Evaluation of Noninvasive Methods to Assess Wave Reflection and Pulse Transit Time From the Pressure Waveform Alone

Jan G. Kips, Ernst R. Rietzschel, Marc L. De Buyzere, Berend E. Westerhof, Thierry C. Gillebert, Luc M. Van Bortel, Patrick Segers

Abstract—Accurate quantification of pressure wave reflection requires separation of pressure in forward and backward components to calculate the reflection magnitude as the ratio of the amplitudes backward and forward pressure. To do so, measurement of aortic flow in addition to the pressure wave is mandatory, a limitation that can be overcome by replacing the unknown flow wave by an (uncalibrated) triangular estimate. Another extended application of this principle is the derivation of aortic pulse transit time from a single pulse recording. We verified these approximation techniques for reflection magnitude and transit time using carotid pressure and aortic flow waveforms measured noninvasively in the Asklepios Study (≥2500 participants; 35 to 55 years of age). A triangular flow approximation using timing information from the measured aortic flow waveform yielded moderate agreement between reference and estimated reflection magnitude ($R^2=0.55$). Approximating the flow by a more physiological waveform significantly improved these results ($R^2=0.74$). Aortic transit time was assessed using pressure and measured or approximated flow waveforms, and results were compared with carotid-femoral transit times measured by Doppler ultrasound. Agreement between estimated and reference transit times was moderate ($R^2<0.29$). Both for reflection magnitude and transit time, agreement between reference and approximated values further decreased when the approximated flow waveform was obtained using timing information from the pressure waveform. We conclude that, in our Asklepios population, results from pressure-based approximative methods to derive reflection magnitude or aortic pulse transit time differ substantially from the values obtained when using both measured pressure and flow information. (Hypertension. 2009;53:142-149.)

Key Words: hypertension ■ blood pressure measurement/monitoring ■ hemodynamics ■ arterial stiffness ■ wave reflection ■ pulse wave velocity

The pressure pulse can be considered as the composite of a forward pressure wave, traveling from the heart to the periphery, and of a reflected pressure wave, traveling backward toward the heart. Early return of this reflected wave boosts (central) systolic blood pressure, increasing the load on the heart and boosting the amplitude of the pressure pulse, factors that have been shown to increase cardiovascular risk. Therefore, analysis of pulse wave velocity and pressure wave reflection have been points of clinical interest for many years now.

Several methods to quantify wave reflection emerged, the most widespread probably being the augmentation index (AIx). AIx is a parameter based on analysis of the pressure waveform and expresses the ratio of augmented pressure (attributed to wave reflection) to pulse pressure. However, because several factors influence its value, AIx might not be the most appropriate parameter for an accurate quantification of the magnitude of wave reflection.

More accurate methods to assess wave reflection are based on wave separation analysis. These methods are based on measurement of pressure and flow, ideally measured simultaneously and at the same anatomic location, preferentially the central aorta. Although approximated approaches, based on aortic flow and carotid or subclavian pressure measurements, are feasible, implementation of these extended measurement protocols in a clinical setting is not evident. In an attempt to merge the benefits of a method based on measurement of pressure waveform alone and of the wave separation analysis, Westerhof et al recently advocated a new method, where the flow wave is approximated by a triangle. Their analysis yields an approximation of the reflection magnitude (RM), the ratio of the amplitude of the

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reflected to the forward wave. The method was found to give promising results, but the initial study was, overall, based on a relatively low number of data sets (29 beats of 19 humans).

In recent work, Qasem and Avolio proposed a new method of deriving pulse transit time and aortic pulse wave velocity from a central pressure waveform. The method is based on assessing the time delay between the forward and backward pressure components, decomposed from a central pressure waveform. The triangular flow wave approximation is used for pressure wave decomposition. Linear regression between calculated and measured carotid-femoral pulse transit time showed promising results in a cohort of 46 subjects.

