The “systolic volume balance” method for the noninvasive estimation of cardiac output based on pressure wave analysis

Theodore G. Papaioannou,* Orestis Vardoulis,* and Nikos Stergiopulos

Laboratory of Hemodynamics and Cardiovascular Technology, Institute of Bioengineering, Swiss Federal Institute of Technology, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Submitted 19 January 2012; accepted in final form 8 March 2012

Papaioannou TG, Vardoulis O, Stergiopulos N. The “systolic volume balance” method for the noninvasive estimation of cardiac output based on pressure wave analysis. Am J Physiol Heart Circ Physiol 302: H2064–H2073, 2012. First published March 16, 2012; doi:10.1152/ajpheart.00052.2012.—Cardiac output (CO) monitoring is essential for the optimal management of critically ill patients. Several mathematical methods have been proposed for CO estimation based on pressure waveform analysis. Most of them depend on invasive recording of blood pressure and require repeated calibrations, and they suffer from decreased accuracy under specific conditions. A new systolic volume balance (SVB) method, including a simpler empirical form (eSVB), was derived from basic physical principles that govern blood flow and, in particular, a volume balance approach for the conservation of mass ejected into and flowed out of the arterial system during systole. The formulas were validated by a one-dimensional model of the systemic arterial tree. Comparisons of CO estimates between the proposed and previous methods were performed in terms of agreement and accuracy using “real” CO values of the model as a reference. Five hundred and seven different hemodynamic cases were simulated by altering cardiac period, arterial compliance, and resistance. CO could be accurately estimated by the SVB method as follows: CO = C × PPao/(T − Tm) (0.861 l/min, 0.041 l/min, respectively, indicating very good agreement between the proposed and previous PCCO methods. eSVB also provided accurate estimation of CO. An in vivo validation study of the proposed methods remains to be conducted.

stroke volume; pressure waveforms; arterial tree model; blood pressure; pulse contour analysis

MONITORING of cardiac output (CO) or stroke volume (SV) is essential for the optimal management of patients, intraoperatively or in the setting of an intensive care unit, since it provides valuable insights into systemic O2 delivery and global tissue perfusion. Moreover, estimation of SV variation in patients under several pathophysiological conditions, after interventions for functional hemodynamic evaluation (13) or in nonhospitalized subjects (18), may provide important information for optimizing diagnostic and treatment strategies.

The history of CO measurement begins in 1870, when Adolf Fick determined CO in animals using O2 concentrations in arterial and venous blood samples (11). However, thermodilution using a pulmonary artery catheter set the basis for CO monitoring in clinical practice at the early 1970s, and it has been considered, for years, as the “gold standard method” for CO assessment in critically ill patients. Nonetheless, the use of this technique is limited due to its invasive nature and the associated severe complications (39). Other less-invasive techniques based on dye dilution have been also used in clinical practice (22). However, none of the aforementioned techniques is easily applicable in daily assessment of hemodynamically unstable patients or in nonhospitalized patients.

Great efforts have been exerted to develop minimally invasive or even noninvasive techniques for CO monitoring (6). During the past century, numerous mathematical methods have been proposed for CO estimation based on arterial blood pressure (BP) waveform analysis (43, 45). Some of these methods, mostly known as “pulse contour CO” (PCCO) monitoring, have been commercialized, but they are still based on invasive recording of arterial pressure waves or require invasive hemodynamic measurements for calibration purposes. Current evidence has indicated that many minimally invasive techniques continue to suffer from decreased accuracy and reliability under certain occasions (22).

The aim of the present study was to develop a simple noninvasive method for the monitoring of CO, based on physical and hemodynamic principles, using pressure wave analysis and a noninvasive calibration method. To validate the new PCCO formula under different hemodynamic conditions, a previously validated one-dimensional (1-D) model of the systemic arterial tree was used. Finally, comparisons of CO estimates between the proposed and previous PCCO methods were performed in terms of agreement and accuracy compared with “real” CO values of the model.

MATERIALS AND METHODS

CO estimation based on systolic volume balance: the systolic volume balance method. During systole, the left ventricle ejects a total volume of blood equal to SV. Part of the SV (VC) is “stored” at the arterial tree due to the expansion of the compliant arterial walls. The remaining part of the SV (Vout,systole) exits the systemic arterial tree during systole through the “terminal” arterial sites, as shown schematically in Fig. 1.

Thus,

\[ SV = V_C + V_{out,systole} \] (1)

By dividing the terms of Eq. 1 by the cardiac period (T) and by substituting V_{out,systole} by the blood flow rate through the terminal arteri...
Fig. 1. Schematic illustration of blood volume flow and distribution in a two-element, lumped model of systemic circulation. SV, stroke volume; VC, blood volume “stored” during systole at the arterial system; R, total vascular resistance; V_{out,systole}, blood outflow during systole through the peripheral arterial sites.

artrial sites during systole (Q_{out,systole}) \times \text{systolic duration (T_s)}, we obtain the following:

$$\frac{SV}{T} = \frac{VC}{T} + \frac{Q_{out,systole} \times T_s}{T}$$

or

$$Q = \frac{VC}{T} + \frac{Q_{out,systole} \times T_s}{T}$$

where Q is CO (mean flow) and Q_{out,systole} is mean Q_{out,systole}. The mean outflow of blood volume during systole is driven by the mean pressure during systole at the terminal arteries (P_{sm,terminal}) and the resistance of the terminal arteries (R_{terminal}), so that:

$$Q = \frac{P_{sm,terminal}}{R_{terminal}}$$

Furthermore,

$$VC = C \times \Delta P$$

where C is total arterial compliance and \( \Delta P \) is the change in pressure. In this study, C was calculated analytically as the sum of all segmental volume compliance values at mean arterial pressure plus the sum of all peripheral compliance at terminal beds.

