Stroke Volume/Pulse Pressure Ratio and Cardiovascular Risk in Arterial Hypertension

Giovanni de Simone, Mary J. Roman, Michael J. Koren, George A. Mensah, Antonello Ganau, Richard B. Devereux

Abstract—Ratio of stroke volume (SV, M-mode echocardiography) to pulse pressure (PP) has been proposed as an estimate of total arterial compliance and has been shown to be related to body size, age, and heart rate in normal adults. SV/PP was estimated in 294 hypertensive patients (98 women) as a raw value by use of SV/body surface area (SVi) and by the ratio of SV/PP to the value predicted by a previously developed equation (%SV/PP). At baseline, the 50 patients who had cardiovascular events over the following 10 years exhibited higher PP and lower SV/PP, SVi/PP, and %SV/PP (all \( P<0.008 \)) than patients without events. Crude risk of follow-up total and fatal cardiovascular events increased with increasing level of PP and decreasing SV/PP, SVi/PP, and %SV/PP (all \( P<0.002 \)). In multivariate logistic regression models with continuous covariates, the risk of total cardiovascular events was independently related to increasing age (\( P<0.0001 \)) and left ventricular (LV) mass index (\( P<0.003 \)) and decreasing values of %SV/PP (\( P<0.006 \)) but not to increasing systolic, pulse, or mean blood pressure or gender. Similar although less strong results were obtained with the use of SVi/PP (\( P<0.02 \)), whereas SV/PP did not enter the model as an independent predictor. Risk of cardiovascular death was only predicted by age and LV mass index. The %SV/PP was also an independent predictor of total cardiovascular events in Cox proportional hazards analysis (exp[b]: 2.49, \( P<0.001 \)) independent of age (exp[b]: 1.05, \( P<0.003 \)) and LV mass index (exp[b]: 1.02, \( P<0.0003 \)), whereas no effect was detected for height. Thus, in patients with arterial hypertension, a reduced ratio of M-mode echocardiographic SV/PP as a percentage of the value predicted by demographic variables is a predictor of cardiovascular morbidity events independent of age and LV mass index. (Hypertension. 1999;33:800-805.)

Key Words: hypertension, arterial ▪ echocardiography ▪ cardiac hypertrophy ▪ prognosis ▪ pulse

The ratio of stroke volume to pulse pressure (SV/PP) has been proposed as an indirect measure of total arterial compliance,1-4 simple enough to be used in epidemiological studies, and based on the principle that in a steady-state condition, the arterial tree can be modeled as an elastic chamber with a constant compliance (2-element Windkessel model). This ratio has been recently shown to increase during body growth because of the increased size of the arterial tree, whereas it remains stable during early adulthood, after the end of body growth, and decreases during late adulthood to old age, possibly because of increased arterial stiffness.5

Decreased arterial compliance may be a stimulus for left ventricular (LV) hypertrophy,6-8 especially the concentric pattern.9 This association may play a role in the increase in cardiovascular risk associated with the presence of concentric LV hypertrophy.10 Although PP might independently predict cardiovascular risk,11-14 there is no information on the ability of SV/PP to predict risk or on whether this prediction is independent of LV hypertrophy. Accordingly, this study was designed to investigate whether SV/PP is an independent marker of cardiovascular risk in arterial hypertension.

Methods

Study Population
Direct follow-up or contact with relatives or physicians of patients who died was possible in 294 (91%) of 322 patients initially evaluated by echocardiography at New York Hospital–Cornell Medical Center between 1976 and 1986 and found eligible for this longitudinal trial. Detailed information about this cohort has been reported extensively.9,15,16

Echocardiography
Two-dimensionally targeted M-mode echocardiograms were performed as previously described.17-23 LV end-diastolic and end-systolic volumes were calculated with the Z-derived method,24 which exhibited a high accuracy for M-mode LV volume calculation even in the presence of dilated LV cavities. SV was calculated in milliliters per beat as end-diastolic minus end-systolic volume and normalized for body surface area (stroke index).25 Reproducibility of various echocardiographic quantitative parameters has been reported

Received August 4, 1998; first decision September 1, 1998; revision accepted November 30, 1998.
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Hypertension is available at http://www.hypertensionaha.org
Reproducibility of PP was assessed with the data set of the Reproducibility Echocardiographic Study by single-measure intraclass correlation of measurements performed by a single observer 3 to 10 days apart (n=261, R²=0.87).

