI).

reflection factor was higher and reflected wave transit time was lower with age (Figure 2). However, after midlife, the increase in augmentation toward an upper limit represented by true amplification ceased and actually reversed. Reduced augmentation was in part a manifestation of reduced wave reflection arriving in the central aorta, as evidence by the reduction in reflection factor, suggesting that alterations in arterial structure in older people may reduce wave reflection or increase damping or dissipation of reflected waves in the periphery. In addition, reflected wave transit time reached a nadir in midlife and then increased slightly in older participants. Later reflected wave arrival reduces augmentation because of less overlap with the forward wave (reflected wave/systolic ejection period in Figure 2B).

Our observations confirm that amplification, which has been estimated to be as high as 80%, may have been overestimated in prior studies,[6,17,18] possibly because those studies calibrated the radial pressure waveform to brachial cuff pressure, which ignores brachial-radial amplification.[19] Through the use of direct noninvasive recording and calibration of the carotid and brachial waveforms, apparent amplification between the carotid and brachial arteries declined from a modest maximum (15%) in our youngest group to a negligible (3%) level beyond 50 to 60 years of age.

## Timing of Wave Reflection

In contrast to a contemporary view,[4] timing of wave reflection had relatively limited relations with central and periph-

**Table 3. Hemodynamic Correlates of Pulse Pressure in Younger and Older Participants**

| | Central Pulse Pressure | | | | Peripheral Pulse Pressure | | | |
|---|---|---|---|---|---|---|---|---|
| Variables | Estimate* | *P* | Partial $R^2$† | Model $R^2$ | Estimate* | *P* | Partial $R^2$† | Model $R^2$ |
| Age <50 y | | | | | | | | |
| Forward pressure wave | 11.3±0.1 | <0.001 | 0.80 | 0.93 | 9.1±0.1 | <0.001 | 0.66 | 0.78 |
| Reflection factor | 3.4±0.1 | <0.001 | 0.11 | | 2.1±0.1 | <0.001 | 0.04 | |
| Reflected wave overlap | 1.3±0.1 | <0.001 | 0.01 | | −0.2±0.1 | 0.03 | 0.0003 | |
| Age ≥50 y | | | | | | | | |
| Forward pressure wave | 21.5±0.1 | <0.001 | 0.90 | 0.97 | 18.3±0.1 | <0.001 | 0.84 | 0.89 |
| Reflection factor | 5.5±0.1 | <0.001 | 0.07 | | 4.3±0.1 | <0.001 | 0.05 | |
| Reflected wave overlap | 0.8±0.1 | <0.001 | 0.002 | | −0.2±0.1 | 0.16 | 0.0001 | |

*Estimates expressed per 1 SD of the independent variable adjusted for sex.

†Represents the increment in response variance explained on stepwise entry of specific regressor variables.

eral pulse pressures. Reflected wave arrival in the proximal aorta, as indicated by an inflection point in the carotid waveform, was midsystolic (not early diastolic) even in our youngest group (<30 years of age). Relatively constrained differences in timing of wave reflection across age decades thereafter contrasted sharply with substantial differences in CFPWV. For example, comparing the <30- and 50- to 59-year-old age groups shows that the reflected wave arrived 17% earlier, whereas CFPWV was 40% higher. Comparing the 50- to 59- versus ≥70-year-old age groups, we see that timing of wave reflection was actually 12% later in the older group even though CFPWV was 83% higher. If CFPWV is a valid surrogate for the average velocity between central aorta and reflecting sites, our observations suggest that the effective location of the dominant reflecting sites was more distal in older participants. The discrepancy between differences in CFPWV and timing of wave reflection across age groups is particularly marked after 50 years of age, when CFPWV reaches and subsequently exceeds muscular artery PWV (carotid-brachial PWV). We have previously proposed that the associated impedance matching between the stiffened aorta and relatively unchanged muscular arteries reduces the component of wave reflection normally arising at this proximal interface and shifts the effective reflecting site distally.[5] Our observation of a reduction in global wave reflection and an increase in reflected wave transit time despite a marked