Hence, Eq. 2 becomes:

$$Q = \frac{C \times \Delta P}{T} + \frac{P_{sm,terminal}}{R_{terminal}} \times \frac{T_s}{T}$$

Here, we make the following assumptions: 1) \( \Delta P \) can be approximated by aortic pulse pressure (PP_{ao}), 2) P_{sm,terminal} is very closely related with mean systolic aortic pressure (P_{sm,aorta}), and 3) the resistance of the terminal arterial sites is the main determinant of total arterial resistance (R). Equation 3 then becomes:

$$Q = \frac{C \times PP_{ao}}{T} + \frac{P_{sm,aorta}}{R} \times \frac{T_s}{T}$$

Since R = P_m/Q, where P_m is mean BP, CO (Q_{SVB}) can be estimated by the following “systolic volume balance” (SVB) equation:

$$Q_{SVB} = \frac{C \times PP_{ao}}{T - \frac{P_{sm,aorta} \times T_s}{P_m}}$$

\text{Simplified empirical form of the SVB method. The estimation of CO based on the SVB method, besides the estimation of arterial compli-} \
\text{ance, requires the determination of peak systolic and diastolic points of the pressure wave. In addition, the end-systolic point of the pressure wave must be determined for the calculation of T_s and P_{ao}. In an attempt to simplify the SVB method (Eq. 4), we assumed that the expression in the denominator \( [T - (P_{sm,aorta} \times T_s)/P_m \}] \) is proportional to the heart period (T). This assumption was motivated by the observation that the ratio of P_{sm,aorta} to P_m is close to unity and does not vary much and by the fact that diastolic duration (T_s) is, within reasonable limits, proportional to T. The above assumptions led to the following empirical formula for CO estimation (Q_{eSVB}):

$$Q_{eSVB} = k \times \frac{C \times PP_{ao}}{T}$$

where eSVB is the empirical SVB method and k is an empirical coefficient reflecting the proportionality between T and the denominator of Eq. 4.

\text{Validation by a 1-D model of the systemic arterial tree. A distributed, 1-D model of the human arterial tree was used to validate the proposed PCCO formulas (SVB and eSVB methods). The 1-D model itself has been validated with in vivo measurements in humans and has been previously found to reproduce accurate pressure and flow waves along the arterial tree (34, 35). Five hundred and seven different hemodynamic conditions were simulated. Central (aortic) and peripheral (brachial) pressure and flow waveforms were obtained for different arterial tree models. Various levels of C (from 0.7 to 3.1 ml/mmHg) and R (from 0.5 to 1.0 mmHg·s·ml⁻¹) and three heart rates (70, 75, and 80 beats/min) were simulated in all possible combinations. Changes in R and C were made with a step of 0.05 of their corresponding units, providing a variety of pressure waves with different morphological features. Estimated values of CO by the SVB and eSVB methods (Eqs. 4 and 5) were compared with “real” CO values computed by the model. The main parameters determined by pulse wave analysis are shown in Fig. 2; the illustrated pressure and flow waves were computed for the reference arterial model (35).

\text{Description of the 1-D model of the arterial tree. In this study, an improved version (35) of the previously described 1-D model of the arterial tree (42) was used to evaluate the proposed SVB and eSVB methods for CO estimation. The model has been previously validated, and it has been shown that it is able to predict pressure and flow waves in good qualitative and quantitative agreement with in vivo measurements, especially with respect to shape and wave details (34, 35). Governing equations for the model were obtained by integrating continuity and longitudinal momentum equations (Navier-Stokes) to obtain their 1-D form with the appropriate boundary conditions. The solution was obtained using an implicit finite difference scheme. All major segments of the arterial tree with a diameter \( \geq 2 \text{ mm} \) and a detailed description of the cerebral circulation (complete circle of...
Walls and distal cerebrovasculature) were incorporated in the model. Distal vessels were terminated with three-element Windkessel models, and intimal shear was modeled using the Witzig-Womersley theory. Blood was assumed to be a Newtonian fluid. The arterial behavior was considered to be nonlinear and viscoelastic based on the methodology proposed by Holenstein et al. (17) and data determined by Bergel (3). Arterial segments were considered as long tapered tubes, and compliance was defined by a nonlinear function of pressure as previously described in detail by Reymond et al. (35). Based on an equation proposed by Langerwouters (21), we used the following relationship between volumetric C and pressure (P):

\[ C(P) = \alpha_1 + \frac{\beta_1}{1 + \frac{P - P_{\text{max,c}}}{P_{\text{width}}}} \]

where \( \alpha_1, \beta_1, P_{\text{max,c}}, \) and \( P_{\text{width}} \) are parameters that have previously been defined in detail (35).

The ventricular-vascular interaction was taken into account using the varying elastance model by Sagawa (38), which allows flexibility when changes occur either in cardiac parameters (i.e., heart rate, contractility, filling pressures, etc.) or in arterial parameters (i.e., R, C, etc.). Forward wave reflections at the arterial bifurcations were minimized by adapting the characteristic impedance of downstream branches. Simulations and computations as well as pressure and flow wave analysis were performed using Matlab (The Mathworks, Natick, MA).

