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# Norms and reference values for pulse wave velocity: one size does not fit all

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**ABSTRACT:** Carotid-femoral pulse wave velocity (PWV) is a gold standard non-invasive marker of arterial stiffness, but its clinical utility has been limited due to the need for normative and reference group data for specific measurement devices. Our community-based sample (N = 502) ranged in age from 40 to 93 years after exclusion of individuals with a history of acute stroke, probable dementia, and diabetes. PWV was assessed with the SphygmoCor® system. Means, medians, SD and 95th percentile values were presented in ten-year age groups for normotensive and hypertensive participants. From among multiple cardiovascular risk factors, a parsimonious regression equation for predicting PWV was developed. Results were compared with the Reference Values for Arterial Stiffness Collaboration (RVASC) study featuring mathematically standardized reference values for an aggregate of clinic sites and measurement devices. As in the RVASC study, a systematic rise in PWV with age was observed with a more pronounced rise for hypertensive individuals, but our specific point estimates of PWV differed from theirs. Our regression models accounted for 48 percent of the variance in PWV using variables routinely available to practicing physicians: age, hypertension status, height, weight, heart rate, mean arterial pressure, creatinine, and glucose. It is important to make available PWV norms and reference group data for specific measurement devices. Development of reference group data for smaller samples is feasible and prediction equations for PWV can be developed from diagnostic information readily available to the practicing physician.

**KEYWORDS:** pulse wave velocity, norms, reference values, risk factors, atherosclerosis

Carotid-femoral pulse wave velocity (PWV) is a gold standard non-invasive marker of arterial stiffness and is itself a predictor of cardiovascular morbidity and mortality [1-11]. The clinical utility of PWV has been restricted by limited normative and reference group data, a situation exacerbated by differences in PWV measurement methods across studies [1-14]. The continuing need for normative and reference values for specific devices has been emphasized in studies comparing PWV measuring devices and meta-analyses [12-14]. There are norms and reference group data for study participants in good health by age and by combined hypertensive-diabetic status [12-19], but to our knowledge, none exists for hypertensive (HT) and normotensive (NT) classifications by decades or HT and NT groups, except for the Reference Values for Arterial Stiffness Collaboration (RVASC) study [20]. In the RVASC study, PWV data were gathered from 13 centers across eight European countries. Subjects were classified as follows: optimal, normal, high normal, grade I, and grade II/III hypertensive blood pressure (BP) categories by age decades, including two additional groups not by decade but above 70 and below 30 years of age. Results for five PWV measuring systems were combined, necessitating the merging of findings from centers using different algorithms and different estimates of path length. Consequently, mathematical adjustments designed to equate transit time and path length estimates across studies were required. The RVASC (20) investigators caution readers that "Even after full adjustment, differences between algorithm and path length were blunted, but not totally abolished." Moreover, they point out that there was a strong data collection center effect that was not accounted for by their standardization procedures.

Thus, our goals were: first, provide normative and reference group data based on a single algorithm (intersecting tangent) employed in a single widely used system (SphygmoCor®); second, to compare our findings with those of the RVASC study in so far as possible, e.g. we present data for persons 80 to 93 years of age rather than combining groups above 70 years of age; and third, to determine a parsimonious regression model for predicting PWV beyond age, hypertension, and necessary control variables such as height and weight, heart rate and mean arterial pressure (MAP). Previous studies have explored relations between cardiovascular risk factors other than hypertension and age that predict PWV [6-8]. Here, we are concerned with the best prediction possible from the fewest variables beyond essential controls.

## METHODS

### Participants

The PWV data were obtained from a community-based sample of 626 participants (61% women; 14% African American) ranging in age from 24 to 93 years (mean age 64.3). They were participants in PWV studies conducted for the first time in the seventh wave (repeated serial data collection) of the Maine Syracuse Longitudinal Study (MSLS), which was initiated in 1975. Recruitment procedures have been described previously [21-23]. Subjects were recruited from the Syracuse, New York community and the surrounding area by means of multi-media advertisement for participation in a study of cognition and BP, and admitted to the study unless they were diagnosed as psychotic or alcoholic, or were receiving treatment for these diseases. Upon diagnosis of hypertension at any wave, individuals were referred to their physician for treatment and 88.6 percent were treated at wave 7.

