Pulse Pressure Is Inversely Related to Aortic Root Diameter Implications for the Pathogenesis of Systolic Hypertension

S. Morteza Farasat, Christopher H. Morrell, Angelo Scuteri, Chih-Tai Ting, Frank C.P. Yin, Harold A. Spurgeon, Chen-Huan Chen, Edward G. Lakatta, Samer S. Najjar

Abstract—Hypertension accelerates the age-associated increase in aortic root diameter (AoD), likely because of chronically elevated distending pressures. However, the pulsatile component of blood pressure may have a different relationship with AoD. We sought to assess the relationship between AoD and pulse pressure (PP) while accounting for left ventricular and central arterial structural and functional properties, which are known to influence PP. The study population was composed of 1256 individuals, aged 30 to 79 years (48% women and 48% hypertensive), none of whom were on antihypertensive medications. Blood pressure was measured in the sitting position with conventional sphygmomanometry. PP was calculated as the difference between systolic and diastolic blood pressures. AoD was measured at end diastole at the level of the sinuses of Valsalva with echocardiography. The relationship between AoD and PP was evaluated with multiple regression analyses. PP was 50±14 mm Hg in men and 54±18 mm Hg in women, and AoD was 31.9±3.5 mm in men and 28.9±3.5 mm in women. After adjusting for age, age², height, weight, and mean arterial pressure, AoD was independently and inversely associated with PP in both sexes. After further adjustments for central arterial stiffness and wall thickness, reflected waves, and left ventricular geometry, AoD remained inversely associated with PP in both men (coefficient = −0.48; P=0.0003; model R²=0.51) and women (coefficient = −0.40; P=0.01; model R²=0.61). Thus, AoD is inversely associated with PP, suggesting that a small AoD may contribute to the pathogenesis of systolic hypertension. Longitudinal studies are needed to examine this possibility. (Hypertension. 2008;51:196-202.)

Key Words: aorta ■ sinus of Valsalva ■ pulse pressure ■ systolic hypertension

Advancing age is characterized by increased central arterial stiffness, which manifests as a rise in pulse pressure (PP) and a marked increase in the prevalence of systolic hypertension among older individuals.1–2 PP, a prominent risk factor for both noncardiovascular3 and cardiovascular4 morbidity and mortality, originates from the pulsatile left ventricular ejections. The proximal aorta stores the pressure and flow that are generated in systole in its elastic wall elements and releases them during diastole.4–8 Thus, PP is influenced by structural and functional properties of both the left ventricle and the proximal aorta.4–8

With advancing age, the central aorta dilates in both humans9 and nonhuman primates.10 These age-associated structural changes are explained by the physical principles of material fatigue and fracture, where exposure to repeated cyclic stretch results in thinning, splitting, and fragmentation of the elastin fibers within the aortic media.11 Similarly, chronic exposure to high intra-arterial pressures in hypertension is thought to accelerate elastin breakdown, thereby promoting proximal aortic dilatation.12,13 Thus, for a given distending pressure, one might expect this process to be even more exaggerated in individuals with high PP whose arteries are subject to a higher degree of pulsatile stretch. However, in a recent study, individuals with systolic hypertension were found to have a smaller “effective” aortic diameter compared with normotensive control subjects.14 That study has been criticized, however, for relying on calculated “effective” aortic diameter instead of using actual measurements of aortic root diameter (AoD).13,15 Accordingly, the aims of the present study were to evaluate the association between directly measured AoD and PP and to examine the impact of measures of central arterial and left ventricular structure and function on this association.

Methods

Study Population

The study population was composed of 1256 normotensive and untreated hypertensive Taiwanese volunteers (602 women), aged 30...
to 79 years, who underwent a cardiovascular evaluation, including complete medical history and physical examination, arterial tonometry and ultrasonography, and echocardiography, as described previously. All of the participants were free from diabetes mellitus, angina pectoris, and peripheral vascular disease and had no clinical or echocardiographic evidence of other significant cardiac diseases. All of the participants gave informed consent, and the study was approved by the institutional review boards.

