Aortic pulse wave velocity and reflecting distance estimation from peripheral waveforms in humans: detection of age- and exercise training-related differences

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Aortic pulse wave velocity (APWV), as assessed by the current “gold standard” carotid-femoral pulse wave velocity (CFPWV), is a robust prognostic marker for cardiovascular morbidity and mortality in older adults (14, 28) and patients with end-stage renal disease (1), diabetes (5), and hypertension (2). CFPWV is based on noninvasive recording of pressure pulse waves from the carotid and femoral arteries (gated to ECG R-wave). The most common method for approximating aortic path length between the two sites is by subtracting the body surface distance from the suprasternal notch (SSN; estimated location of the aortic valve) to the recording site at the carotid artery from the distance of the SSN to the recording site at the femoral artery (34). This distance divided by the time delay between the carotid and femoral pressure pulse waves yields the CFPWV.

There is a growing interest in determining APWV from a single peripheral pulse waveform because femoral waveforms cannot be reliably obtained in some obese adults, and retrospective determination of APWV may be desired in studies where invasive or noninvasive blood pressure recordings were obtained but CFPWV was not measured prospectively. An indirect method for assessing APWV using pulse waveform analysis has been proposed (4, 20) wherein an arterial pressure waveform is recorded from a peripheral artery (e.g., radial or brachial) and then a mathematical transfer function is applied to the peripheral waveform to derive an estimated ascending aortic pressure pulse waveform (4, 6, 27). This aortic pressure pulse waveform can be decomposed mathematically into a forward-traveling and a reflected backward-traveling wave using a validated triangular aortic flow waveform approximation method (20, 35). APWV can then be estimated by dividing the reflecting distance by the time delay between the forward and reflected wave. The reflecting distance is defined as the distance between the aortic valve and the reflecting site in the periphery that has been suggested to be generally located distally from the aortic bifurcation (e.g., iliac arteries) (24).

This indirect method for estimating APWV is based on several assumptions, including that the peripheral pressure waveform can indeed be accurately converted into an aortic pressure waveform and that the reflecting distance can be accurately determined. Validity of the latter assumption has been debated extensively (8, 13, 17, 36), in part because the reflection site is not an anatomically defined location in humans. The conventional view has been that the reflecting distance shortens with aging (i.e., moves proximally toward the heart), leading to early arriving reflected waves in systole (16, 22). In contrast, evidence from the Framingham Heart Study first advanced the notion that reflecting distance lengthens with normal aging (14, 15), a concept that has been supported by several other groups (9, 36). Sugawara et al. (24) proposed an “effective reflecting distance” (ERFD) that was located somewhere distally from the aortic/iliac artery bifurcation and the...
exercise training (7, 11, 23, 29, 31).

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cohort of subjects (validation cohort), we tested the hypotheses
values against directly measured CFPWV values. In an additional
EfRD based on demographic and anthropometric parameters in
to compute a reliable estimate of APWV that can discriminate
commonly obtained demographic and anthropometric parameters
length determined from body surface measurements as an esti-
transit time. APWV was then calculated using the aortic path
waves transformed into aortic pulse waves and decomposed into
height/4

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femoral recording site and suggested that the EfRD moves
distally with aging based on MRI-documented anatomical
elongation of the ascending aorta with advancing age (25).

Because the reflecting distance from the aortic valve to the
peripheral reflecting site must be known to calculate APWV from
a single peripheral waveform, Weber et al. (34) proposed that
an equation based on anthropometric parameters (EfRD = body
height/4 + 7.28 cm) could be used but did not perform pulse wave
analysis to estimate APWV using this equation. Qasem and
Avolio (20) derived APWV from noninvasive radial artery pulse
waves transformed into aortic pulse waves and decomposed into
forward- and backward-traveling waves to estimate the pulse
transit time. APWV was then calculated using the aortic path
length determined from body surface measurements as an esti-
EfRD. However, it is currently unknown whether EfRD
can indeed be derived from such anatomical landmarks or other
customarily obtained demographic and anthropometric parameters
to compute a reliable estimate of APWV that can discriminate
differences in APWV in select groups of adults known to differ
significantly in CFPWV.