The objective of this study was threefold: (1) to verify the triangular flow wave approximation method and the assessment of the RM as proposed by Westerhof et al.; (2) to verify the assessment of aortic pulse wave velocity from a single pulse recording as proposed by Qasem and Avolio; and (3) to explore the possibility of approximating the flow wave by using a person-specific, time-scaled, normalized average flow waveform and to assess its impact on the estimates of RM and pulse wave velocity.

**Materials and Methods**

We refer to the online data supplement for an extended version of the Methods section (please see http://hyper.ahajournals.org). Only a summary is given here.

**Asklepios Population**

A total of 2325 data sets, including noninvasive aortic flow and carotid artery pressure measurements recorded within the framework of the Asklepios Study, are used. Carotid pressure waveforms were obtained using applanation tonometry at the left common carotid artery, after an earlier described calibration scheme based on brachial artery tonometry. The aortic flow waveform was assessed using pulse Doppler ultrasound (Vivid7, GE Vingmed Ultrasound) in the left ventricular outflow tract. Carotid-femoral pulse wave velocity (PWV) was measured by Doppler ultrasound (TTref), which serve as a reference here.

**Triangular Waveform Construction**

Following Westerhof et al., a triangular flow waveform was constructed. Although the authors of that study obtained timing information from the pressure waveform, we approximated the flow using timing information for start, peak, and end of flow from the measured flow waveform itself. By doing so, we can evaluate the isolated effect of the triangular shape approximation, independent of errors introduced via the assessment of the timing from the pressure waveform. As such, these results can be considered as the best possible results that can be obtained with a triangular approximation of the flow waveform. The root mean square error (RMSE) between the approximated flow waveform and the measured one is calculated and expressed as mean (SD).

**Linear Wave Separation Analysis and Derived Parameters**

Using flow and pressure, forward ($P_f$) and backward ($P_b$) pressure waveforms were calculated using the linear wave separation technique as first described by Westerhof et al. The forward and backward pressure waveforms derived using the measured flow serve as a reference. Agreement between the approximated (derived using approximated flow) and reference forward (and backward) pressure waveform is assessed by calculating the RMSE between the 2 waveforms. The amplitudes of the approximated forward ($P_{f,approx}$) and backward ($P_{b,approx}$) pressure waves are compared to the reference forward ($P_{f,ref}$) and backward ($P_{b,ref}$) pressure amplitudes via linear regression analysis ($R^2$ values), and their mean difference is displayed as mean (SD).

**RM Assessment**

Reference ($R_{ref}$) and approximated RM ($R_{approx}$) are calculated as the ratio of the amplitudes of backward over forward pressure wave: $R = P_b/P_f$, with * referring to either the reference or the approximation. Agreement between reference and approximation was studied via linear regression analysis ($R^2$ values) and Bland-Altman analysis. In addition, we also calculated the AIX as a measure of wave reflection. We refer to previous work for a description of how AIX was derived.

**PWV Assessment: Time Delay Between $P_f$ and $P_b$**

To assess the time delay between $P_f$ and $P_b$, Qasem and Avolio proposed to first modify the pressure waveforms. Basically, it is assumed that the forward pressure wave reaches its peak at the moment of peak flow. The backward pressure wave arrives at the moment of peak flow and only plays a role from that moment on. After normalization of the modified forward and backward pressure waveforms, the time lag between $P_f$ and $P_b$ was obtained using cross-correlation techniques, assuming that the correct time lag is the value for which there is maximum cross-correlation between the 2 normalized waveforms. Following Qasem and Avolio, the pulse transit time (TT) is obtained as half of the time lag.

This method was applied using either the measured flow waveform ($Q_{meas}$) or the approximated waveform (triangular flow waveform). TTs obtained from these approaches are indicated as TT*, with * referring to either the measured approach or the approximative approach. TT’s were also compared with the carotid-femoral pulse TTs measured by Doppler ultrasound (TTref), which serve as a reference here.