Carotid-femoral PWV (m/s) was measured for the first time at the seventh (final) wave (2006-2009) of the MSLS and cardiovascular disease (CVD) risk factor covariates from that wave were employed. Thus the present data analysis is cross-sectional. In an initial analysis of the 626 participants for whom PWV data were obtained, subjects were excluded in the following sequence: (1) dementia (n=2); (2) history of acute stroke (n=14); (3) diabetes (n= 93); and (4) under 40 years of age (n=15). Individuals under 40 years of age were excluded due to the small number of subjects in that range. The final dementia-free sample consisted of 502 individuals. Cardiovascular risk factor and demographic data were available for an additional 174 persons meeting these criteria but missing PWV data. Their PWV values were derived by multiple imputations [24], thus increasing the sample size to 676 for a secondary set of analyses.

The clinical diagnosis of dementia was determined from cognitive data and family informant-report, medical records or chart review [21-23] using the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [25]. Prevalent stroke, defined as a focal neurological deficit of acute onset persisting more than 24 hours, was based on self-report and record review, confirmed by hospitalization, treatment for stroke, or both. Diabetes mellitus was defined by treatment with insulin, oral anti-diabetic agents, or by a fasting glucose level ≥ 7 mmol/l. MAP was calculated as diastolic BP+1/3 (systolic BP – diastolic BP). The demographic and cardiovascular morbidity characteristics of the sample are presented in Table 1 .

### Procedure

The University of Maine approved this investigation and informed consent for data collection was obtained from all participants. Participants were admitted to the study center on the day of the study, followed by medical history interview and then PWV measurements.

### Blood Pressure (BP) and Pulse Wave Assessment

Brachial artery pressures were measured using a Critikon Dinamap ProCare 100 (oscillometric method) instrument. All precautions, training and procedures in BP measurement recommended by the Committee Report: Blood Pressure Publication Guidelines were observed [26].

Following 10 minutes of supine rest, 15 consecutive automated brachial BP measurements were taken at 1 minute intervals, 5 supine, 5 standing, and 5 sitting. The resulting 15 measurements were averaged and used for analyses outlined below. After an additional 10 minutes rest, five supine brachial artery BP measurements were obtained, averaged and used for calibration of the SphygmoCor® device [27]. This procedure permitted us to maintain the BP measurement protocol that has been used since the since the beginning of the MSLS study and to obtain additional supine measurements for device calibration purposes.

PWV was assessed noninvasively using the SphygmoCor® system. Electrocardiogram-gated carotid and femoral waveforms were recorded using applanation tonometry. Carotid-femoral path length was measured as the difference between the surface distances joining (1) the suprasternal notch, the umbilicus and the femoral pulse and (2) the suprasternal notch and the carotid pulse. Carotid-femoral transit time was estimated in 8-10 sequential femoral and carotid waveforms as the average time difference between the onset of the femoral and carotid waveforms. The foot of the pulse wave was identified using the intersecting tangent method. PWV was calculated as the carotid-femoral path length divided by the carotid-femoral transit time [27-28]. This is an established, non-invasive and reproducible method to determine arterial stiffness [10, 27-28] and no adjustments are required for transit time and path length [29, 30].

### Predictors and Covariables

Hypertension was defined as taking anti-hypertensive medications at wave 7 or exhibiting an average (over 15 measurements) brachial artery systolic and diastolic BP equal to or greater than 140/90 mmHg. The methods used to assess CVD risk variables and other covariates at wave 7 have been presented in detail previously [21-23].

Two major diagnostic groups were employed: (1) a NT group (n= 206); and (2) a HT group (n= 296) using major selection criteria employed in the RVASC study (20) but with the inclusion of treated