Therefore, we tested the hypothesis that an equation for the
EfRD based on demographic and anthropometric parameters in
healthy adults can be used to reliably estimate APWV from
peripheral pulse waveforms by comparing determined APWV
values against directly measured CFPWV values. In an additional
cohort of subjects (validation cohort), we tested the hypotheses
that (1) the EfRD estimated from demographic/anthropometric
parameters can reliably detect the distal shift of the reflecting site
with aging (i.e., longer EfRD in older subjects) (9, 24, 36) and (2)
APWV derived from peripheral pressure waveforms detects the
well known increase in CFPWV with sedentary aging in humans
that is attenuated in older adults who perform habitual endurance
exercise training (7, 11, 23, 29, 31).

METHODS

Subjects

Derivation cohort. Forty nonsmoking men and women (age range
18–76 yr) were recruited and had CFPWV (SphygmoCor, AtCor
Medical; see below for details) and either intrabrachial artery blood
pressure waveforms (n = 25) or finger volume pulse waveforms (n = 15,
EndoPAT, Itamar Medical; see below for details) recorded.
Subjects also had height and weight recorded, from which body mass
index [BMI = weight (in kg) ÷ height (in m)2] and body surface area
[BSA = 0.20247 × height (in m)0.725 × weight (in kg)0.425; DuBois
formula] were calculated (Table 1).

Validation cohort. Forty-four additional healthy young (age 18–35
yr) and older (age 55–75 yr) men and women were recruited and
stratified into three groups based on age and sedentary or exercise-
training status: young sedentary (n = 6; 5 women), older endurance
exercise-trained (n = 14; 2 women), and older sedentary adults (n = 24;
16 women). Subjects were nonsmokers, non-diabetic, and free of
other clinical diseases as assessed by medical history, physical examina-
tion, blood chemistry, and resting and exercise 12-lead ECG (Table 2).
Subjects were excluded if they were taking any prescription medica-
tions, herbal supplements, antioxidants, or aspirin. Sedentary young
and older subjects performed no or minimal regular aerobic exercise
(i.e., <30 min/day, <2 days/wk) for at least the last 2 yr. The
endurance exercise-trained subjects performed regular vigorous aer-
obic exercise (competitive running, triathlons, and/or cycling) for >5
days/wk and >45 min/session for at least the last 5 yr.
All measurements were performed after an 8- to 12-h overnight fast
and 24-h abstention from alcohol and caffeine. All procedures were

Table 1. Subject characteristics of derivation cohort

<table>
<thead>
<tr>
<th>Intra-brachial Artery Waveforms (n = 25)</th>
<th>Finger Volume Pulse Waveforms (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td><strong>Male/female, n</strong></td>
</tr>
<tr>
<td>38 ± 4</td>
<td>7/18</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>69 ± 2</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>161 ± 1</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>24 ± 0.4</td>
</tr>
<tr>
<td><strong>Body surface area, m²</strong></td>
<td>1.79 ± 0.03</td>
</tr>
<tr>
<td><strong>Systolic BP, mmHg</strong></td>
<td>125 ± 3</td>
</tr>
<tr>
<td><strong>Diastolic BP, mmHg</strong></td>
<td>68 ± 1</td>
</tr>
<tr>
<td><strong>Resting heart rate, beats/min</strong></td>
<td>58 ± 2</td>
</tr>
<tr>
<td><strong>½Δt_b, ms</strong></td>
<td>78 ± 2</td>
</tr>
<tr>
<td><strong>CFPWV, m/s</strong></td>
<td>7.37 ± 0.29</td>
</tr>
<tr>
<td><strong>EfRD, cm</strong></td>
<td>57 ± 2</td>
</tr>
<tr>
<td><strong>Estimated APWV, m/s</strong></td>
<td>7.47 ± 0.27</td>
</tr>
<tr>
<td><strong>Estimated EfRD, cm</strong></td>
<td>57 ± 1</td>
</tr>
</tbody>
</table>

Data are means ± SE (n = 40). BP, blood pressure; CFPWV, carotid-femoral pulse wave velocity via SphygmoCor; ½Δt_b, one-half of the time delay between forward- and backward-traveling pressure waves determined by pulse wave analysis; True EfRD, true effective reflecting distance calculated as CFPWV × ½Δt_b; Estimated EfRD, estimated aortic pulse wave velocity derived from pulse wave analysis; Estimated EfRD, estimated effective reflecting distance calculated from regression equation using age and body mass index as parameters. *Significant difference between intrabrachial artery waveforms and finger volume pulse waveforms (P < 0.05).