**Averaged Physiological Flow Waveform**

In a third part of this study, approximation via triangular flow waveform profiles was left aside, and the analysis (assessment of RM and TT) was repeated using a more physiological flow waveform ($Q_{phys}^{approx}$) obtained from normalizing and averaging measured flow waveforms. Using data from 74 subjects (32 women and 42 men; 3.1% of the total database), the average flow waveform was calculated after normalizing each individual flow curve in time and amplitude. The subjects used to construct the physiological flow waveform were subjects where aortic flow was available but where other data were missing for various technical reasons. To approximate the actual flow waveform, the averaged and normalized waveform was scaled in time using the timing of the beginning and ending of each individual measured flow waveform.

**Synthesized Aortic Pressure**

The analysis (assessment of RM and TT) was repeated by using synthesized aortic instead of carotid pressure, obtained from radial tonometry via a generalized pressure transfer function.

**Results**

Basic population and hemodynamic data are given in Table 1. The mean age of the subjects (1209 women and 1116 men) was 46 years, ranging from 35 to 55 years. A total number of 651 subjects with hypertension were included, of whom 237 were under drug treatment.

**Triangular and Averaged Flow Waveform Approximation**

Table 2 gives an overview of the impact of the different flow waveform approximations on the forward and backward pressure waveforms and derived parameters. The RMSE
between approximated and measured flow waveform decreased markedly from the triangular (0.12) to the averaged waveform approximation (0.04; see Table 2). Note that these errors were based on a normalized peak flow of 1.0, ie, the minimal error was 4%.

Agreement Between Approximated and Reference RM
The RMSE between the approximated and reference forward pressure waves varied between 1.1 mm Hg (averaged waveform) and 2.4 mm Hg (triangular waveform). Regression analysis between the amplitudes of the approximated forward and backward pressure waves and the reference waves reveals that the highest correlations were found for the averaged waveform. Also, the mean difference $P_f^\text{approx} - P_f^\text{ref}$ (or $P_b^\text{approx} - P_b^\text{ref}$) was smaller when using the averaged waveform (see Table 2).

Mean reference RM was 0.48 (0.09), whereas mean RMs for triangular and averaged flow waveforms were 0.48 (0.10) and 0.48 (0.09), respectively. Figure 1 shows the results of the linear regression and Bland-Altman analysis between approximations of RM and $RM^\text{ref}$. Bland-Altman analysis shows a constant mean difference of 0 for both flow approximations, with a tighter dispersion around the mean when the averaged waveform is used.

Agreement Between Approximated and Measured Pulse TT
Pulse TT (carotid-femoral) measured directly with ultrasound ($TT^\text{ref}$) was 67.8 ms (11.9 ms), whereas 77.9 ms (23.3 ms) was the mean pulse TT found based on the principle of wave decomposition using the measured pressure and aortic flow ($TT^\text{avg}$). When using a triangular flow approximation, estimated pulse TT ($TT^\text{tri}$) was 72.5 ms (14.8 ms), whereas the averaged flow approximation yielded a $TT^\text{avg}$ of 75.9 ms (20.1 ms). The best agreement between the TT estimated using the measured flow waveform and either of the approximated flow waveforms was found when using the averaged flow waveform ($TT^\text{avg}$; $R^2$=0.82). However, when studying the relation between $TT^\text{approx}$ and $TT^\text{ref}$, $R^2$ values were not higher than 0.28 (Figure 2A and 2B). Interestingly, also, the agreement between $TT^\text{meas}$ and $TT^\text{ref}$ was weak ($R^2$=0.27; Figure 2C). Bland-Altman plots show a strong trend of overestimation toward higher TT values for all of the cases (Figure 2D through 2F).

Synthesized Aortic Pressure
Using synthesized aortic pressure instead of carotid pressure waveforms for the calculation of RM (Figure 3A and 3B), agreement ranged from $R^2$=0.66 (triangular flow) to $R^2$=0.79 (averaged flow). TTs were also recalculated using aortic pressure, yielding levels of agreement below $R^2$=0.13 for both flow waveforms (see Figure 3C and 3D).