**Table 1.** Sample characteristics by diagnostic category.

| | Normotensive n= 206 | Hypertensive N= 296 | |
|---|---|---|---|
| Age (years) | 61.0 (11.7) | 67.4 (11.3) | <0.001 |
| PWV (m/s) | 8.9 (2.0) | 11.0 (2.9) | <0.001 |
| BMI (kg/m$^2$) | 27.1 (5.1) | 30.4 (6.2) | <0.001 |
| Waist (cm) | 86.4 (15.2) | 96.5 (13.9) | <0.001 |
| SBP (mmHg)[1] | 116.6 (12.3) | 137.4 (20.0) | <0.001 |
| DBP (mmHg)[1] | 73.2 (7.8) | 79.9 (10.4) | <0.001 |
| PP (mmHg)[1] | 43.3 (10.0) | 57.5 (16.4) | <0.001 |
| MAP (mmHg)[1] | 87.7 (8.3) | 99.1 (12.1) | <0.001 |
| HR (beats/min) | 57.7 (7.9) | 60.3 (9.6) | 0.002 |
| Glucose (mg/dl) | 88.6 (9.2) | 94.6 (11.0) | <0.001 |
| Creatinine (mg/dl) | 1.0 (0.2) | 1.1 (0.2) | 0.006 |
| Cholesterol (mg/dl) | 200.3 (37.4) | 185.0 (39.2) | <0.001 |
| HDL (mg/dl) | 58.8 (16.4) | 51.7 (14.6) | <0.001 |
| LDL (mg/dl) | 122.4 (31.1) | 109.7 (33.2) | <0.001 |
| Triglycerides (mg/dl) | 97.3 (67.8) | 117.5 (58.4) | <0.001 |
| Total/HDL | 3.6 (1.0) | 3.8 (0.9) | 0.10 |
| Alcohol (oz/wk) | 1.4 (2.4) | 1.5 (2.6) | 0.59 |
| Cigarettes/wk | 7.6 (38.3) | 8.5 (34.1) | 0.79 |
| Height (cm) | 166.2 (9.2) | 167.9 (10.5) | 0.06 |
| Weight (kg) | 75.0 (16.4) | 85.6 (18.9) | <0.001 |
| Homocysteine (µmol/l) | 9.1 (2.1) | 10.8 (3.6) | <0.001 |
| Duration of hypertension | | 16.1 (14.3) | |
| Education (years)[2] | 15.3 (2.7) | 14.4 (2.7) | <0.001 |
| % Women | 70.9 | 58.5 | 0.004 |
| % Anti-hypert Meds | | 85.8 | |
| % CVD[2] | 0.5 | 13.9 | <0.001 |
| % African American | 9.2 | 12.2 | 0.30 |
| % APOE-ε4 | 29.0 | 29.9 | 0.08 |

[1]brachial pressure

[2]CVD: cardiovascular disease (includes myocardial infarction, coronary artery disease, and heart failure)

Note: a t-test was used for continuous variables; a chi-square test was used for categorical variables [28].

HT individuals so as to achieve maximum cell size for cross tabulation of age and HT groups. Methods for adjusting for treatment are defined in the results section.

**Statistical Analysis Plan**

SAS version 9.2 and Stata 11 were used for all analyses. The following steps were employed: (1) description of, and statistical comparisons between, demographic and clinical parameters of the NT and HT groups; (2) multiple imputation of missing PWV values; (3) presentation of descriptive reference group data by age and BP classifications; and (4) multiple regression analyses with two purposes, (a) determine the statistical significance of age effects, HT group effects, and their interactions, and (b) determination of the increased prediction of PWV afforded by adding other CVD risk factors to the PWV equation involving age and HT parameters.

Because of the positively skewed nature of the PWV values, sensitivity analyses were performed including analysis of log PWV, robust regression and examination of residuals and influence statistics. Diagnostic results were within acceptable values and revealed no issues. The pattern of results was identical for log PWV and raw score data and results are reported for raw scores which are most directly interpretable.

Using available CVD covariables and demographics, the imputation procedure used chained equations to construct 10 imputed data sets designed to provide the missing PWV data. Results from analyses were combined across imputations using Rubin's rules [31]. Agreement obtained with imputation and listwise deletion was high and the similarity of the pattern of significant results for the observed PWV and the imputed + observed values was high as discussed below. This allowed us to determine the impact of missing data on our findings and increase our sample size for a secondary presentation of the normative and reference value data. Missing data fractions were within statistically acceptable limits.

**RESULTS**

**Sample Characteristics**

Table 1 shows the demographic and cardiovascular risk factors for HT and NT groups for the observed data and p-values for differences among the groups. For most of the variables presented, compared to the NT cohort, persons in the HT cohort exhibited a higher prevalence of CVD risk factors or higher clinical values ($p<0.05$), were older ($p< 0.05$) and somewhat less educated ($p<0.05$), although education differences were slight in absolute terms.