**SV/PP Estimation**

Blood pressure (BP) was measured at the first and fifth Korotkoff phases with the use of an arm-cuff sphygmomanometer at the end of the initial echocardiograms. Brachial PP was calculated as the difference between systolic and diastolic BP and used as a raw inverse estimate of total arterial compliance together with SV/PP and the ratios of stroke index to pulse pressure (SVi/PP). The value of SV/PP (mL/beat/mm Hg) was also compared with the value predicted by a multiple regression equation developed in 393 normotensive, normal-weight adults previously studied with the use of Teichholz’s method to determine LV volumes. The new equation developed with the use of the Z-derived method of calculation of LV volumes in the same population was

\[
SV/PP = \frac{0.013 \cdot \text{body wt (kg)} - 0.007 \cdot \text{age (y)}}{-0.004 \cdot \text{heart rate}} + 1.307
\]

(Multiple R=0.45, SEE=0.34 mL/mm Hg, P<0.0001). The ratio of observed to predicted SV/PP was computed to generate a variable adjusted for body size, age, and heart rate (%predicted SV/PP). The distribution of %predicted SV/PP was evaluated in the reported 393 normal adults, and the fifth percentile was identified (71.6% of the estimated).

Because of the known decline with age of PP augmentation from the central aorta to the peripheral arteries, the central PP determined by carotid aplanation tonometry was estimated with the use of a formula derived method of calculation of LV volumes.

\[
PP_{\text{central}} = PP_{\text{brachial}} \cdot 0.49 + \text{age} \cdot 0.30 + 7.11
\]

This equation explained 38% of variance of central PP (P<0.0001).

**Statistical Analysis**

Data were analyzed with commercially available statistical packages. Standard analyses were carried out with the use of 1-way ANOVA with the step-down multiple-stage F post hoc test (Ryan-Einot-Gabriel-Welsch F test) and least-squares linear regression. Differences between regression lines were tested by computing F statistics of between-slopes sum of squares of standardized variables.

Discriminant analysis based on logistic regression was used to identify variables that independently predicted cardiovascular morbidity or death by computing the exponentials of the coefficients of regression (which is equivalent to a relative risk) and the relative 95% confidence limit. A stepwise procedure (forward conditional) was adopted using continuous variables and gender as a discrete variable (1=women, 2=men). To compute positive coefficients of regression consistent with those obtained with the other variables, SV/PP, SVi/PP, and the ratio of observed-to-predicted SV/PP entered the models in the form of their inverse values (ie, 1/(SV/PP)=PP/SV).

Product-limit Kaplan-Meyer estimation of survival functions and Cox proportional hazard analysis were computed for patients with normal or reduced %predicted SV/PP.

The null hypothesis was rejected at a 2-tailed value of P<0.05.

**Results**

Hypertensive patients were followed through a mean 10-year period. During the follow-up, 50 (17%) subjects experienced at least 1 cardiovascular complication, and 14 of them died.

Table 1 shows that the subgroup of patients who had fatal or nonfatal cardiovascular events were older (P<0.0001) and had higher body mass index (P<0.02), systolic, diastolic, and pulse pressures (all P<0.002), and lower SV/PP, SVi/PP, and %predicted SV/PP (P<0.007) than event-free patients. Only age and systolic and pulse pressure were higher in patients with follow-up fatal cardiovascular events (all P<0.0001).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Event-free (n=244)</th>
<th>All Events (n=50)</th>
<th>Fatal Events (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46±13</td>
<td>56±10§</td>
<td>61±8§</td>
</tr>
<tr>
<td>Women/men, No.</td>
<td>84/160</td>
<td>14/36</td>
<td>4/10</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.8±4.0</td>
<td>27.3±4.4*</td>
<td>27.6±5</td>
</tr>
<tr>
<td>Plasma cholesterol, mmol/L</td>
<td>6.13±1.86</td>
<td>6.18±2.69</td>
<td>5.90±3.05</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71±12</td>
<td>69±13</td>
<td>65±11</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>151±19</td>
<td>167±26§</td>
<td>174±298</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>95±11</td>
<td>101±12†</td>
<td>100±14</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>56±16</td>
<td>66±22§</td>
<td>75±26§</td>
</tr>
<tr>
<td>SV/PP, mL·beat⁻¹·mm Hg⁻¹</td>
<td>1.49±0.51</td>
<td>1.27±0.56‡</td>
<td>1.21±0.64</td>
</tr>
<tr>
<td>SVi/PP, mL·beat⁻¹·m²⁻¹·mm Hg⁻¹</td>
<td>0.78±0.25</td>
<td>0.66±0.29‡</td>
<td>0.63±0.33</td>
</tr>
<tr>
<td>SV/PP % of predicted</td>
<td>88.14±27.92</td>
<td>75.15±31.97†</td>
<td>73.44±38.03</td>
</tr>
</tbody>
</table>

*p<0.05; †P<0.01; ‡P<0.005; §P<0.0001 vs event-free patients.