Comparison with other PCCO methods. Estimates of CO by the SVB and eSVB methods (Eqs. 4 and 5) were compared with the respective CO values determined using previously described PCCO methods (Table 1). Only formulas based on pulse contour analysis were evaluated. Methods that were very similar with each other or with their algorithms not clearly presented in the literature were excluded. For each formula, including eSVB, we estimated average \( k \) as follows:

\[ k = \frac{\sum_{i=1}^{n} k(i)}{n} \]

where \( i \) is the particular case out of the total number (n) of 507 hemodynamic conditions simulated and \( k(i) \) is the empirical coefficient computed to yield the correct CO value for each formula and for each case.

Statistical analysis. Agreement, accuracy, and association between the computed (“real”) and estimated CO values were evaluated using Pearson’s correlation coefficient \( (r) \), intraclass correlation coefficient (ICC), coefficient of variation (CV), root mean square error (RMSE), mean difference (bias), SD of differences, and Bland-Altman analysis. \( r \) was used to examine the association of the estimated CO with the model’s mean flow rate. ICC was used to assess the agreement of quantitative measurements in the sense of consistency and conformity (2). ICC assesses the agreement of measurements by comparing the variability of different measurements (e.g., estimated vs. “real” CO) of the same case with the total variation across all measurements and all cases. ICC values range from -1 for perfect disagreement to 0 for

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference(s)</th>
<th>Year</th>
<th>Method</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlanger and Hooker</td>
<td>10</td>
<td>1904</td>
<td>F1</td>
<td>( Q = k \times \frac{PP}{T} )</td>
</tr>
<tr>
<td>Liljestrand and Zander</td>
<td>23</td>
<td>1928</td>
<td>F2</td>
<td>( Q = k \times \frac{1}{T} \times \frac{PP}{P_{s}+P_{d}} )</td>
</tr>
<tr>
<td>Herd et al.</td>
<td>16</td>
<td>1966</td>
<td>F3</td>
<td>( Q = k \times \frac{P_{m}-P_{d}}{T} )</td>
</tr>
<tr>
<td>Harley et al.</td>
<td>14</td>
<td>1969</td>
<td>F4</td>
<td>( Q = k \times PP \times \frac{T_{s}}{T} )</td>
</tr>
<tr>
<td>Kouchoukos et al.</td>
<td>20</td>
<td>1970</td>
<td>F5</td>
<td>( Q = k \times \frac{P_{m}}{T} \times \left(1 + \frac{T_{s}}{T_{d}} \right) )</td>
</tr>
<tr>
<td>Wesseling et al.</td>
<td>45</td>
<td>1972</td>
<td>F6</td>
<td>( Q = k \times \frac{PP}{T} )</td>
</tr>
<tr>
<td>Erlanger et al.</td>
<td>10</td>
<td>1973</td>
<td>F7</td>
<td>( Q = k \times PP )</td>
</tr>
<tr>
<td>Bourgeois et al.</td>
<td>1976</td>
<td>F8</td>
<td>( Q = k \times \frac{(P_{m} - P_{d}) + \frac{P_{m}}{\tau}}{T} )</td>
<td></td>
</tr>
<tr>
<td>Wesseling et al.</td>
<td>48</td>
<td>1983</td>
<td>F9</td>
<td>( Q = k \times \frac{P_{m}}{T} \times (163 + HR - 0.48 \times P_{m}) )</td>
</tr>
<tr>
<td>AC power method</td>
<td>36, 43</td>
<td>2005</td>
<td>F10</td>
<td>( Q = k \times \frac{1}{T} \times \left(\frac{1}{T} \int (P(t) - P_{\text{mean}})^{2} \times dt \right) )</td>
</tr>
<tr>
<td>SVB method</td>
<td>Present study</td>
<td></td>
<td>SVB</td>
<td>( Q = \frac{C \times PP}{P_{\text{mean,area}} \times T_{d} \times \frac{P_{m}}{T}} )</td>
</tr>
<tr>
<td>eSVB method</td>
<td>Present study</td>
<td></td>
<td>eSVB</td>
<td>( Q = k \times \frac{C \times PP}{T} )</td>
</tr>
</tbody>
</table>

CO, cardiac output; Q, flow rate; SVB, systolic volume balance; eSVB, empirical SVB; \( k \), correction/calibration coefficient; PP, pulse pressure; T, cardiac period; \( P_{s} \), systolic arterial pressure; \( P_{d} \), diastolic arterial pressure; \( P_{m} \), mean pressure; \( T_{e} \), ejection duration; \( T_{d} \), duration of diastole; \( P_{m} \), area under the systolic part of the pressure wave; \( P_{\text{mean,area}} \), end-systolic pressure; \( \tau \), time constant of the exponential decay of the diastolic portion of the pressure contour; HR, heart rate; \( P(t) \), pressure at time instant t; C, total arterial compliance; \( P_{aortic} \), aortic PP; \( P_{\text{mean,aorta}} \), mean systolic pressure at the aorta.
random agreement and to +1 for perfect agreement. ICC values can be interpreted as follows: 0–0.2 indicates poor agreement, 0.3–0.4 fair agreement, 0.5–0.6 moderate agreement, 0.7–0.8 strong agreement, and >0.8 almost perfect agreement (30). Variability between CO estimates and values of the model was assessed by the between-measures coefficient of variation (ratio of SD to the mean value). RMSE was used to describe accuracy between values predicted by the PCCO estimators and CO values computed by the model, encompassing both random and systematic errors. RMSE is the square root of the square of the difference between a true test point and an interpolated test point divided by the total number of test points in the arithmetic mean. RMSE can range from 0 to ∞, with lower values indicating greater accuracy. Finally, Bland-Altman analysis was performed as previously described (4). According to this method, the differences between two CO values (estimated—computed) are plotted against their mean value. Limits of agreement were defined as mean − 2SD and mean + 2SD. P values of <0.05 were considered to represent statistical significance. Statistical analysis was performed by SPSS 20 (SPSS, Chicago, IL).