Table 2. Subject characteristics of validation cohort

<table>
<thead>
<tr>
<th><strong>Young Sedentary</strong> (n = 6)</th>
<th><strong>Older Sedentary</strong> (n = 24)</th>
<th><strong>Older Trained</strong> (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td>22 ± 2</td>
<td>62 ± 1 *</td>
</tr>
<tr>
<td><strong>Male/female, n</strong></td>
<td>1/5</td>
<td>8/16</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>61 ± 2</td>
<td>71 ± 2 *</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>171 ± 4</td>
<td>168 ± 2</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>20.7 ± 0.5</td>
<td>24.9 ± 0.6 *</td>
</tr>
<tr>
<td><strong>Body surface area, m²</strong></td>
<td>1.71 ± 0.05</td>
<td>1.80 ± 0.04</td>
</tr>
<tr>
<td><strong>Systolic BP, mmHg</strong></td>
<td>102 ± 10</td>
<td>122 ± 3 *</td>
</tr>
<tr>
<td><strong>Diastolic BP, mmHg</strong></td>
<td>57 ± 2</td>
<td>73 ± 2 *</td>
</tr>
<tr>
<td><strong>Resting heart rate, beats/min</strong></td>
<td>53 ± 2</td>
<td>67 ± 2</td>
</tr>
<tr>
<td><strong>V˙O₂max, ml · kg⁻¹ · min⁻¹</strong></td>
<td>38.7 ± 2.1</td>
<td>26.5 ± 0.9 *</td>
</tr>
</tbody>
</table>

Data are means ± SE (n = 44). V˙O₂max, maximal exercise oxygen consumption. *Significant difference vs. young sedentary subjects (P < 0.05). †Significant difference vs. older sedentary subjects (P < 0.05).
approved by the Institutional Review Boards of the Mayo Clinic and the University of Iowa (derivation cohort), and the Human Research Committee of the University of Colorado at Boulder (validation cohort). The nature, benefits, and risks of the study were explained to the volunteers, and their written, informed consent was obtained before participation.

Measurements

Invasive brachial artery blood pressure waveforms. Invasive brachial artery blood pressure waveforms of the derivation cohort were recorded at the Mayo Clinic Center for Translational Science Activities Clinical Research Center using a 20-gauge catheter inserted into the brachial artery by a physician using sterile technique. The catheter was attached to a Cardiocap/5 (GE Healthcare) device that provided the analog pressure waveforms to the Windaq data acquisition software (DATAQ). The data sampling rate was 250 Hz. The invasive brachial artery waveforms for the young sedentary, older sedentary, and older endurance exercise-trained subjects (i.e., validation cohort) were collected at the University of Colorado at Boulder Clinical Translational Research Center. Brachial artery waveforms were obtained via an 18-gauge catheter inserted into the brachial and was attached to a Cardiocap/5 (GE Healthcare) device that provided the analog pressure waveforms to the Windaq software (DATAQ). The data sampling rate was 500 Hz.

Finger volume pulse waveforms. Finger volume pulse waveforms were obtained noninvasively by recording finger arterial pulsatile volume changes using a pair of plethysmographic bio-sensors attached to the EndoPAT device (Itamar Medical). One finger probe was placed on the index finger of the hand undergoing hyperemia testing (right hand), and a second probe was placed on the contralateral index finger (left hand). Baseline waveforms before the hyperemic test phase were used for data analysis in the present study.

Carotid-femoral pulse wave velocity. CFPWV was measured noninvasively by recording carotid and femoral artery pressure waveforms via applanation tonometry using the SphygmoCor device (AtCor Medical). The two waveforms were gated to the ECG R-wave to calculate the pulse transit time (PTT) between the foot of the carotid and femoral waveforms. The carotid-femoral transit distance (CFTD) is estimated based on the distance from the suprasternal notch (SSN; assumed location of the aortic valve) to the carotid recording site (SSN-C) and the distance from the SSN to the femoral recording site (SSN-F). The CFTD is then estimated as CFTD = (SSN-F) – (SSN-C), and PWV is calculated as CFTD/PTT.