**Unadjusted Relative Risk**

Risk of cardiovascular morbidity or mortality increased by 3% and 4%, respectively, for each mm Hg of increase in PP [exp(b) (95% confidence interval)=1.03 (1.01 to 1.05) and 1.04 (1.02 to 1.07), respectively, both P<0.001], by 5% and 6% for each 0.1 mL/mm Hg decrease in SV/PP ratio [exp(b)=4.97 (2.07 to 11.92), P<0.0003, and 5.96 (1.88 to 18.89), P<0.002, respectively]. With the use of SVi/PP, risk of both total cardiovascular events and fatal events increased by 3% for each 0.1 mL·m²·mm Hg⁻¹·beat⁻¹ [exp(b)=3.02 (1.80 to 5.09), P<0.0001 and 3.04 (1.54 to 6.02), P<0.002, respectively]. Similarly, risk of cardiovascular morbidity and mortality increased by ~4% for each unit of decrease in %predicted SV/PP [exp(b)=3.74 (1.98 to 7.02), P<0.0001 and 4.13 (1.72 to 9.92), P<0.002, respectively].

**Multivariate Analysis for Prediction of Cardiovascular Risk**

Multiple logistic regression was used to detect the independent effect of SV/PP, SVi/PP, and %predicted SV/PP in separate models that also included systolic BP, age, gender, and LV mass index. In addition to age (P<0.001) and LV mass index (P<0.005), decrease in %predicted SV/PP was independently related to the risk of all cardiovascular events (P<0.001) (Table 2). Similar results were attained with the SV/PP [exp(b)=1.94/mL·m²·mm Hg⁻¹ decrease (1.12 to 3.35), P<0.02]. SV/PP did not remain an independent predictor of total and fatal cardiovascular events after consideration of age and LV mass index.

Other discriminant models were also generated for SVi/PP and %predicted SV/PP, substituting systolic BP with PP or mean BP, and the results were identical as with systolic BP. In every model, the iteration history showed that after age,
LV mass index entered as the second most powerful predictor, followed negatively by %predicted SV/PP, which exhibited a residual association with adverse events higher than either systolic, pulse, or mean pressure. For instance, after age and LV mass index, the \( r \)-to-enter of %predicted SV/PP was 0.13 \((P, 0.01)\), higher than that of systolic BP \((r=0.09, P=0.04)\). After the entry of %predicted SV/PP into the model, the residual \( r \)-to-enter of systolic BP was close to 0, with \( P=0.5 \). Interestingly, the exp(b) of age and LV mass index were not reduced by the entry of %predicted SV/PP as the third variable into the model \((1.07 \text{ and } 1.03, \text{respectively, in the model with systolic BP, before entry of } \%\text{predicted SV/PP})\).

Risk of cardiovascular death was only predicted by age and LV mass index in all models including SVi/PP or %predicted SV/PP and also including systolic BP (or PP or mean BP) and gender.

**Time-Dependent Procedures**

The inverse of %predicted SV/PP was evaluated in Cox proportional hazard analysis. Patients were classified in relation to the 5th percentile of the distribution in the reference population\(^5\) to generate survival curves (Figure). A low value of %predicted SV/PP was found in 100 patients, and among them 26 had follow-up adverse events (odds ratio=2.5 [1.3 to 4.6], \( P<0.005 \)). As shown in the Figure, after adjusting for age, LV mass, and height (as another potential predictor of cardiovascular risk), event-free survival was lower in patients with %predicted SV/PP from 4 years after enrollment to the end of follow-up. The inverse of %predicted SV/PP was used as a continuous variable for final Cox model. The probability of future cardiovascular events increased with decreasing %predicted SV/PP \([\exp(b)=2.49 (1.37 \text{ to } 4.54), P<0.003]\), independent of age \([\exp(b)=1.05 (1.02 \text{ to } 1.08), P<0.002]\) and LV mass index \([\exp(b)=1.02 (1.01 \text{ to } 1.03), P<0.0003]\), whereas height did not enter the model.