**Table 4. Hemodynamic Correlates of the Pulse Pressure Difference Between Younger and Older Participants**

| | Central Pulse Pressure | | | | Peripheral Pulse Pressure | | | |
|---|---|---|---|---|---|---|---|---|
| Model* and Variables | Estimate† | *P* | Partial $R^2$‡ | Model $R^2$ | Estimate† | *P* | Partial $R^2$‡ | Model $R^2$ |
| 1 | | | | | | | | |
| Age | 1.8±0.4 | <0.001 | 0.39 | 0.39 | −1.5±0.4 | <0.001 | 0.43 | 0.43 |
| Age (if ≥50 y) | 10.4±0.4 | <0.001 | | | 12.5±0.4 | <0.001 | | |
| 2 | | | | | | | | |
| Forward pressure wave | 17.1±0.1 | <0.001 | 0.89 | 0.91 | 13.8±0.1 | <0.001 | 0.84 | 0.87 |
| Age | 4.6±0.2 | <0.001 | 0.02 | | 0.74±0.2 | <0.001 | 0.027 | |
| Age (if ≥50 y) | −1.8±0.2 | <0.001 | | | 2.7±0.2 | <0.001 | | |
| 3 | | | | | | | | |
| Forward pressure wave | 18.6±0.06 | <0.001 | 0.89 | 0.97 | 14.7±0.1 | <0.001 | 0.84 | 0.90 |
| Reflection factor | 4.9±0.05 | <0.001 | 0.072 | | 3.3±0.1 | <0.001 | 0.045 | |
| Age | 2.2±0.1 | <0.001 | 0.004 | | −0.9±0.2 | <0.001 | 0.014 | |
| Age (if ≥50 y) | −0.9±0.1 | <0.001 | | | 3.3±0.2 | <0.001 | | |
| 4 | | | | | | | | |
| Forward pressure wave | 18.4±0.06 | <0.001 | 0.89 | 0.97 | 14.7±0.09 | <0.001 | 0.84 | 0.90 |
| Reflection factor | 4.6±0.05 | <0.001 | 0.072 | | 3.3±0.08 | <0.001 | 0.045 | |
| Age | 1.7±0.1 | <0.001 | 0.004 | | −1.0±0.2 | <0.001 | 0.014 | |
| Age (if ≥50 y) | −0.4±0.1 | <0.001 | | | 3.4±0.2 | <0.001 | | |
| Reflected wave overlap | 0.86±0.05 | <0.001 | 0.001 | | 0.15±0.08 | 0.056 | 0.0001 | |

*All models were adjusted for sex. Age slope and slope difference for age ≥50 years are included in model 1; additional variables entered the model stepwise in the order shown.

†Estimate±SE expressed per 1 SD of continuous variables.

‡Represents the increment in response variance explained on stepwise entry of specific regressor variable.

increase in CFPWV after 50 years of age is consistent with this hypothesis.

### Characteristic Impedance and CFPWV Across Adulthood

We observed nonlinear and at times divergent differences in characteristic impedance and CFPWV across age groups (Figure 1C and 1D and Table I in the online-only Data Supplement). Before 50 years of age, characteristic impedance was lower and CFPWV was higher with increasing age, whereas after 50 years of age, both variables were comparably higher with advancing age. As suggested previously,[16,20] differing age relations for these related measures of aortic function suggest that aortic diameter may be involved. Characteristic impedance and CFPWV are related directly to wall stiffness and inversely to aortic diameter; however, characteristic impedance is markedly (5-fold) more sensitive to diameter. Thus, if wall stiffening is accompanied by a modest increase in diameter, characteristic impedance can fall even as PWV increases, similar to the pattern we found before 50 years of age. After 50 years of age, the parallel increases in characteristic impedance and CFPWV across age groups are consistent with an increase in wall stiffness with limited change in diameter. These observations raise the possibility that early increases in aortic diameter may be adaptive rather than pathological, serving to stabilize pressure pulsatility in the wake of increasing aortic wall stiffness. However, adaptive aortic remodeling may be limited by the presence of vascular risk factors that accumulate with age, leading to parallel increases in CFPWV, characteristic impedance, forward wave amplitude, and pulse pressure in older people.