RESULTS

Pulse contour analysis methods for CO estimation depend on the morphology of pressure waves. Separate or combined changes in parameters, such as C, R, and heart rate, which were simulated by the 1-D model, introduced changes in pressure wave morphology, providing a variety of different pressure profiles; brachial systolic BP ranged from 57 to 139.4 mmHg, brachial diastolic BP ranged from 38.8 to 87.8 mmHg, and mean BP ranged from 57.3 to 103.6 mmHg. Representative pressure and flow waves in the ascending aorta for three different levels of C, R, and heart rate, respectively, are shown in Fig. 3.

Fig. 3. Pressure and flow waves at the root of the ascending aorta for three different levels of total arterial compliance (C; A and B), total vascular resistance (R; C and D), and heart rate [in beats/min (b.p.m.); E and F], respectively. In each case, only one parameter was changed and the others remained constant.
Estimation of CO by SVB and eSVB methods and comparison with other PCCO methods based on aortic pressure wave analysis. Indexes of agreement, accuracy, variability, and correlation between computed ("real") and estimated CO values by the SVB and eSVB methods are shown in Table 2. The respective indexes were determined for other PCCO methods as well, which were also calibrated by the same method. All of them used parameters derived by aortic pressure wave analysis. Among all the investigated PCCO methods, the SVB and eSVB methods for CO estimation (Eqs. 4 and 5) presented the highest correlation ($R^2$) and agreement (ICC) and the lowest variation (CV) and error bias (RMSE, mean difference, and SD of difference) compared with the "real" CO computed by the model (Table 2). The correlation and agreement between estimated and model-derived CO values are shown by scatterplots and Bland-Altman plots in Fig. 4.

Table 2. Correlation, agreement, and accuracy between computed ("real") and estimated CO values derived from aortic pressure wave analysis

<table>
<thead>
<tr>
<th>Method</th>
<th>$R^2$</th>
<th>Intraclass Correlation Coefficient</th>
<th>Mean Difference, l/min</th>
<th>SD of Mean Difference, l/min</th>
<th>Coefficient of Variation, %</th>
<th>RMSE, l/min</th>
<th>Limits of Agreement, l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVB</td>
<td>0.958</td>
<td>0.851</td>
<td>0.031</td>
<td>0.362</td>
<td>3.4 (SD 2.1)</td>
<td>0.013</td>
<td>−0.7, 0.7</td>
</tr>
<tr>
<td>eSVB</td>
<td>0.728</td>
<td>0.805</td>
<td>0.034</td>
<td>0.366</td>
<td>3.6 (SD 2.2)</td>
<td>0.005</td>
<td>−0.7, 0.8</td>
</tr>
<tr>
<td>F1</td>
<td>0.099</td>
<td>−0.185</td>
<td>0.333</td>
<td>1.609</td>
<td>14.0 (SD 10.4)</td>
<td>0.010</td>
<td>−2.9, 3.5</td>
</tr>
<tr>
<td>F2</td>
<td>0.026</td>
<td>0.105</td>
<td>0.221</td>
<td>1.281</td>
<td>11.5 (SD 7.2)</td>
<td>0.113</td>
<td>−2.3, 2.8</td>
</tr>
<tr>
<td>F3</td>
<td>0.129</td>
<td>−0.191</td>
<td>0.392</td>
<td>1.785</td>
<td>15.2 (SD 11.0)</td>
<td>0.017</td>
<td>−3.2, 4.0</td>
</tr>
<tr>
<td>F4</td>
<td>0.063</td>
<td>−0.145</td>
<td>0.332</td>
<td>1.609</td>
<td>13.8 (SD 10.3)</td>
<td>0.025</td>
<td>−2.9, 3.5</td>
</tr>
<tr>
<td>F5</td>
<td>0.040</td>
<td>−0.149</td>
<td>0.187</td>
<td>1.217</td>
<td>11.2 (SD 8.5)</td>
<td>0.085</td>
<td>−2.2, 2.6</td>
</tr>
<tr>
<td>F6</td>
<td>0.171</td>
<td>−0.331</td>
<td>0.170</td>
<td>1.203</td>
<td>11.4 (SD 7.0)</td>
<td>0.082</td>
<td>−2.2, 2.6</td>
</tr>
<tr>
<td>F7</td>
<td>0.217</td>
<td>−0.285</td>
<td>0.317</td>
<td>1.603</td>
<td>14.0 (SD 10.4)</td>
<td>0.031</td>
<td>−2.9, 3.5</td>
</tr>
<tr>
<td>F8</td>
<td>0.224</td>
<td>−0.214</td>
<td>0.528</td>
<td>2.121</td>
<td>17.5 (SD 12.8)</td>
<td>0.007</td>
<td>−3.7, 4.8</td>
</tr>
<tr>
<td>F9</td>
<td>0.075</td>
<td>−0.256</td>
<td>0.091</td>
<td>0.923</td>
<td>8.7 (SD 5.5)</td>
<td>0.064</td>
<td>−1.7, 1.9</td>
</tr>
<tr>
<td>F10</td>
<td>0.187</td>
<td>−0.241</td>
<td>0.360</td>
<td>1.740</td>
<td>14.7 (SD 10.9)</td>
<td>0.029</td>
<td>−3.1, 3.8</td>
</tr>
</tbody>
</table>

RMSE, root mean square error. CO estimations by the SVB and eSVB methods were derived by Eqs. 4 and 5, respectively. See Table 1 for detailed equations for the F1–F10 methods.