**Relation to Measures of LV Geometry**

LV mass index was related to systolic BP \((r=0.29, P<0.0001)\) and more weakly to PP \((r=0.16, P<0.005)\) but not to SV/PP, SVi/PP, or %predicted SV/PP \((r<0.02)\). In contrast, relative wall thickness was more closely related to SV/PP \((r=-0.29, P<0.0001)\), SVi/PP \((r=-0.31, P<0.0001)\), and %predicted SV/PP \((r=-0.31, P<0.0001)\) than to systolic BP \((r=0.18, \text{standardized slope differences calculated with the inverse of systolic BP: all } P<0.005\)) or to PP \((r=0.03)\).

Table 3 shows that the severity of BP elevation was associated with the presence of LV hypertrophy, whereas reduced SV/PP-based measures were associated with concentric LV geometry either with or without an increase in LV mass. Eccentric LV hypertrophy was associated with higher levels of SV/PP-based measures. It is noteworthy that PP was not significantly different among patients with the 4 LV geometric patterns.

**Discussion**

The SV/PP has a physiological basis in the 2-element Windkessel model.\(^4,32\) However, stroke volume includes part of blood ejected after that the pressure curve reaches its peak, whereas to reproduce the 2-element Windkessel model, only the part of blood ejected within the time of

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**Table 2. Multivariate Prediction of Total Cardiovascular Events by Abnormal SVi/PP or %Predicted SV/PP**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exp(b)</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>( P ) &lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.06</td>
<td>1.02</td>
<td>1.09</td>
<td>0.0009</td>
</tr>
<tr>
<td>LV mass index, g/m(^2)</td>
<td>1.03</td>
<td>1.01</td>
<td>1.04</td>
<td>0.003</td>
</tr>
<tr>
<td>1/(SVi/PP in mL - ( \cdot ) mm Hg(^{-1} ))</td>
<td>1.94</td>
<td>1.12</td>
<td>3.35</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender and systolic BP</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.06</td>
<td>1.02</td>
<td>1.09</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV mass index, g/m(^2)</td>
<td>1.02</td>
<td>1.01</td>
<td>1.04</td>
<td>0.005</td>
</tr>
<tr>
<td>1/(SV/PP as %predicted)</td>
<td>2.33</td>
<td>1.21</td>
<td>4.50</td>
<td>0.001</td>
</tr>
<tr>
<td>Gender and systolic BP</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>NS</td>
</tr>
</tbody>
</table>

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Age-adjusted and LV mass index–adjusted cumulative probability of event-free survival curves, based on proportional hazard assumptions for patients with normal (dashed line) or low (continuous line) ratio of SV to brachial PP as a percentage of the value predicted age, body size, and heart rate.
peak pressure should be measured. Because the value of SV is higher than the volume stored at each systole, the assumption made for use of SV/PP is that SV is closely related to the volume stored in the arterial tree at each systole.

Another limitation of the calculation of SV/PP is the use of peripheral instead of central PP. We studied the relation between central and peripheral PP by using age in the regression model as the variable mostly affecting the difference. However, only ≈40% of variance could be explained by that model, and the extent of this relation did not change by adding height and gender as independent correlates. Thus, other variables and/or method error not considered in the regression model may influence differences between central and peripheral pulse pressure. Accordingly, a more direct measure of central PP may be needed to further improve the predictive value of the index proposed in the current study. Calibrated carotid tonometry merged with ultrasound arterial wall identification provides more direct measures of the compliance of conduit arteries than the simple calculation of SV/PP. A major advantage of this direct method is the elimination of the age-dependent decline in the overestimation of central PP by peripheral measurements in young individuals, which results in underestimation of systemic arterial compliance by the SV/PP. In this study, this error has been in part attenuated by using the multiple regression equation including age.

Keeping in mind the above considerations, in previous studies we demonstrated that in adults, body size is an important covariate of SV/PP, more important than gender, paralleling the known association between body size and the size of the aorta. Therefore, the physiological effect of body size on SV/PP needs to be taken into account when a clinical application of this ratio is attempted.

There are several studies addressing the potential independent negative prognostic implication of decreased arterial compliance. In addition to data suggesting an adverse effect of high PP, reduced arterial compliance measured through more direct methods has been reported to be related to concentric LV hypertrophy, cardiovascular risk factors, and prevalent cerebrovascular disease.