**Preliminary Adjustment**

A majority of HT participants were treated by wave 7. In order to compare our data with RVASC data for subcategories of HT it was necessary to estimate untreated BP values. Following Tobin et al., we added a "reasonable constant" to systolic and diastolic BP for treated HT individuals [32]. With age and BMI controlled, differences between treated and untreated systolic and diastolic values in our study were 8 and 4 mmHg respectively. These values were used as constants. Results were essentially the same with the addition of 10 and 5 mmHg constants used in other studies [33-34]. Consequently, we utilized the 8 and 4 mmHg adjustment for all BP classifications and calculation of MAP. To check on the effectiveness of the adjustment we compared treated and untreated HT individuals with respect to PWV values after our adjustments for treatment and found no statistically significant effects of treatment ($p= 0.93$).

**MSLS Classifications**

Figure 1 shows a systematic rise in PWV with age and consistently higher PWV values for the HT group. The top and bottom portions of Table 2 show, respectively, reference group data samples based on the observed and imputed PWV values. Both show the RVASC PWV data where comparisons are possible due to reporting of data for the same age groups. PWV values were higher for the HT participants, and increased with age within the NT and HT categories, and at each age the HT cohort exhibited higher PWV values. This same pattern was seen for medians and for the 95$^{th}$ percentile of the distribution. Regardless of whether observed or imputed means are employed in the analysis, agreement with the RVASC study is generally good. Mean values for the RVASC study are within one-half SD from the MSLS means.

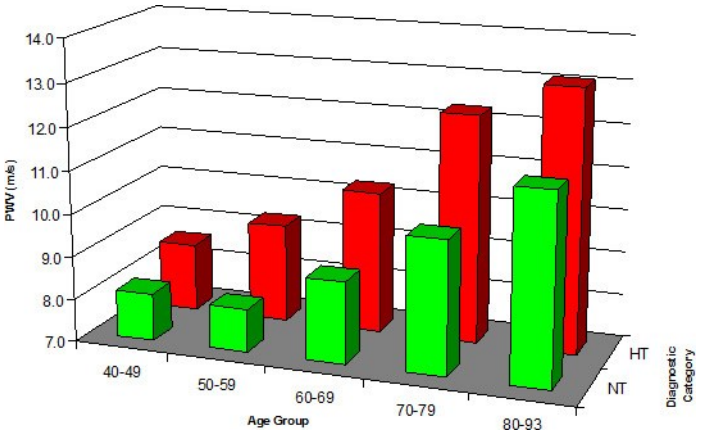


**Figure 1.** A bar plot showing trends for age within HT and NT groups.

The regression equation for the categorical regression with age centered was as follows: PWV = 9.152 + 0.844 × age group + 1.479 × HT + 0.453 × age group × HT; $R^2 = 0.36$. The age group ($p< 0.001$), HT ($p<0.001$) and the age group x HT ($p<0.01$) effects were all statistically significant.

**More Refined Diagnostic Groups**

Visual inspection indicates a high agreement between imputed and observed values of PWV. Consequently, using the imputed data we were able to achieve cell sizes sufficient to reproduce reference group data for some more specific diagnostic categories employed in RVASC and defined in Table 3. We show difference scores for PWV values for RVASC and our study. While sample size is quite low at younger ages for our cells representing the RVASC hypertension grade II/III categories, the progression of increased

**Table 2.** Normative and reference group data for PWV by hypertensive status and age group.

| Group/Observed | Age Group | N | Mean | SD | Median | 95th | RVASC M | MSLS-RVASC |
|---|---|---|---|---|---|---|---|---|
| Normotensive | 40-49 | 34 | 8.1 | 1.3 | 7.8 | 10.4 | 7.4 | 0.7 |
| | 50-59 | 69 | 8.0 | 1.3 | 7.9 | 10.6 | 8.2 | -0.2 |
| | 60-69 | 48 | 8.9 | 1.9 | 8.5 | 12.1 | 9.7 | -0.8 |
| | 70-79 | 40 | 10.1 | 2.1 | 10.0 | 14.6 | | |
| | 80-93 | 15 | 11.4 | 2.6 | 10.5 | 17.1 | | |
| Hypertensive | 40-49 | 17 | 8.6 | 1.5 | 8.2 | 11.8 | 9.0 | 0.4 |
| | 50-59 | 63 | 9.3 | 1.5 | 9.3 | 11.7 | 9.6 | -0.3 |
| | 60-69 | 85 | 10.3 | 2.3 | 9.9 | 14.2 | 11.4 | -1.1 |
| | 70-79 | 84 | 12.3 | 3.1 | 11.7 | 18.5 | | |
| | 80-93 | 47 | 13.1 | 3.1 | 12.6 | 18.5 | | |