Fig. 4. Bland-Altman plots (A and C) and scatterplots (B and D) for the computed (model) mean blood flow ($Q$) versus the estimated mean flow by the two methods [the systolic volume balance (SVB) method from Eq. 4 and the empirical SVB (eSVB) method from Eq. 5], respectively. Aortic pressure waves were analyzed. Dotted lines indicate equality between the estimated and model values. The estimated CO values shown in the graphs were derived without the use of any empirical coefficient. $R^2$ and $P$ value refer to the linear correlation between estimated and computed (model) mean $Q$ values.
The SVB method, when applied on aortic pressure waves, did not require any empirical coefficient or calibration for the estimation of the model’s CO. The estimation of CO by the SVB method had a small bias of 0.031 l/min with an SD of differences of 0.362 l/min and a low RMSE of 0.013 l/min (Table 2). The simplified estimate of CO by the eSVB method required an empirical coefficient. The average value of this coefficient, based on the total of the hemodynamic simulations, was found to be 1.831, with a CV of 6% and a SD of 0.11. Interestingly, the eSVB method estimated CO also quite accurately, with a bias of 0.034 l/min, SD of differences of 0.366 l/min, and a very low RMSE of 0.005 l/min (Table 2).

Application of SVB, eSVB, and other PCCO methods on brachial pressure waves. The hypothesis that the SVB and eSVB methods for monitoring CO can be applied on brachial pressure wave analysis was further investigated. Therefore, brachial pulse pressure, mean systolic pressure, and mean arterial blood pressure were determined by analyzing the brachial pressure waves that were derived by the 1-D model for the total of the simulated cases. In this case, an empirical coefficient, \( k \), was introduced in the SVB formula, as follows:

\[
Q_{SVB} = k \times \frac{C \times P_{Pao}}{T - T_{P_{sm},aorta} \times T_s} \frac{P_m}{P_{m}}
\]

\( R^2 \), ICC, CV, RMSE, mean difference, SD of differences, and limits of agreement of the two formulas, based on brachial pressure wave analysis, are shown in Table 3. The correlation and agreement between the computed and estimated mean flows are shown in Bland-Altman plots and scatterplots in Fig. 5.

The SVB method was also effective when brachial pressure was used as a substitute to the aortic pressure wave. In this case, an average empirical coefficient of 0.67 was calculated. The variability of the brachial empirical coefficient for the SVB formula (Eq. 4), among the examined cases, was again very low (CV of 5.1% and SD of 0.035). Compared with the model’s CO value, the estimated CO value based on brachial pulse wave analysis had also low bias (0.042 l/min), SD of differences (0.341 l/min), and RMSE (0.041 l/min). The simplified empirical estimate of CO by the eSVB method had an average correction coefficient of 1.275, which again had a low variation for the examined cases (CV of 4.7% and SD of 0.06).

The eSVB method estimated CO using brachial pressure parameters also quite accurately, with a bias of 0.019 l/min, SD of differences of 0.282 l/min, and a very low RMSE of 0.027 l/min (Table 3).

### DISCUSSION

In the present report, a new, noninvasive pressure pulse contour analysis method for monitoring CO is proposed. The new formula, including a second simpler empirical form of the same formula, was derived from basic physical principles that govern blood flow and, in particular, a volume balance approach for the conservation of mass ejected into and flowed out of the arterial system during systole. In the present model study, it was demonstrated that the SVB method could accurately estimate CO based on aortic pressure wave analysis, without requiring any calibration or empirical coefficient. The SVB method and its empirical simplified form, the eSVB method, estimated CO accurately, also based on brachial pressure wave analysis, using a single empirical coefficient. The two methods were validated in silico by comparing their CO estimates with actual CO values computed by a 1-D model of the arterial tree. The model allowed the simulation of different hemodynamic conditions by altering heart rate, C, and R. The accuracy of the SVB and eSVB methods was compared with the accuracy of previously described PCCO methods, and it was found to be superior in all aspects of agreement and variability when all methods were calibrated/corrected by single average coefficient. It should be acknowledged that the inclusion of \( C \) in the proposed formulas (SVB and eSVB) may, in part, explain the superiority of the SVB and eSVB methods compared with the other examined PCCO methods. However, another potential characteristic that may account for this superiority is the different physical approach for estimating blood flow balance during cardiac systole, which differs from other PCCO approaches, as shown in Table 1.