Data Analyses

True EjRD and estimated APWV in the derivation cohort. True EjRD and estimated APWV in the derivation cohort were determined using the freely available HemoLab software (http://haraldstauss.com/HaraldStaussScientific/hemolab). First, the peripheral waveforms (i.e., intrabrachial artery pressure and finger volume pulse) were converted into ascending aortic pressure waveforms using the model transfer function published by Sugimachi et al. (26, 27) that is implemented in the HemoLab software (Fig. 1). This model transfer function depends on three parameters (wave transmission delay along the tube; peripheral capacitance × peripheral resistance; and characteristic impedance of tube divided by peripheral resistance). The values for these parameters as provided by Sugimachi et al. (26, 27) are for the transfer function from the radial artery to the aorta. Because we applied the transfer function to the brachial artery pressure and finger volume pulse waveforms instead of to the radial artery pressure waveforms, we could have adjusted the value for the parameter “wave transmission delay along the tube” accordingly. However, we opted to use the originally published values for all three parameters, because it has been demonstrated that the model transfer function is insensitive to changes in its parameters, even if the values of the parameters change by a factor of four (27). Because of the insensitivity of the model transfer function to changes in its parameters, a potential amplification between brachial and radial artery pressure pulse as suggested by Segers et al. (21) and Verbeke et al. (32) may only have a minor effect on the calculated arterial pressure waveforms.

Second, the calculated ascending aortic pressure waveforms were decomposed into the forward- and backward-traveling (reflected) waves and their time delay (Δt_f-b), calculated according to the algorithm published by Westerhof et al. (35) and Qasem and Avolio (20), which is also implemented in the HemoLab software. We then determined the true EjRD by computing the product of CFPWV (determined by SphygmoCor) and ½Δt_f-b. Using the true EjRD as the dependent variable, we developed a regression equation by entering available demographic and anthropometric parameters from the derivation cohort into the model, including age, gender, height, weight, BMI, body surface area (BSA), and systolic blood pressure. This was done by linear backward stepwise regression analyses using Akaike’s
information criterion (AIC) using the R Statistical software (3). The analysis revealed that EfRD can be estimated using only age in years and BMI in kg/m² as parameters. Adding gender, height, weight, BSA, or systolic blood pressure into the regression equation did not improve estimation of EfRD significantly. The regression resulted in the equation: EfRD (in cm) = 0.173·age + 0.661·BMI + 34.548. Estimated APWV was then calculated by dividing EfRD (estimated by the regression equation above) through ½Δt₁₋₂. The estimated EfRD (based on the regression equation) and the estimated APWV were then validated against the true EfRD (based on ½Δt₁₋₂ and CFPWV) and the directly measured CFPWV, respectively, by inter-Pearson’s and intraclass (ICC) correlation and Bland-Altman analyses. In contrast to the Pearson’s interclass correlation coefficient R², the intraclass correlation coefficient ICC considers whether the correlated parameters (e.g., CFPWV and APWV) agree in terms of absolute values. For example, if two parameters, x and y, are correlated according to a linear transformation, such as y = 3x + 5, the Pearson’s interclass correlation coefficient R² will be 1.0, whereas the intraclass correlation coefficient ICC will be <1.0. Bland-Altman plots show the dependency of the difference of two estimates of the same parameter from the absolute value of the parameter. Ideally, the difference of the two estimates of the same parameter should be close to zero for all absolute values of the parameter. Bland-Altman plots can also reveal whether the disagreement between two estimates of the same parameter depends on the absolute value of the parameter. In such a case, a linear trend may be observed in the Bland-Altman plot.

The effect of age and exercise training on EfRD and APWV. The effect of age and exercise training on EfRD and APWV was investigated in the validation cohort of young sedentary, older sedentary, and older endurance exercise trained subjects from a subset of subjects from previous studies with high-quality intra-arterial brachial artery blood pressure recordings available (18, 19). The estimated EfRD was determined from the regression equation derived above from the derivation cohort. The estimated APWV was then calculated based on the estimated EfRD and ½Δt₁₋₂ determined from the intra-arterial brachial artery blood pressure recordings by applying the model transfer function (26, 27) and decomposing the resulting ascending aortic pressure waveform into the forward- and backward-traveling waves (20, 35).