| Group/Imputed | Age Group | N | Mean | SD | Median | 95th | RVASC M | MSLS-RVASC |
|---|---|---|---|---|---|---|---|---|
| Normotensive | 40-49 | 42 | 8.1 | 1.3 | 7.9 | 10.4 | 7.4 | 0.7 |
| | 50-59 | 90 | 8.1 | 1.2 | 8.0 | 10.6 | 8.2 | -0.1 |
| | 60-69 | 62 | 8.9 | 1.7 | 8.7 | 11.8 | 9.7 | -0.8 |
| | 70-79 | 54 | 10.3 | 1.9 | 10.4 | 14.0 | | |
| | 80-93 | 24 | 11.5 | 2.1 | 11.0 | 15.6 | | |
| Hypertensive | 40-49 | 24 | 8.7 | 1.4 | 8.4 | 11.4 | 9.0 | -0.3 |
| | 50-59 | 79 | 9.4 | 1.4 | 9.4 | 11.7 | 9.6 | -0.2 |
| | 60-69 | 112 | 10.4 | 2.1 | 10.4 | 14.2 | 11.4 | -1.00 |
| | 70-79 | 112 | 12.2 | 2.7 | 11.9 | 18.1 | | |
| | 80-93 | 77 | 13.2 | 2.5 | 13.4 | 18.0 | | |

PWV across age and HT groups is consistent with expectations. Deviations of RVASC mean PWV values from MSLS mean PWV values are within 1 SD or less of the SD values reported for MSLS. The trend across BP groups and age is illustrated in Figure 2.

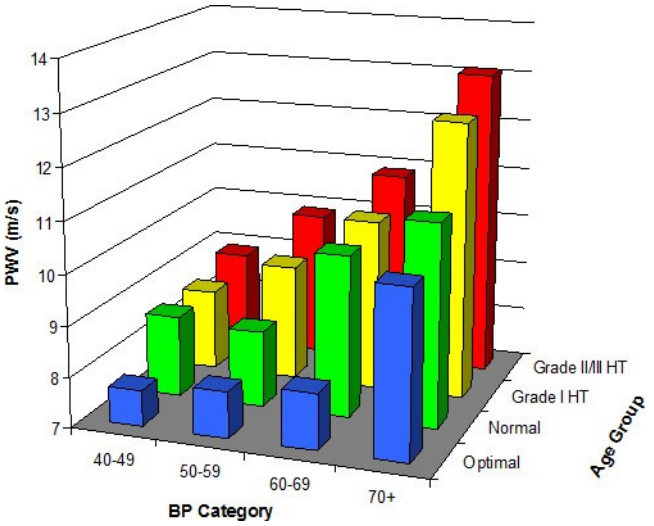


**Figure 2.** A bar plot showing trends for age within BP categories.

**Table 3.** Mean imputed PWV (m/s) values by blood pressure category and age group.

| Age Group | Blood Pressure Category | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Optimal[1] | | | | Normal[2] | | | | Grade I HT[3] | | | | Grade II/III HT[4] | | | |
| | N | M | SD | MSLS-RVASC | N | M | SD | MSLS-RVASC | N | M | SD | MSLS-RVASC | N | M | SD | MSLS-RVASC |
| 40-49 | 22 | 7.7 | 1.2 | 0.7 | 20 | 8.6 | 1.3 | 0.9 | 19 | 8.6 | 1.4 | 0.0 | 5 | 8.9 | 1.3 | -0.9 |
| 50-59 | 59 | 7.9 | 1.2 | 0.3 | 31 | 8.5 | 1.2 | -0.1 | 73 | 9.3 | 1.4 | -0.3 | 6 | 9.9 | 1.2 | -0.6 |
| 60-69 | 39 | 8.1 | 1.1 | -1.0 | 23 | 10.2 | 1.6 | 0.2 | 99 | 10.4 | 2.0 | -0.7 | 13 | 10.9 | 2.8 | -1.3 |
| 70+ | 40 | 10.3 | 1.7 | 0.1 | 38 | 11.0 | 2.3 | -0.8 | 146 | 12.5 | 2.7 | -0.4 | 43 | 13.1 | 2.3 | -0.9 |

Note: High normal and normal groups were combined to increase sample size.