### TABLE 3. Blood Pressure and SV/PP-Based Measures in Different Left Ventricular Geometric Patterns

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Geometry (&lt;i&gt;n&lt;/i&gt; = 158)</th>
<th>Concentric Remodeling (&lt;i&gt;n&lt;/i&gt; = 52)</th>
<th>Eccentric Hypertrophy (&lt;i&gt;n&lt;/i&gt; = 47)</th>
<th>Concentric Hypertrophy (&lt;i&gt;n&lt;/i&gt; = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm Hg</td>
<td>151 ± 20</td>
<td>152 ± 19</td>
<td>158 ± 22</td>
<td>161 ± 26*</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>94 ± 10</td>
<td>98 ± 13</td>
<td>99 ± 10*</td>
<td>100 ± 15*</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>57 ± 17</td>
<td>54 ± 15</td>
<td>59 ± 17</td>
<td>61 ± 20</td>
</tr>
<tr>
<td>SV/PP, mL · beat&lt;sup&gt;−1&lt;/sup&gt; · mm Hg&lt;sup&gt;−1&lt;/sup&gt;</td>
<td>1.46 ± 0.47</td>
<td>1.27 ± 0.45*</td>
<td>1.69 ± 0.45*</td>
<td>1.32 ± 0.59*</td>
</tr>
<tr>
<td>%Predicted SV/PP&lt;sub&gt;1&lt;/sub&gt;</td>
<td>87 ± 25</td>
<td>76 ± 24*</td>
<td>101 ± 38*</td>
<td>75 ± 28*</td>
</tr>
</tbody>
</table>

*p < 0.05, *<i>p</i> < 0.001 compared with normal geometry.

**SV/PP as an Independent Marker of Cardiovascular Risk**

When the effects of age, body size, and heart rate on the SV/PP ratio are taken into account, this measure was a marker of cardiovascular risk independent of age, height, and LV mass index in the present series of patients with arterial hypertension. The predictive value of the adjusted SV/PP was greater than that of systolic BP or PP, a biological variable associated with SV/PP and measures of arterial compliance.

In the context of a limited range of BP as seen in a purely hypertensive population, SV/PP-based variables may be prognostically more important than isolated BP measurements because their variability has not been constrained by diagnostic criteria. The coefficient of variability of systolic BP in the whole study population was 13.9% compared with 33.5% for SV/PP as percentage of predicted (<i>P</i> < 0.0001). Thus in hypertension, SV/PP-based measures may be more important for prediction of cardiovascular events than measures of arterial pressure because their biological variability is higher (in part because of the flow component). Accordingly, the present results should be interpreted in the context of the type of population studied and cannot be automatically generalized to unselected populations.

From the prognostic point of view, the use of SV/PP as a %predicted increased the prediction of cardiovascular complications of arterial hypertension compared with use of the simpler SV/PP. The inclusion of age, body size, and heart rate in the computation of %predicted SV/PP might have strengthened the relation with adverse events because each of these covariates has been related to adverse outcome in patients with cardiovascular disease. Moreover, further adjustment for age may attenuate or eliminate the overestimation of central PP by peripheral measurements in young, disease-free individuals.

The finding of an independent relation of SV/PP-based measures to cardiovascular morbidity has not been previously reported but is not surprising. Interestingly, similar to previous studies, whereas BP is more associated with increased LV mass, SV/PP-based measures are more related to concentric LV geometric patterns and may contribute to explaining the relatively higher risk associated with these patterns. There was not a statistically independent effect of low
% predicted SV/PP on cardiovascular mortality in our study population, but the lack of this association might be due to both the relatively small number of cardiovascular deaths and the strong association between LV hypertrophy and the occurrence of cardiovascular death that has been previously reported.\textsuperscript{10,16,46}

Conclusions
Reduced values of the ratio between SV and PP as a percentage of predicted by individual body size, age, and heart rate is a predictor of cardiovascular morbidity independent of age and presence of LV hypertrophy in arterial hypertension. Studies on more direct indexes of arterial stiffness should be advisable to detect the interest of this parameter in the prediction of cardiovascular risk.

Acknowledgment
This study was supported in part by grant HL-18323 from the National Heart, Lung, and Blood Institute, Bethesda, Md.

References


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Hypertension. 1999;33:800-805
doi: 10.1161/01.HYP.33.3.800

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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