Discussion
We applied the triangular flow wave approximation method to estimate RM as proposed by Westerhof et al on 2325 noninvasively recorded data sets, consisting of carotid artery pressure and aortic flow waveforms. Despite the fact that we used timing information directly from the measured flow waveforms, the correlation that we found between approximated and actual RM for the triangular flow wave approximations ($R^2$=0.55) was still considerably lower than the values reported by Westerhof et al ($R^2$=0.79 to 0.85).

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**Table 1. Basic Clinical Data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>2325</td>
</tr>
<tr>
<td>Age, y</td>
<td>45.9 (6.0)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6 (4.1)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>127 (14)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>80 (10)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>63.6 (9.4)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) unless otherwise specified. BMI indicates body mass index; BP, blood pressure. The database contains 1209 women and 1116 men.

**Table 2. Approximation Errors on Flow and Forward and Backward Pressure**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measured ($Q^\text{ref}$)</th>
<th>Triangular ($Q^\text{tri}$)</th>
<th>Averaged ($Q^\text{avg}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSE $Q$, AU</td>
<td>NA</td>
<td>0.12 (0.02)</td>
<td>0.04 (0.03)</td>
</tr>
<tr>
<td>Accuracy of estimating forward component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMSE $P_f$, AU</td>
<td>NA</td>
<td>2.38 (1.50)</td>
<td>1.08 (0.82)</td>
</tr>
<tr>
<td>$</td>
<td>P_f^\text{approx} - P_f^\text{ref}</td>
<td>$, mm Hg</td>
<td>42.61 (9.45)</td>
</tr>
<tr>
<td>$</td>
<td>P_b^\text{approx} - P_b^\text{ref}</td>
<td>$, mm Hg</td>
<td>NA</td>
</tr>
<tr>
<td>$R^2$ approx vs ref</td>
<td>NA</td>
<td>0.70</td>
<td>0.89</td>
</tr>
<tr>
<td>Accuracy of estimating backward component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMSE $P_b$, AU</td>
<td>NA</td>
<td>2.38 (1.50)</td>
<td>1.08 (0.82)</td>
</tr>
<tr>
<td>$</td>
<td>P_b^\text{approx} - P_b^\text{ref}</td>
<td>$, mm Hg</td>
<td>20.22 (5.35)</td>
</tr>
<tr>
<td>$R^2$ approx vs ref</td>
<td>NA</td>
<td>2.97 (5.59)</td>
<td>0.13 (1.88)</td>
</tr>
</tbody>
</table>

$Q$ indicates flow; $|P_f|$, amplitude of the forward pressure component $P_f$; $|P_b|$, amplitude of the backward pressure component $P_b$; ref, reference; approx, approximate; AU, arbitrary units. Data for RMSE and pressure amplitudes are expressed as mean (SD).
approximating the flow wave by a subject-specific, time-scaled, averaged physiological flow waveform, the correlation between approximated and actual RM improved substantially ($R^2 = 0.74$).

A first issue that needs to be addressed is the question of how well the flow waveforms are actually described by a triangle. It is seen from Table 2 that the triangular approximation yields a RMSE from the measured flow waveform of 0.12, which is 3 times higher than the value of 0.04 that can be achieved when using a more physiological waveform. Another observation is that, using a triangular flow, the agreement between approximated and actual RM only reached an $R^2$ value of 0.55, which is still considerably lower.

Figure 1. A and B, Linear regression plots between approximated and reference RM. Trend line equations and $R^2$ values are reported. D and E, Bland-Altman plots between approximations of RM and RM$^{\text{ref}}$. Mean value (solid line) and mean $\pm 2$ SD (dashed lines) are displayed. C, Relation between AIx and RM$^{\text{ref}}$. RM$^{\text{tri}}$ and RM$^{\text{avg}}$ are approximations of RM using triangular flow and averaged flow, respectively, whereas RM$^{\text{meas}}$ is the reference RM using measured flow.