We have defined reference values for a comprehensive family of key noninvasive hemodynamic variables and demonstrated heterogeneous differences in the prevalence of abnormal values for specific components of hemodynamic load in younger and older participants. In younger participants, abnormalities in mean arterial pressure predominate largely because of an increased prevalence of elevated cardiac output. After 50 years of age, when the risk for developing hypertension and cardiovascular disease is high, increased prevalence of elevated aortic impedance to pulsatile flow contributes to higher systolic and pulse pressure. These data underscore a need for interventions that target aortic stiffness and abnormal pulse pressure, particularly in older people. Most available antihypertensive drugs were designed to reduce mean arterial pressure, which changes relatively little (2 mm Hg/decade) during the age range (>50 years) when systolic (10 mm Hg/decade) and pulse (12 mm Hg/decade) pressures increase rapidly and hypertension and cardiovascular disease become highly prevalent. This dissociation between hemodynamic abnormality and therapeutic effect may contribute to the high failure rate of antihypertensive therapy and the high prevalence of isolated systolic hypertension among treatment failures.[21] The changing demographics of our aging society suggest that treatment failures may increase over the next few decades unless interventions effective at reducing or preventing aortic stiffening are developed and implemented.

### Study Limitations

A number of potential limitations of our study need to be considered. Because the cohorts were made up of white participants of European descent, we were unable to assess potential ethnicity-related differences in hemodynamics; thus, our findings may not be generalizable to other races or ethnicities. Our discussion of the relative effects of wall stiffness and diameter on characteristic impedance and PWV pertains to measurement at the same site. CFPWV represents the average properties of the entire aorta and the iliac and femoral arteries. Thus, a component of differing age relations of characteristic impedance, which measures proximal aortic properties, and CFPWV, which assesses the full length of the aorta, may be attributable to differences in distal aortic stiffness rather than proximal aortic diameter. However, prior work has demonstrated far greater age-related alterations in proximal compared with distal large-artery stiffness, making it unlikely that predominant distal stiffening explains our observations.[22] The cross-sectional, observational design of our study limits our ability to infer that the observed differences in arterial function in various age groups are related to aging or risk factor accumulation per se. Other historical or generational factors may have contributed to the observed differences among age groups. Prospective studies with repeated assessment of arterial properties over time are required to define the age-related change in arterial function. Our study also has several strengths, including a large sample size and routine ascertainment of a comprehensive noninvasive panel of arterial function measures and coexistent cardiovascular disease risk factors in a community-based sample, which provides excellent power, facilitates adjustment for multiple covariates, and limits referral biases. The Framingham cohort will also enable analysis of the relations between hemodynamics and various novel risk factors and biomarkers that are being assessed.

### Conclusions

We have shown that forward wave amplitude, which is determined by characteristic impedance and peak flow in the proximal aorta, is the predominant hemodynamic correlate of pulse pressure across the adult age spectrum and that differences in forward wave amplitude account for an overwhelming majority of the accelerated increase in pulse pressure after midlife. Differences in relative wave reflection contribute modestly to variability in pulse pressure, whereas variable timing of wave reflection plays a minimal role. In young adults, abnormalities in mean arterial pressure and cardiac output (steady flow load) have a predominant effect on blood pressure, whereas abnormal pulsatile load plays an increasingly important role after 50 years of age. Prospective observational and interventional studies are needed to define mechanisms that contribute to aortic wall stiffening with advancing age and risk factor exposure and to clarify the role of aortic diameter in aortic function.

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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 remaining authors report no conflicts.

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## CLINICAL PERSPECTIVE

Blood pressure increases substantially and nonlinearly with age across the adult lifespan. Mean arterial pressure and pulse wave velocity increase and pulse pressure decreases before 50 years of age, whereas systolic and pulse pressures and pulse wave velocity increase markedly thereafter, at a time when the prevalence of hypertension and cardiovascular disease is high. The pathogenesis of nonlinear age trajectories of blood pressure components has been debated vigorously in recent years, with some suggesting that elevated pulse wave velocity and premature wave reflection account for the increase in pulse pressure. We found that forward wave amplitude is the predominant hemodynamic correlate of pulse pressure across the adult age spectrum and accounts for an overwhelming majority of the accelerated increase in pulse pressure after 50 years of age. Differences in relative wave reflection contribute modestly to variability in pulse pressure, whereas reflected wave timing plays a minimal role. Differing age relations of pulse wave velocity and pulse pressure, which were divergent before 50 years of age and concordant thereafter, suggest that alterations in aortic diameter may modulate changes in pulse pressure in the face of changes in wall stiffness and pulse wave velocity. Additional studies are needed to define the mechanisms that contribute to aortic wall stiffening with advancing age and risk factor exposure and to clarify the role of aortic diameter. A fuller understanding of the pathogenesis of increased pulse pressure and systolic hypertension is needed and will facilitate development of more rational approaches to the treatment of hypertension.