Definition of Variables

**Anthropometric and Hemodynamic Variables**

Height, weight, body mass index (BMI [kg/m²]) = weight [kg]/height [m²], body surface area (BSA [m²] = 0.007184 × height [cm]'0.425 × weight [kg]'0.13), and resting heart rate (HR) were recorded for all of the subjects. Brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the sitting position with conventional sphygmomanometry using an appropriately sized cuff. Reported blood pressures represent the average of ≥2 consecutive measurements. Brachial PP was calculated as SBP - DBP, and mean arterial pressure (MAP) was calculated as DBP + (PP/3). Carotid SBP and PP, which closely reflect central aortic SBP and PP,12 were derived by calibrating the right common carotid artery pressure waveforms with DBP and MAP.

**Cardiac Variables**

All of the subjects underwent transthoracic echocardiography by the same experienced sonographer using a Hewlett-Packard Sonos 500U system (Hewlett-Packard) equipped with a 2.5-MHz transducer. Left ventricular wall thicknesses and internal dimensions were measured from 2D guided M-mode echocardiograms as described previously.16 Average left ventricular wall thickness (AWT) was calculated as the average of the posterior and interventricular septal wall thicknesses at end diastole. Stroke volume (SV) was calculated from left ventricular volumes derived from end-diastolic (LVED) and end-systolic left ventricular internal diameters using the Teichholz method.18

**Arterial Variables**

AoD was measured at end diastole at the level of the sinuses of Valsalva from 2D guided M-mode echocardiograms. AoD measurements were made in triplicates, and the average was used in the analyses. Carotid-femoral pulse wave velocity (PWV) was calculated from sequential nondirectional Doppler flow at the right common carotid and femoral arteries (Parks model 802, Parks Medical Electronics, Inc).16 Carotid augmentation index (AGI) was derived from the right common carotid artery pressure waveforms recorded with applanation tonometry.20 The right common carotid artery far wall intima-media thickness (IMT) was measured from frozen digitized images obtained with B-mode ultrasonography using a 7-MHz probe.21

**Statistical Analysis**

All of the analyses were performed separately for men and women using SPSS 14.0 (SPSS Inc.). Correlations between variables were assessed with Pearson’s correlation coefficient (r). Multiple regression analyses were used to assess the independent determinants of PP. Independent variables were selected based on their known or expected associations with PP. Because PP increases with age in a nonlinear manner, all of the models included age and age² to adjust for both linear and quadratic relationships of PP with age. In addition to the age terms, the base models included height, weight, HR, and MAP as independent variables. Subsequently, AoD was added to the models to determine its independent association with PP. Because left ventricular and central arterial properties both influence PP, arterial (PWV, AGI, and IMT) and cardiac (AWT and LVED) variables were successively added to the models to examine their contributions to PP and to determine their potential impact on the association between AoD and PP. The independent determinants of carotid PP (cPP) were assessed with similar analyses using the same independent variables. To address collinearity between age and age², centered values of age were used in the multiple regression analyses.22 Variance inflation factors were monitored and were <2.5 in all of the models, ensuring lack of multicollinearity among the independent variables. Data are presented as mean±SD unless otherwise specified. Statistical significance was inferred for P<0.05.

**Results**

**Characteristics of the Study Population**

Participants were nearly evenly distributed in the fourth to eighth decades of age. Table 1 summarizes the clinical, arterial, and cardiac characteristics of the study cohort.

**Association of the Study Variables With PP**

Table 2 shows the correlations of PP and cPP with the study variables. PP and cPP were strongly associated with age, PWV, AGI, and AWT in both sexes. As shown in Figure 1, AoD was positively associated with PP in both men (r=0.09; P=0.02) and women (r=0.20; P<0.0001). Because AoD and PP both increased with advancing age and increasing MAP (Figure 2), multiple regression analyses were performed to assess the independent association of AoD with PP.