Statistical analysis

Data are presented as means ± SE. Differences between characteristics of subjects with intra-arterial pressure recordings and finger volume pulse recordings in the derivation cohort (Table 1) were tested for statistical significance using unpaired t-tests. Group differences in subject characteristics (Table 2), EfRD, and estimated APWV in the validation cohort were tested for statistical significance using one-way ANOVA for independent measures. If a significant F test resulted, post hoc Fisher’s tests were performed to determine differences between groups of sedentary young, older sedentary, and older exercise-trained subjects.

RESULTS

Validation of estimated APWV against directly measured CFPWV (derivation cohort)

Directly measured CFPWV (SphygmoCor) and estimated APWV (from waveform analysis) values as well as true EfRD (derived from CFPWV and ½Δt₁₋₂) and estimated EfRD (derived from regression equation with age and BMI as parameters) for the two groups of subjects in the derivation cohort (intra-arterial blood pressure and finger volume pulse waveforms) are provided in Table 1. The correlations between true EfRD and estimated EfRD and between directly measured CFPWV and estimated APWV are shown in Fig. 2. There was a significant correlation between true and estimated EfRD (Pearson's R² = 0.239; ICC = 0.397; 95% confidence interval for ICC: 0.104–0.627; P < 0.05). An even stronger correlation was found between measured CFPWV and estimated APWV (Pearson’s R² = 0.428; ICC = 0.643; 95% confidence interval for ICC: 0.420–0.794; P < 0.05).

Bland-Altman plot analysis for the agreement between estimated EfRD (based on regression equation) and true EfRD (based on ½Δt₁₋₂ and CFPWV) is shown in Fig. 3, left. The mean difference between the two estimates for EfRD was 0.00 ± 1.46 cm. This excellent agreement between the two estimates for EfRD was expected, because the regression equation was derived from the same data set. However, a linear trend in the Bland-Altman plot indicates that the regression equation overestimates short EfRDS and underestimates long EfRDS.

The Bland-Altman plot for the agreement between the estimated APWV (based on waveform analysis and using the regression equation to estimate EfRD) and directly measured CFPWV (SphygmoCor) is shown in Fig. 3, right. There was excellent agreement between the two estimates of pulse wave velocity, as indicated by the small mean difference between the two estimates of 0.04 ± 0.19 m/s. No linear trend was obvious in the Bland-Altman plot, indicating that the agreement between the two estimates of pulse wave velocity does not depend on the absolute value of pulse wave velocity.

The significant correlation between directly measured CFPWV and estimated APWV (ICC = 0.643) together with the small average disagreement between the two measures (0.04 ± 0.19

Fig. 2. Correlations between true effective reflecting distance (EfRD) and estimated EfRD and between measured carotid-femoral pulse wave velocity (CFPWV) and estimated aortic pulse wave velocity (APWV). Pearson’s R² values and intraclass correlation coefficients (ICC) were calculated with data from subjects with invasive brachial artery blood pressure (BP) recordings (○) and subjects with noninvasive finger volume pulse recordings (○) pooled. Both correlations were statistically significant (P < 0.05).
Effect of age and exercise training on EfRD and APWV (validation cohort)

Subject characteristics for the three groups of young and older sedentary and older endurance exercise-trained subjects are provided in Table 2. There was no difference between groups in height and BSA, but body weight was slightly higher in both groups of older subjects, leading to somewhat higher BMI values in the older compared with the younger subjects. However, average BMI was within the normal range (<25 kg/m²) in all three groups. Age, maximal O₂ consumption, and resting heart rate differed among groups as expected from the study design.

EfRD calculated using the regression equation established in the derivation cohort was significantly higher in both groups of older subjects compared with the group of young subjects in the validation cohort (Fig. 4, top). This result is consistent with the known distal shift of the reflecting side with age (25). Endurance exercise training did not affect EfRD in older subjects. The travel time of the forward pressure wave from the aortic valve to the peripheral reflecting site (½Δt₁₋₁; Fig. 4, middle) was shorter in older sedentary than in young sedentary subjects. This finding is consistent with our finding of a higher APWV in older sedentary compared with young sedentary subjects (Fig. 4, bottom). Endurance exercise training in older subjects significantly prolonged the travel time of the aortic pressure wave ½Δt₁₋₁ compared with sedentary older subjects (Fig. 4, middle). Again, this finding is consistent with our finding of a slower APWV in older endurance-trained subjects than in older sedentary subjects (Fig. 4, bottom).