One of the important findings of the present study was that the SVB formula accurately predicted CO without the use of an empirical coefficient when parameters from aortic pressure waves were used. This is a result of the fact that the SVB method is directly derived from first principles, i.e., conservation of mass in the systemic tree during systole. In the present model study, it was demonstrated that the SVB method could accurately estimate CO based on aortic pressure wave analysis, without requiring any calibration or empirical coefficient. The SVB method and its empirical simplified form, the eSVB method, estimated CO accurately, also based on brachial pressure wave analysis, using a single empirical coefficient. The two methods were validated in silico by comparing their CO estimates with actual CO values computed by a 1-D model of the arterial tree. The model allowed the simulation of different hemodynamic conditions by altering heart rate, C, and R. The accuracy of the SVB and eSVB methods was compared with the accuracy of previously described PCCO methods, and it was found to be superior in all aspects of agreement and variability when all methods were calibrated/corrected by single average coefficient. It should be acknowledged that the inclusion of \( C \) in the proposed formulas (SVB and eSVB) may, in part, explain the superiority of the SVB and eSVB methods compared with the other examined PCCO methods. However, another potential characteristic that may account for this superiority is the different physical approach for estimating blood flow balance during cardiac systole, which differs from other PCCO approaches, as shown in Table 1.

One of the important findings of the present study was that the SVB formula accurately predicted CO without the use of an empirical coefficient when parameters from aortic pressure waves were used. This is a result of the fact that the SVB method is directly derived from first principles, i.e., conservation of mass in the systemic tree during systole. Also, the ICC between the estimated and the model’s CO values was >0.8.

<table>
<thead>
<tr>
<th>Method</th>
<th>( R^2 )</th>
<th>Intraclass Correlation Coefficient</th>
<th>Mean Difference, l/min</th>
<th>SD of Mean Difference, l/min</th>
<th>Coefficient of Variation, %</th>
<th>RMSE, l/min</th>
<th>Limits of Agreement, l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVB</td>
<td>0.924</td>
<td>0.861</td>
<td>0.042</td>
<td>0.341</td>
<td>2.9 (SD 2.2)</td>
<td>0.041</td>
<td>−0.7, 0.6</td>
</tr>
<tr>
<td>eSVB</td>
<td>0.743</td>
<td>0.853</td>
<td>0.019</td>
<td>0.282</td>
<td>2.6 (SD 3.8)</td>
<td>0.027</td>
<td>−0.6, 0.5</td>
</tr>
<tr>
<td>F1</td>
<td>0.106</td>
<td>−0.171</td>
<td>0.424</td>
<td>1.786</td>
<td>16.1 (SD 10.9)</td>
<td>0.034</td>
<td>−3.1, 4.0</td>
</tr>
<tr>
<td>F2</td>
<td>0.010</td>
<td>0.060</td>
<td>0.256</td>
<td>1.377</td>
<td>12.7 (SD 7.4)</td>
<td>0.122</td>
<td>−2.5, 3.0</td>
</tr>
<tr>
<td>F3</td>
<td>0.168</td>
<td>−0.195</td>
<td>0.266</td>
<td>0.993</td>
<td>17.6 (SD 11.8)</td>
<td>0.003</td>
<td>−3.5, 4.5</td>
</tr>
<tr>
<td>F4</td>
<td>0.070</td>
<td>−0.137</td>
<td>0.426</td>
<td>1.797</td>
<td>16.0 (SD 10.8)</td>
<td>0.050</td>
<td>−3.2, 4.0</td>
</tr>
<tr>
<td>F5</td>
<td>0.039</td>
<td>−0.149</td>
<td>0.183</td>
<td>1.205</td>
<td>11.1 (SD 7.4)</td>
<td>0.084</td>
<td>−2.2, 2.6</td>
</tr>
<tr>
<td>F6</td>
<td>0.172</td>
<td>−0.355</td>
<td>0.167</td>
<td>1.194</td>
<td>11.3 (SD 6.9)</td>
<td>0.081</td>
<td>−2.2, 2.6</td>
</tr>
<tr>
<td>F7</td>
<td>0.207</td>
<td>−0.246</td>
<td>0.145</td>
<td>1.795</td>
<td>16.2 (SD 10.9)</td>
<td>0.057</td>
<td>−3.2, 4.0</td>
</tr>
<tr>
<td>F8</td>
<td>0.339</td>
<td>−0.326</td>
<td>0.356</td>
<td>1.801</td>
<td>15.3 (SD 10.6)</td>
<td>0.033</td>
<td>−3.2, 4.0</td>
</tr>
<tr>
<td>F9</td>
<td>0.075</td>
<td>−0.258</td>
<td>0.089</td>
<td>0.915</td>
<td>8.7 (SD 5.5)</td>
<td>0.063</td>
<td>−1.7, 1.9</td>
</tr>
<tr>
<td>F10</td>
<td>0.144</td>
<td>−0.265</td>
<td>0.228</td>
<td>1.389</td>
<td>12.3 (SD 8.6)</td>
<td>0.025</td>
<td>−2.5, 3.0</td>
</tr>
</tbody>
</table>

See Table 1 for detailed equations for the F1–F10 methods.
indicating an excellent agreement (30). These results suggest that, overall, the proposed SVB method for CO estimation, based on aortic pressure wave analysis, is robust, as indicated by the very low systemic bias and narrow limits of agreement. When the simplified eSVB method was applied to aortic pressure waves, the estimation of CO was made with similar accuracy; however, an average $k$ of 1.83 was used (much higher than unity). This was due to the fact that the denominator of the SVB formula (Eq. 4) was replaced by a much higher value ($T$), thus necessitating a correction using an empirical coefficient. This finding shows that the calculation of SV as the product of $C$ times pulse pressure (SV = $C \times$ pulse pressure) leads to a significant underestimation of SV. The bias of CO estimation by the eSBV method was even lower, with quite narrow limits of agreement (Table 2).