**Independent Determinants of PP**

In the first set of multiple regression models (Table 3, model A), PP was significantly associated with age, age², weight, and MAP in both sexes. When AoD was added to the models (Table 3, model B), it was independently and inversely associated with PP in both men (coefficient = -0.39; P=0.003) and women (coefficient = -0.30; P=0.054). Additional analyses showed that the association between AoD and PP became inverted only after adjustments were made for both MAP and age.

![Table 1. Anthropometric, Hemodynamic, Arterial, and Cardiac Profiles of the Study Cohort](http://hyper.ahajournals.org/)
Adding the arterial (Table 3, model C) and cardiac (Table 3, model D) variables to the models strengthened the inverse association of AoD with PP in both sexes. The independent determinants of PP in the fully adjusted models included age, age², weight, MAP, and AoD in both sexes, along with PWV and AWT in men and LVED in women (Table 3, model D; model $R^2=0.51$ in men; model $R^2=0.61$ in women). After adjusting for covariates, AoD accounted for 10.2% and 6.6% of the overall variance in PP in men and women, respectively. As illustrated in Figure 3, each 1-mm increase in AoD was associated with a 0.5-mm Hg and 0.4-mm Hg decrease in PP in men and women, respectively.

The directionality and magnitude of associations between PP and AoD were not affected when SV or ejection fraction were substituted for LVED or when BSA or body mass index were used as measures of body size in the models instead of height and weight.

When AoD was replaced with the ratio of AoD:BSA (AoD “indexed” to BSA) in the models, significant, inverse associations between PP and indexed AoD were also found. Similarly, replacing LVED, AWT, and SV with their corresponding values indexed to BSA did not alter these results.

When the analyses were repeated for cPP, similar inverse associations with comparable magnitudes were observed between cPP and AoD in both men and women (model $R^2=0.50$ and women (coefficient $= -0.45; P = 0.0007$; model $R^2=0.50$) and women (coefficient $= -0.41; P = 0.01$; model $R^2=0.61$; please see Table S1 available at http://hyper.ahajournals.org). Notably, unlike PP, which was not associated with HR, cPP was significantly and inversely related to HR in all of the examined models (all $P<0.0001$).

### Discussion

In the present study, we examined the relationship of AoD with PP and cPP in a large sample of normotensive and untreated hypertensive individuals of a broad age range. We found that, after adjusting for age, MAP, and body size, a smaller AoD was associated with higher PP and cPP. These inverse associations persisted even after adjusting for measures of central arterial and left ventricular structure and function.

#### AoD and PP

Four previous studies have reported inverse associations between AoD and PP. Vasan et al\(^23\) found an independent, inverse association between AoD and PP in the Framingham cohort ($n=4001$; age range: 20 to 89 years) and speculated that intimal-medial hypertrophy or reflex smooth muscle activation induced by an increased PP may underlie this association. Similarly, in a substudy of the Losartan Intervention for Endpoint Reduction Trial ($n=964$; age range: 55 to 80 years), Bella et al\(^26\) observed an inverse association between AoD and PP and hypothesized that the higher compliance of a larger aortic root may blunt the rise in systolic pressure and, thus, result in a lower PP. Agmon et al\(^25\) also found an inverse association between AoD and PP in a subgroup of the Stroke Prevention: Assessment of Risk in a Community population ($n=373$; age range: 51 to 101 years) and attributed it to the confounding effects of antihypertensive therapy and atherosclerotic stiffening of the proximal aorta. In a smaller study, Jondeau et al\(^26\) found that AoD was inversely associated with cPP (but not brachial PP) in the healthy control group, but was positively associated with PP in subjects with Marfan syndrome who have known alterations in their aortic wall properties. The authors speculated that the inverse association between AoD and cPP in the healthy cohort was because of reduced wave reflection as a result of higher aortic compliance in those with larger aortic diameters.