DISCUSSION

The novel finding of this study is that an equation that uses age and BMI provides a reliable estimation of the EfRD. This finding is significant, because it allows for determination of APWV from peripheral blood pressure/finger volume pulse waveforms using the transfer function technique. APWV determined using the established equation for EfRD in combination with waveform analysis of peripheral pulse waves resulted in a strong correlation with the gold standard measurement of CFPWV in a cohort of healthy adults. We found a good ICC of 0.64 between the two measurements, and Bland-Altman analysis revealed a high agreement between the two techniques with an overall mean difference between estimated APWV and CFPWV of only 0.04 m/sec.

We also applied the regression equation to a second validation cohort of young sedentary, older sedentary, and older endurance exercise-trained subjects that resulted in values for APWV that are consistent with published values for these groups (7, 11, 12, 23, 29–31). It is well established that young sedentary adults have lower APWVs than exercise-trained older adults who have lower APWVs than sedentary older adults (7, 11, 12, 23, 29–31). Thus a reliable equation for the reflecting distance should result in APWVs that differentiate between these three populations at a statistically significant level. In addition, a reliable equation should also demonstrate the distal shift of the reflecting site (i.e., lengthening of the reflecting distance) with age (9, 24, 36). Based on these criteria, the regression equation resulted in EfRDS that demonstrated the age-related distal shift of the reflecting site and resulted in APWVs that differentiate between all three groups of subjects. These findings suggest that the established regression equation indeed provides reliable estimates for the reflecting distance in healthy young and older adults.

It is important to consider the parameters that define our regression equation for EfRD. Initially, the input parameters for the linear backward stepwise regression analyses included age, gender, height, weight, BMI, BSA, and systolic blood pressure. However, including gender, height, weight, BMI, and systolic blood pressure into the linear regression model does not improve the model significantly. The finding that the subject’s height only enters the regression equation through BMI may be surprising because intuition suggests that the reflecting distance depends on aortic length, which is influenced by the height of the subjects. However, the EfRD is a functional distance that does not correspond to any anatomically defined distance. Furthermore, the aortic bifurcation moves caudally with age (9, 24, 33, 36), increasing EfRD, whereas body height typically declines with advanced age. Thus EfRD may be more dependent on age than on the actual height of the subjects. Indeed, age was identified as a significant parameter determining EfRD in our linear backward stepwise regression analysis. In this regard, it has been demonstrated that the aortic bifurcation is located at the level of L3 in fetuses, moves to the level of L4 in adults, and finally

m/s) suggests that waveform analysis of peripheral pressure or volume pulse recordings allows for reliable estimation of central (aortic) pulse wave velocity.

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It is important to consider the parameters that define our regression equation for EfRD. Initially, the input parameters for the linear backward stepwise regression analyses included age, gender, height, weight, BMI, BSA, and systolic blood pressure. However, including gender, height, weight, BMI, and systolic blood pressure into the linear regression model does not improve the model significantly. The finding that the subject’s height only enters the regression equation through BMI may be surprising because intuition suggests that the reflecting distance depends on aortic length, which is influenced by the height of the subjects. However, the EfRD is a functional distance that does not correspond to any anatomically defined distance. Furthermore, the aortic bifurcation moves caudally with age (9, 24, 33, 36), increasing EfRD, whereas body height typically declines with advanced age. Thus EfRD may be more dependent on age than on the actual height of the subjects. Indeed, age was identified as a significant parameter determining EfRD in our linear backward stepwise regression analysis. In this regard, it has been demonstrated that the aortic bifurcation is located at the level of L3 in fetuses, moves to the level of L4 in adults, and finally
reaches the level of L5/S1 in advanced age (33). The second significant parameter identified in the linear regression model is BMI. Huybrechts et al. (9) found that BMI significantly contributes to the difference between MRI-based and tape measurement-based aortic path lengths used for direct CFPWV determination. This study, therefore, confirms the result of our regression analysis and provides evidence that BMI (in addition to age) independently contributes to the EfRD. Furthermore, because the two validation cohorts differed by BMI significantly, we developed individual regression equations for each cohort. Although for the brachial artery BP cohort BMI was still necessary to estimate EfRD, BMI did not improve the estimation of EfRD for the finger volume pulse cohort. In addition, the individual regression equations did not result in different estimates for EfRD than the pooled regression equation.