[1]Optimal: <120/80 mmHg

[2]Normal: ≥120/80 mmHg and <140/90 mmHg

[3]Grade I HT: ≥140/90 mmHg and <160/100 mmHg

[4]Grade II/III HT: ≥160/100 mmHg

### Norms versus Reference Values

RVASC investigators make a distinction between normal PWV values and reference group values. This is possible in the present study if we use the optimal or normal BP groups, or both as normative (in the sense of normal) groups. There was only one NT individual with CVD (diagnosed coronary artery disease in the 60 to 69 year-old normal BP diagnostic group). Removing that individual made no difference in results obtained for this group for either the observed or imputed data. As an option to the normal BP group as a basis for "normal BP" values one may use the optimal BP diagnostic group (Table 3).

Using only the observed data for the expanded regression analysis (Table 3 top), the regression equation was as follows: PWV = 10.059 + 1.069 × age group + 0.447 × BP diagnostic category + 0.081 × age group × BP. Significant age group ($p<0.001$) and BP diagnostic group ($p< 0.001$) group interactions were observed and the age group x BP diagnostic group interaction p value was 0.06; $R^2= 0.38$.

Next we determined how well the RVASC equations predicted PWV data obtained in the MSLS. Applying the RVASC equations, RVASC-Table 6 top [20], to the observed data obtained in the MSLS, we calculated Ŷ PWV for each subject as a function of HT or age. These equations accounted for 36 percent variance in our PWV values ($R^2= 0.36$; $p <0.001$).

### Men Versus Women

Means for PWV for men and women were 10.7 and 9.8 m/s respectively ($p< 0.001$). Preliminary analyses indicated the absence of a quadratic effect for age, and sex did not interact signifi-

cantly with age or HT groups (all p values> 0.14). With adjustment of the full model (discussed below), the least-square means for men and women were 10.2 and 10.0 m/s respectively (p= 0.41).

**Expanded Models with Risk Factors**

Figure 3 presents a scatter plot and regression lines (slopes) for the observed data with age as a continuously distributed variable. The final steps in our analyses were designed to identify a parsimonious regression model that would increase the prediction of PWV beyond that possible with age and HT parameters alone. The first set of variables, considered essential controls [15-21], were fixed in the model: Age + HT + (HT × Age) + Height + Weight + Heart Rate + MAP + Lipid Lowering Drugs (1 = drug). Anti-hypertensive treatment effects were not significant and not included in the model. Once fixed variables were entered into the equation, candidate variables (footnote, Table 4) were entered with a stepwise backward elimination procedure. Variables that did not enter the equation significantly (p< 0.10) via the backward elimination procedure were not included in the final equation.

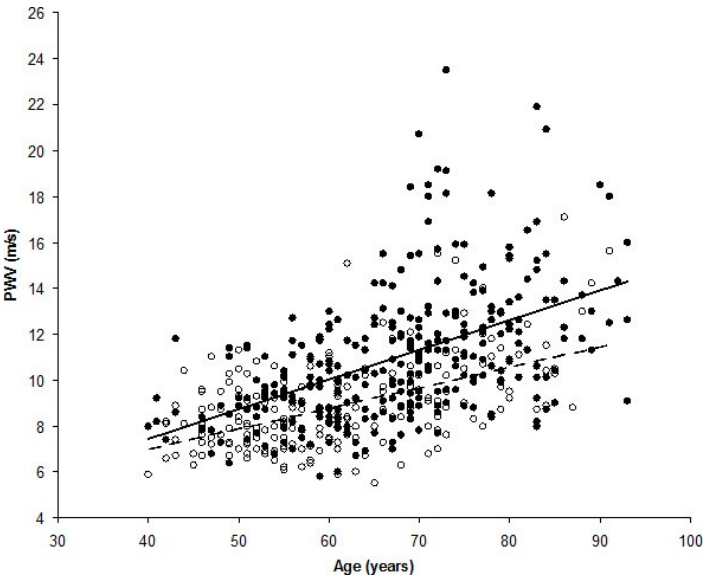


**Figure 3.** Association between age and PWV for the hypertensive (dots, solid line) and normotensive (circles, dashed line) groups. The regression equation for age and hypertension for the overall sample (with age centered) was: PWV = 9.210 + 0.089 × age + 1.437 × hypertension + 0.041 × age × hypertension; $R^2$ = 0.36.