It should be noted that these 4 studies\(^23–26\) assessed the role of PP as a predictor of AoD. Conversely, our study evaluated the role of AoD as a determinant of PP.

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**Table 2. Correlates of PP and cPP in Men and Women**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PP Men</th>
<th>PP Women</th>
<th>cPP Men</th>
<th>cPP Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.44§</td>
<td>0.51§</td>
<td>0.44§</td>
<td>0.53§</td>
</tr>
<tr>
<td>Height</td>
<td>-0.16§</td>
<td>-0.23§</td>
<td>-0.16§</td>
<td>-0.26§</td>
</tr>
<tr>
<td>Weight</td>
<td>-0.07*</td>
<td>0.11‡</td>
<td>-0.06</td>
<td>0.11‡</td>
</tr>
<tr>
<td>BSA</td>
<td>-0.11†</td>
<td>0.02</td>
<td>-0.10†</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>0.02</td>
<td>0.23§</td>
<td>0.03</td>
<td>0.25§</td>
</tr>
<tr>
<td>HR</td>
<td>0.00</td>
<td>0.01</td>
<td>-0.11‡</td>
<td>-0.10†</td>
</tr>
<tr>
<td>SBP</td>
<td>0.79§</td>
<td>0.88§</td>
<td>0.76§</td>
<td>0.84§</td>
</tr>
<tr>
<td>DBP</td>
<td>0.21§</td>
<td>0.38§</td>
<td>0.20§</td>
<td>0.36§</td>
</tr>
<tr>
<td>MAP</td>
<td>0.50§</td>
<td>0.66§</td>
<td>0.48§</td>
<td>0.63§</td>
</tr>
<tr>
<td>cSBP</td>
<td>0.77‡</td>
<td>0.86§</td>
<td>0.79§</td>
<td>0.86§</td>
</tr>
<tr>
<td>AoD</td>
<td>0.09†</td>
<td>0.20§</td>
<td>0.08†</td>
<td>0.20§</td>
</tr>
<tr>
<td>PWV</td>
<td>0.40§</td>
<td>0.47§</td>
<td>0.38§</td>
<td>0.45§</td>
</tr>
<tr>
<td>AGI</td>
<td>0.38§</td>
<td>0.43§</td>
<td>0.39§</td>
<td>0.49§</td>
</tr>
<tr>
<td>IMT</td>
<td>0.22§</td>
<td>0.32§</td>
<td>0.23§</td>
<td>0.33§</td>
</tr>
<tr>
<td>AWT</td>
<td>0.25§</td>
<td>0.42§</td>
<td>0.25§</td>
<td>0.41§</td>
</tr>
<tr>
<td>LVED</td>
<td>0.05</td>
<td>0.18§</td>
<td>0.08†</td>
<td>0.22§</td>
</tr>
<tr>
<td>SV</td>
<td>0.11‡</td>
<td>0.24§</td>
<td>0.13§</td>
<td>0.26§</td>
</tr>
</tbody>
</table>

*§P<0.1; †P<0.05; ‡P<0.01; §P<0.0001.

Values represent Pearson’s correlation coefficients. BMI indicates body mass index; cSBP, carotid SBP.
Our study confirms a significant, albeit modest, inverse association between AoD and PP. Importantly, however, our study examines and refutes some of the mechanisms that were proposed to underlie this inverse relationship: (1) we found this association to be independent of other measures of central arterial structure and function; (2) none of our subjects were receiving antihypertensive therapy, indicating that the association between AoD and PP is not attributable to the effect of antihypertensive medications; and (3) we found an inverse association between AoD and cPP, indicating that the inverse association between AoD and (brachial) PP is not simply because of an inappropriate site of pressure measurement, as had been proposed.