A second essential finding of this study was that the proposed methods (SVB and eSVB) were also effective when brachial pressure wave analysis was performed for the calculation of the required parameters. The radial artery is commonly used in clinical practice for the invasive recording of pressure waves. In the present study, we aimed to propose a PCCO method based on brachial waveforms with the ultimate purpose of noninvasive recording of BP in future clinical setting. In this case, an average empirical coefficient of 0.67 was calculated for the SVB method and 1.275 for the eSVB method. Interestingly, the variability of brachial $k$ among the examined cases was very low for both SVB and eSVB estimations of CO. Again, the ICC between the estimated and model’s CO values was >0.85, indicating an excellent agreement, even though the brachial pressure wave was used and the CO values were corrected by a single empirical coefficient. Since the variability of $k$ for the examined cases was low for both methods (SVB and eSVB), it could be suggested that both of them could be used in different hemodynamic conditions, possibly by using a single empirical coefficient without the need for repeated “calibrations.”

It was found that CO could be estimated with similar accuracy between aortic and brachial pressure wave analysis, with the latter requiring a correction coefficient, probably due to the phenomenon of pulse pressure amplification from central to peripheral arteries. However, pulse pressure amplification can vary due to 1) physiological conditions (28, 50), 2) pathophysiological conditions (1, 37), or 3) pharmaceutical interventions (31). In some extreme hemodynamic cases, this phenomenon may be even reversed (15, 29). In such cases, PCCO methods could be inaccurate and would require recalibration. Another possible way to account for pulse pressure amplification changes could be the use of transfer functions to derive aortic pulse pressure from radial pressure waves, as previously suggested (5, 19), but again these functions could be inaccurate under specific or extreme hemodynamic and vascular conditions.

Finally, the proposed CO estimators (SVB and eSVB) were compared against other PCCO methods (Table 1) of similar...
complexity/simplicity and with clearly described equations in the literature. To perform comparisons of equal validity, each formula was calibrated with the same way, as described in MATERIALS AND METHODS (Comparison with other PCCO methods). Both SVB and eSVB had higher accuracy than the other 10 examined PCCO methods when applied to both brachial and aortic pressure wave analysis. It is noteworthy that the other estimators of CO had more than two times wider limits of agreements than the SVB and eSVB methods. This result points out that correction or calibration of the other formulas by a single coefficient is ineffective, in contrast to SVB and eSVB. For this reason, most of these PCCO methods require repeated calibrations to provide more consistent results, a possible reason for which these methods are still under criticism (25).

Bland-Altman plots demonstrated that the SVB method for CO estimation (Eq. 4) had the lowest bias and narrowest limits of agreement compared with the other methods for both aortic and brachial pressure wave analysis. The simplified estimation of CO based on the eSVB method (Eq. 5) was also very accurate, but it required a correction (k = 1.83), whereas such a correction in the SVB method (Eq. 4) was not necessary. There was a trend for the difference of CO estimation from the model’s CO value to increase slightly with the increase in mean flow. A similar or inverse trend, however, has also been previously observed for other PCCO estimators (46).

In vivo validation studies (e.g., with thermodilution or dye dilution as the reference method for CO measurement) have previously reported bias and limits of agreement for various PCCO methods that ranged from 0 to 0.23 l/min and from −0.74 to 2.09 l/min, respectively (8), with the narrowest limits of agreement being −0.74 to 0.74 l/min. Sun et al. (43), in a meta-analysis of clinical data, validated various PCCO formulas using different calibration techniques. It was found that for several PCCO methods, the 95% limits of agreement for the best possible calibration technique for every formula ranged, in total, from −2.66 to 1.89 l/min, with the narrowest limits of agreement being −1.76 to 1.41 l/min (43). However, interpretation of the reported values of accuracy in the present study should not be made compared with previously reported data for two main reasons. First, most validation studies of PCCO methods have been derived using, as a reference, gold standard thermodilution or dye dilution techniques. These techniques already have their own limitations/errors for measuring CO, in contrast to the precise CO calculations made by the present 1-D model. Second, each PCCO method has been calibrated differentially in previous studies or by using repeated calibrations per patient. Therefore, the results of the present study cannot prove whether the proposed SVB and eSVB methods are superior to other PCCO methods or commercial systems in a clinical setting, where the latter are repeatedly calibrated invasively (e.g., by dye dilution methods), or were analyzed using invasive recordings of pressure waves.

Direct comparisons with the exact methods used by commercial systems of CO monitoring using pulse contour analysis were not made in the present study. The commercial LiDCO system (LiDCO Group, London, UK) uses the power of the arterial blood pressure signal, deriving the “beat power factor (r.m.s.-root mean square) which is proportional to the nominal stroke volume ejected into the aorta,” as previously described (36). However, this method entails additional processing steps that are not clearly and comprehensively described in the literature, and, therefore, the exact replication of this methodology was not possible. Alternatively, we took into consideration the “power method” to estimate SV (Table 1, formula 10), which is a main component of the LiDCO system. Similarly, the method used by the Vigileo System (Edwards Lifesciences, Irvine, CA) was also not fully described in the literature, thus not allowing its exact computational reproduction. Moreover, this system uses statistical parameters based on human data, which were also not known to us. Also, an advanced form of formula 9 (Table 1) proposed by Wesseling et al. (48) in 1993 was not replicated computationally for the same reasons.