As may be seen in Table 4, also for the observed data, the basic age + HT + (HT × Age) model accounted for 36 percent of the variance in PWV; the final model, each variable adjusted for all others, accounted for 47 percent. Of all the candidate variables, only creatinine and glucose entered the equation significantly with alpha = 0.10, and account for a small portion of variance, $\Delta R^2$= 0.024. The same risk factors were significant and the regression model was similar when the larger imputed PWV data set was employed, when sex (p= 0.41) was included in the model, and when other non-significant associations were excluded. A regression table based on the imputed data is not shown as the same pattern of significant associations and $R^2$ values was obtained. Similarity of results obtained for observed and imputed values was confirmed by a Wald test of equality of coefficients between the least squares deletion model (observed values) and the multiple imputation model: F(10,594)= 0.05, p> .999.

**Final Analyses**

African American versus other ethnic group status did not enter into the regression equation significantly (p= 0.19) and the pattern of results was not affected by excluding African Americans from the sample.

The CVD variable could not be adjusted statistically because of its very low prevalence in the NT groups. However, when persons with CVD (see Table 1) were excluded from the analyses, the pattern of results was nearly identical to those presented above.

**DISCUSSION**

We provide PWV normative and reference group data by NT and HT groups for the SphygmoCor® device, a system that uses an intersecting target algorithm, a function shared with numerous other systems [13]. The rise in PWV with age and hypertension, and the interaction between hypertension and age is consistent with the RVASC [20] study and others. Our data clearly indicate the limitations with respect to a focus on a single clinically significant fixed threshold value for elevated PWV, e.g., 12 m/s as has been recommended [9]. In our community-based study only for the 70 to 79 year old HT group do we see mean PWV values at the recommended 12 m/s threshold value. Mean and median values for younger subjects (60 to 69, or younger), HT or NT, fall below this threshold. For the classification based on more refined diagnostic groups (see Table 3), only the mean values for 70+ year old, Grade I and Grade II/III HT individuals were at or above the 12 m/s threshold.

The validity of the RVASC regression equations using age and HT parameters is exemplified by the fact that they account for almost the same amount of variance (36 percent) in our own PWV values, as do our own equations when limited to those parameters. Moreover, the agreement between the RVASC PWV reference values and ours is remarkably high given the difference in sample size between the studies. This finding endorses the usefulness of their data under circumstances where norms and reference groups for one's specific device and laboratory are unavailable, but does not obviate the need for system-specific studies such as the present. Limitations elucidated by the RVASC team include two points relevant to this issue: (1) their mathematical calculations attenuated but did not totally abolish differences in PWV on the basis of different algorithms and methods for determining path length; and (2) there was a strong data collection center effect for PWV that was not accounted for by their standardization procedures.

Our third study goal was to develop a parsimonious model, using multiple risk factors that would allow a prediction of PWV beyond that afforded by age and hypertension. We found that a group of risk factor variables readily available to most practicing

**Table 4.** Raw multivariable regression coefficients (*b*), standard errors (SE) expressing the relationship between risk factors and PWV (m/s) with each *b* adjusted for all others.[1,2]

| Covariables | *b* | SE | Cumulative $R^2$ | Delta $R^2$ |
|---|---|---|---|---|
| Intercept | -4.772* | 2.061 | | |
| Age (years)[3] | 0.105*** | 0.013 | 0.297 | |
| Hypertension (1= yes) | 0.117 | 0.258 | | |
| Hypert × Age[3] | 0.041** | 0.017 | 0.360 | 0.063 |
| Height (cm) | 0.013 | 0.011 | | |
| Weight (kg) | 0.018** | 0.007 | | |
| Heart Rate (bpm) | 0.039*** | 0.011 | | |
| MAP (mmHg) | 0.045*** | 0.009 | | |
| Lipid Meds (1=yes) | -0.315 | 0.209 | 0.450 | 0.090 |
| Creatinine (µmol/l)[2] | 1.433** | 0.532 | | |
| Glucose (mmol/l)[2] | 0.034*** | 0.009 | 0.474[4] | 0.024 |

[1] 8 and 4 mmHg respectively are added to treated BP levels prior to analysis; the pattern of significant results is the same without adjustment. Findings are the same with waist circumference substituted for height+weight or in absence of adjustment for lipid medications.