AoD Paradox in Systolic Hypertension

According to traditional views, chronic hypertension results in accelerated elastin breakdown and proximal aortic dilatation. To reconcile the paradox between these views and the inverse association between AoD and PP, it is important to emphasize that this inverse association became evident only after adjusting for age and the resistive component of blood pressure (MAP). In other words, higher distending pressures are associated with larger AoD (Figure 2D). But, for a given distending pressure (and age), higher pulsatile pressures are associated with a smaller AoD. Consistent with this interpretation, in an experimental dog model, Wang et al found that the distending component of aortic pressure was proportional to the proximal aortic volume (calculated from measured aortic diameters), whereas the pulsatile component of aortic pressure was proportional to the aortic characteristic impedance, which was inversely related to aortic cross-sectional area.

Recently, Mitchell et al found that middle-aged and older individuals with systolic hypertension have a smaller “effective” aortic diameter than normotensive control subjects. However, their study was criticized for relying on calculated, rather than measured, aortic diameter. In addition, the “effective” aortic diameter was calculated from the aortic characteristic impedance, which relates central arterial pressure and flow characteristics in early systole. Therefore, it likely represents AoD in the systolic phase of the cardiac cycle. Furthermore, the level of aorta to which the “effective” aortic diameter applies is uncertain. Thus, our study, in which AoD at the sinuses of Valsalva was directly measured with echocardiography, complements the findings of Mitchell et al. Taken together with the previous studies, the robust inverse association between AoD and PP supports the possibility that a small AoD may play a causative role in the pathogenesis of systolic hypertension, as first suggested by Mitchell and colleagues.

Proximal Aortic Properties and PP

PP is the result of a complex interplay between left ventricular ejection and the arterial system and is influenced by the...
The relationship between model-predicted PP and AoD. After adjusting for covariates, PP was inversely associated with AoD. Compare the regression lines for men (solid line) and women (dashed line) with those depicting the unadjusted relationship between AoD and PP in Figure 1. Adjusted PP was calculated from the regression equations in Table 3, model D (please see the online data supplement 2) by setting AoD to the observed range and the remaining variables to their mean values for men and women in the study cohort.

Although the age-associated increase in aortic stiffness markedly reduces the distensibility of the proximal aorta, the concomitant increase in AoD has been viewed as a compensatory mechanism, which aims to alleviate the reduction in aortic wall tension, which, in turn, leads to secondary structural changes. Thus, for comparable aortic wall properties (stiffness), a smaller AoD will present a higher impedance to generating systolic pressure, thereby sparing sensitive end organs from the detrimental effects of excessive pressure pulsatility. The buffering capacity of the proximal aorta is influenced by its structural (wall thickness and composition), functional (stiffness), and geometric (diameter) properties. In addition to serving as a conduit for delivering blood to the periphery, the proximal aorta provides more than half of the “buffering” capacity of the entire arterial system. Through this buffering function, the proximal aorta converts the pulsatile flow generated by left ventricular ejections into a relatively steady flow at the level of the microcirculation, thereby sparing sensitive end organs from the detrimental effects of excessive pressure pulsatility. The buffering capacity of the proximal aorta is influenced by its structural (wall thickness and composition), functional (stiffness), and geometric (diameter) properties. In addition to serving as a conduit for delivering blood to the periphery, the proximal aorta provides more than half of the “buffering” capacity of the entire arterial system. Therefore, the proximal aorta converts the pulsatile flow generated by left ventricular ejections into a relatively steady flow at the level of the microcirculation, thereby sparing sensitive end organs from the detrimental effects of excessive pressure pulsatility. The buffering capacity of the proximal aorta is influenced by its structural (wall thickness and composition), functional (stiffness), and geometric (diameter) properties.
eral changes that culminate in increased aortic stiffness.\textsuperscript{3} Alternatively, the inverse association of AoD with PP may reflect an attenuated increase in AoD with advancing age among individuals with high PP, which may be because of greater deposition and cross-linking of collagen molecules in the aortic media.\textsuperscript{9}

**HR Dependency of Central PP**

We found that HR was independently and inversely associated with cPP (please see Table S1) but not with PP. Wilkinson et al\textsuperscript{10} also found that increasing HR by right atrial pacing reduces cPP without changing PP, suggesting HR dependency of cPP but not PP.