Assessment of accuracy: methodological considerations. It is generally accepted that there is no single method or statistic parameter to assess accuracy of a measurement. At first, the reference method (gold standard) for comparison should be selected. For in vivo validation studies, thermodilution using a pulmonary artery catheter is generally accepted as the clinical gold standard (32). However, this method can be applied, usually, to a limited number of patients under only a specific range of hemodynamic conditions and presents a non-negligible risk for complications (24). Dye dilution techniques for CO monitoring are less invasive but are still susceptible to errors due to inherent methodological limitations (27, 33). Mathematical models of the cardiovascular system have served for years as a primary methodological tool for the understanding of physical principles of human circulation (41, 49). They have been also used to develop and validate new methods and technologies for the assessment of hemodynamic and vascular parameters (40, 44). In the present study, the proposed SVB method and other methods for PCCO monitoring were compared with a validated, extensive model of the arterial tree (34, 35), which provides realistic and accurate representation of pressure and flow waves along the arterial tree. The main advantage of the validation via such a model is that the “true” CO is precisely known and thus the comparison of the estimates to the real CO value was not contaminated by errors in the measurement of the CO value, providing thus a very accurate framework for the assessment of accuracy.

There are several statistical methods and parameters for assessing accuracy without, however, any consensus on which one is the most appropriate (7, 32). In the present study, the accuracy and agreement of the PCCO estimators compared with the “real” CO values computed by the 1-D model were assessed by a wide variety of statistical measures and methods (2, 4, 32). In addition to classic correlation coefficients and CV, accuracy and agreement were assessed by calculating bias, limits of agreement, RMSE, and ICC. Thus, several different facets of accuracy, agreement, consistency, and variability between the estimated and model’s mean flow values were evaluated.

Applicability: measurement of parameters involved in the new formulas. Current PCCO monitoring techniques rely on the invasive recording of arterial pressure waves, often requiring repeated calibration. The proposed SVB and eSVB methods of CO estimation have the potential of totally noninvasive applicability. The SVB method requires the measurement of pulse pressure (systolic − diastolic BP), P_{sm}, P_m, T_e, T, and C. Currently, it is possible to record noninvasively peripheral pressure waves by cuff oscillometric techniques (9, 12, 47) or...
arterial tonometry (26). Therefore, systolic, diastolic, and mean BP can be easily measured. $P_{m}$, systolic-ejection duration, and $T$ can be also measured either by analyzing the pressure waveform alone or in combination with ECG. The simplified eSVB method (Eq. 5) is even more attractive in terms of clinical practice because it requires only the measurement of pulse pressure and $T$ in addition to $C$. The determination of $C$ is a critical parameter for CO estimation by the proposed SVB and eSVB methods. The physical principles that were used to derive the SVB and eSVB methods indicated the necessity of $C$ for the estimation of CO by pulse contour analysis. In the present study, values of $C$ were computed analytically for each simulated arterial tree, but in a clinical setting the estimation of $C$ must be made indirectly. Similar to some commercial PCCO systems, $C$ values can be incorporated in the SVB and eSVB formulas using bibliographic-epidemiological data of compliance (per age and sex) with a correction for a patient’s mean BP based on the Langerwouters’ formula (21). Also, if relative SV changes are of interest, $C$ or a surrogate marker of $C$ could be measured once [e.g., by a pulse pressure method (40) or pulse wave velocity], and the relative changes of $C$ as a function of pressure could then be monitored using Langerwouters’ equation or a similar law relating $C$ to pressure changes.

**Limitations.** It must be underscored that the interpretation of the reported results in this study regarding the accuracy of the new SVB and eSVB methods for the estimation of CO should be made with caution and should not be directly extrapolated to real clinical settings or human measurements. The present study does not provide any direct evidence regarding the clinical superiority of the new methods compared with existing methods or commercial systems, which remain to be tested in future clinical trials. Although the proposed SVB and eSVB methods are based on basic physical principles that are independent from the 1-D model, the statistical results for comparisons of the methods in this study depend, in part, on the total number of the simulated cases (size) and the “input” parameters that were modified. Thus, a larger sample size and the modification of several other parameters of the model, such as cardiac function parameters, size of the arterial tree model, and physiological or disease states, could possibly provide an even wider range of simulated hemodynamic conditions. It should be also highlighted that in specific hemodynamic and vascular conditions, where local wave reflections are intense or when BP amplification between central to peripheral arteries is unbalanced, pulse contour analysis methods may be susceptible to errors regarding the estimation of CO.

**Conclusions.** The continuous monitoring of CO is essential in several clinical and research settings. Currently, a number of minimally invasive techniques exist, but they suffer from inherent technical limitations. A new method, based on SBV, for PCCO monitoring has been proposed with the potential of noninvasive application. The proposed method (SVB) and its simplified empirical form (eSVB) presented good accuracy, which were superior compared with other methods. The latter is a major advantage that may allow CO monitoring without the necessity for repeated calibrations. Further in vivo validation studies remain to be conducted to validate the performance of SVB and eSVB methods on monitoring CO under different hemodynamic conditions or under various interventions.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**

Author contributions: T.G.P. and O.V. performed experiments; T.G.P. and O.V. analyzed data; T.G.P., O.V., and N.S. interpreted results of experiments; T.G.P. prepared figures; T.G.P. and O.V. edited and revised manuscript; T.G.P. and N.S. approved final version of manuscript; N.S. conception and design of research.

**REFERENCES**