It should be noted that Kips et al. (10) reported on the accuracy of decomposition of the central pressure waveform into a forward and backward-traveling wave using the triangular approximation method vs. a method when measured aortic flow and pressure are known. Based on their analyses, the authors concluded that “results from pressure-based approximative methods to derive reflection magnitude or aortic pulse transit time differ substantially from the values obtained when using both measured pressure and flow information.” Although the obtained values for pulse transit time were different in their study, there was still a significant correlation between the transit times calculated using triangular approximation and transit time calculated based on measured pressures and flows ($R^2 = 0.28$). This significant correlation indicates a systematic (nonrandom) error that explains the difference in transit time values obtained using triangular approximation vs. measured pressures and flows. Thus, although the absolute values were different from the true values when the triangular approximation is used, the relative magnitude of the values (e.g., when groups of subjects are compared) may still be correct.

Our results also confirm the age-related increase in APWV in sedentary adults and that older adults who perform habitual endurance exercise show an attenuation of APWV. McEniery et al. (12) reported APWV values of ~6 m/s in 20-yr-old and ~8 m/s in 60-yr-old healthy subjects. Furthermore, Shibata and Levine (23) reported APWV values of ~6.0 m/s in 20- to 42-yr-old healthy subjects and ~9.5 m/s and ~7.7 m/s in 65- to 77-yr-old sedentary and trained healthy subjects, respectively. Thus the values of 6.4 ± 0.3 m/s in young adults and 9.6 ± 0.2 m/s and 8.1 ± 0.2 m/s for the APWV in the sedentary and exercise-trained older subjects in our study appear to be reasonable and are consistent with APWV values reported in previous studies (7, 11, 12, 23, 29–31).

Another important finding of this study is that the time delay between the forward and reflected waves (Fig. 4, middle) was significantly longer in endurance exercise-trained adults than in sedentary older adults, whereas the estimate for reflecting distance was the same (Fig. 4, top). Thus the lower APWV (Fig. 4, bottom) in endurance exercise-trained older adults compared with sedentary older adults is likely caused by a true inhibitory effect of habitual aerobic exercise training on aortic stiffening rather than simply an exercise-related change in the location of the reflecting site in older adults.

Our study should be interpreted in the context of several limitations. First, because the SSN-femoral path length was measured with a tape measure on the body surface, CFPWV may have been overestimated in subjects with abdominal obesity in the derivation cohort. However, the derivation cohort using intrabrachial artery waveforms was fairly lean as was the validation cohort (mean BMI of ~25 kg/m²), making this unlikely. It is more likely that the derivation cohort that used finger volume pulse waveforms was overestimated given that they consisted of adults with a mean BMI in the obese range. Second, the regression equation was derived from peripher closing pressure and volume waveforms during the resting state; therefore, it is unknown how the equation would estimate EfRD during states of sympathoexcitation (e.g., cold pressor test, mental stress test, exercise). Last, although the prediction equation seemed to do well at demonstrating differences between young, old, and old exercise-trained subjects, it does not appear that it would do as well at classifying at the individual level (e.g., is APWV “normal” or “healthy” for a given indi-
 Perspectives

We have established a novel equation based on demographic and anthropometric parameters that allow estimation of the reflecting distance required for calculation of APWV by the transfer function technique. Application of this equation to brachial artery blood pressure recordings in young sedentary, older sedentary, and older exercise-trained subjects resulted in values for APWV that are consistent with APWV values reported by others using more direct estimates of APWV. The equation for EfRD resulted in APWV values that separated groups of young sedentary, older sedentary, and older exercise-trained subjects and revealed the well known distal shift of the reflecting site that occurs with aging (9, 24, 36). This finding suggests that the equation for EfRD can be used to reliably estimate APWV from peripheral pulse waveforms.

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AUTHOR CONTRIBUTIONS

G.L.P. and H.M.S. prepared figures; G.L.P. and H.M.S. drafted manuscript; analyzed data; G.L.P., D.R.S., and H.M.S. interpreted results of experiments; research; G.L.P., D.P.C., J.G.F., D.R.S., T.B.C., J.N.B., and H.M.S. performed

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