**Limitations**

A major limitation of our study is that AoD was only measured at the level of the sinuses of Valsalva. Three previous studies found that the independent associations of aortic diameters with age, body size, and blood pressure differed according to the level at which the diameters were measured.\textsuperscript{25,34,35} Two of these studies\textsuperscript{34,35} did not report the associations between aortic diameters and PP. The third study\textsuperscript{25} found that PP was inversely associated with proximal (sinuses of Valsalva and ascending aorta) but not distal (aortic arch and descending aorta) aortic diameter. Our study cohort was drawn from a Taiwanese population with epide-

**Perspectives**

The age-associated increase in PP is a well-recognized risk factor for both noncardiovascular\textsuperscript{1} and cardiovascular\textsuperscript{2} morbidity and mortality and is largely attributed to proximal aortic stiffening. The inverse association between AoD and PP raises the possibility that AoD may play a causative role in the pathogenesis of systolic hypertension.\textsuperscript{14} However, longitudinal studies are needed to rigorously test this hypoth-

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**Disclosures**

None.

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PULSE PRESSURE IS INVERSELY RELATED TO AORTIC ROOT DIAMETER

IMPLICATIONS FOR THE PATHOGENESIS OF SYSTOLIC HYPERTENSION

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## ONLINE SUPPLEMENT 1

### TABLE S1. The independent determinants of central pulse pressure in men and women assessed in hierarchical multiple regression models

<table>
<thead>
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<th>Variable</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<td></td>
<td>B</td>
<td>SE</td>
<td>P</td>
<td>B</td>
</tr>
<tr>
<td><strong>MEN</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
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<td>...</td>
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<td>...</td>
<td>3.020</td>
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<td>...</td>
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<td>LVED</td>
<td>...</td>
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<td>-0.088</td>
<td>0.056</td>
<td>0.11</td>
<td>-0.065</td>
</tr>
<tr>
<td>HR</td>
<td>-0.231</td>
<td>0.050</td>
<td>&lt;0.0001</td>
<td>-0.232</td>
</tr>
<tr>
<td>MAP</td>
<td>0.609</td>
<td>0.031</td>
<td>&lt;0.0001</td>
<td>0.615</td>
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<tr>
<td>AoD</td>
<td>...</td>
<td>-0.299</td>
<td>0.148</td>
<td>0.04</td>
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<tr>
<td>PWV</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.001</td>
</tr>
<tr>
<td>AGI</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.133</td>
</tr>
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<td>IMT</td>
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<td>...</td>
<td>...</td>
<td>3.996</td>
</tr>
<tr>
<td>AWT</td>
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<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>LVED</td>
<td>...</td>
<td>...</td>
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</tr>
</tbody>
</table>

* Values of age were centered around the mean age for men and women.

Ellipses (…) indicate variables that were not included in a model. B: regression coefficient, SE: standard error, other abbreviations as in table 1.
ONLINE SUPPLEMENT 2

Adjusted pulse pressure in figure 3 was calculated from the following regression equations from table 3, model D for men and women.

**Men:** PP = 0.386 * Age + 0.017 * Age² + 0.126 * Height - 0.175 * Weight - 0.031 * HR + 0.478 * MAP - 0.477 * AoD + 0.005 * PWV + 0.017 * AGI + 1.977 * IMT + 0.893 * AWT + 0.139 * LVED - 15.531

**Women:** PP = 0.412 * Age + 0.014 * Age² - 0.038 * Height - 0.161 * Weight + 0.004 * HR + 0.610 * MAP - 0.396 * AoD + 0.003 * PWV + 0.053 * AGI + 3.573 * IMT + 0.528 * AWT + 0.281 * LVED - 9.304