[2]Variables up to and including lipid medications were fixed in the model (could not be eliminated). Once the fixed variables were entered into the equation, the following candidate variables were entered into a stepwise backward elimination: education (years), plasma homocysteine (µmol/l), cigarettes/wk (or heavy smoking, >15/day), glucose (mmol/l), creatinine (µmol/l), triglycerides (mmol/l) (or other lipid values in separate analyses), alcohol consumption (g/wk), APOE genotype (ε4/no ε4), race/ethnicity (African American versus other), and c-reactive protein.

[3]Age is centered

[4]model $R^2$ (df = 10; 485)

*p< 0.05, **p< 0.01, ***p< 0.001

physicians (Table 4) allowed us to account for 47 percent of the variance in PWV as opposed to the 36 percent accounted for by the age and hypertension variables. These findings are consistent with findings that CVD risk factors other than hypertension and age are predictors of PWV [6-8].

In terms of the question of which CVD risk factors are dominant with respect to the prediction of PWV, our results are consistent with a recent comprehensive review and meta-analysis of 65 studies [35]. The conclusion reached in this study was that the contribution of risk factors to the prediction of PWV other than age, hypertension, or BP is either small or non-significant. Viewed from a general perspective, our findings are entirely consistent with this conclusion. The point we wish to make in our analysis is that additional variables that account for a small percentage of variance in PWV beyond that accounted for by age and hypertension do increase the prediction of PWV.

After age + hypertension, age x hypertension interactions and essential controls were fixed in our regression model, only glucose and creatinine entered into the regression model significantly. It is of interest that glucose was positively associated with PWV despite the fact that persons with diabetes mellitus were excluded from the analyses. In the Caerphilly Prospective Study [6], glucose was positively associated with PWV, but only at baseline. In the same study, creatinine, an index of kidney disease, was significantly associated with PWV both at baseline and after 20 years of follow-up [6].

**Study Limitations**

As was true for the RVASC investigation, our study was limited because PWV was not measured longitudinally. Physicians treat age cohorts (people born at the same time) differently and thus cross-sectional norms and reference groups are of value, but longitudinal data are necessary to answer the need for data relevant to serial treatment of the same patients over time.

It is possible discrepancies in point estimates between RVASC and our study related to our smaller sample, but results were the same when imputation of missing data allowed us to increase sample size, and dissimilarity between our study and RVASC was not systematically seen as a function of cell size in our study.

Over- or under-adjustment of BP to estimate the untreated condition may have resulted from the Tobin *et al.* [32] adjustment procedure, although the same results for various regression anal-

yses were observed with conventional covariance analyses using raw scores with anti-hypertensive drug treatment as a covariate. Moreover, our adjustments with the purpose of obtaining untreated BP value estimates in those who were treated cannot explain differences between point estimates in the RVASC and MSLS studies since those differences are there for untreated NT individuals.

We had too few participants to permit construction of normative values for African American participants. Shiburi *et al.* [19] provides reference values by age for SphygmoCor® measurements obtained in South Africans of African Ancestry. Normative values in other cultures and minority groups need to be provided within extensive BP classifications as well as age groups.

## CONCLUSIONS

Reference values for clinically significant PWV values must take age into account. There is relatively good agreement between PWV norms and reference group values for a large aggregate sample (RVASC) using multiple instruments and the much smaller MSLS sample, but an inexact match for within-cell PWV values confirms the need for normative and reference group values derived in one's own region with one's own measuring device. From an actuarial prospective, predicting PWV from CVD risk factors, the largest proportion of the best predictions of PWV values may be based on relatively few CVD risk factors readily available to most diagnostic and treatment centers.

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