Figure 2. A through C, Linear regression plots between approximated and reference pulse TT. Trend line equations and $R^2$ values are reported. D through F, Bland-Altman plots between approximations of TT and TT$^{\text{ref}}$. Mean value (solid line) and mean $\pm 2$ SD (dashed lines) are displayed. TT$^{\text{tri}}$ and TT$^{\text{avg}}$ are approximations of TT using triangular flow and averaged flow, respectively; TT$^{\text{meas}}$ uses measured flow, whereas TT$^{\text{ref}}$ is obtained via the carotid-femoral pathway via Doppler ultrasound.
than the values reported by Westerhof et al.8 These observations indicate that, at least in our setting, the triangle is a relatively poor approximation of the measured waveforms, which is the main reason for the discrepancy between our findings and those of Westerhof et al.8

A logical subsequent question is why the triangle is a poorer approximation in this study. A first possible reason can be sought in the different nature of the population. Westerhof et al8 used a mixed population of 19 subjects, aged from 29 to 57 years, with a mean age of 50 years, with data obtained from various sources, including digitized data. All of the subjects underwent catheterization and were patients. The examples displayed in the article show a more triangular pattern than the waveforms that we measured in our middle-aged, healthy subjects. It is further clear from their figure that mean RM is in the range of 0.6 to 0.7, which is substantially higher than the value of 0.48 in our study. To assess the impact of RM on the morphology of the measured flow waves, we also calculated averaged, normalized flow waveforms for the database, with subjects grouped into 4 strata of values of RM (data not shown). The effect of increased RM on the flow wave morphology is a slight shift of the peak to the left, but there is no real better resemblance with a triangular waveform for the higher RM. A second possible reason can be sought in methodologic differences between the 2 studies. The flow waveforms as used by Westerhof et al8 were aortic flow velocity waveforms, measured with an invasively applied electromagnetic flow velocity sensor.
whereas we used flow velocity waveforms measured using ultrasound in the left ventricular outflow tract. Ultrasound data were measured by an experienced cardiologist following best-practice guidelines. On the other hand, literature sources state that both techniques are equivalent; so it is unclear whether the method used to acquire the flow does play a role in our findings.

In an attempt to increase the levels of correlation reported thus far for approximated RM, we tested a new approximation principle, based on an averaged and normalized aortic flow waveform. As is clear from Table 2 and Figure 1, using an averaged physiological waveform performs significantly better in estimating RM than using a triangular flow waveform. As for the triangular approximations, there is no systematic difference between RM_{avg} and RM_{ref}, as evident from the Bland-Altman plot (Figure 1E).

Another possible reason for the low levels of correlation can be sought in the fact that the pressure waveforms as used by Westerhof et al were not carotid waveforms but invasively measured aortic waveforms. Although carotid pressure is generally accepted as a surrogate for central aortic pressure, we calculated RMs based on synthesized aortic pressure waveforms to assess whether this methodologic difference could possibly explain the different results but could not find important qualitative differences. Compared with the corresponding values using carotid pressure waveforms, agreement between RM calculated with the measured and approximated flow waveforms was slightly better when using synthesized aortic pressure. On the other hand, agreement between estimated and measured pulse TTs using synthesized pressure waveforms was lower than the corresponding values using carotid pressure.

Interestingly, the agreement between RM obtained using the carotid on the one hand and synthesized aortic waveforms on the other hand, both using the measured flow waveform, showed only poor correlation ($R^2=0.14$; see Figure 3E). Our data do not allow us to address which of the 2 pressure waveforms, the carotid or reconstructed radial pressure waveform, is closest to the actual central aortic pressure. Nevertheless, it is an important finding that derived parameters, sensitive to wave morphology, can be quite different when using carotid or reconstructed pressure waveforms. This was demonstrated earlier for the AIx, but this conclusion also seems to pertain to estimates of the RM.

The 2 reported approximations, RM_{tri} and RM_{avg}, can be considered as the best possible approximations in terms of timing, because they make use of the actual timing of the beginning, peak, and end of the measured flow to construct an approximated flow waveform. As such, they indicate the theoretical potential of the approximation technique. It is, therefore, also important to determine the further degradation in accuracy when timing information is obtained from the pressure waveform. An averaged flow waveform was scaled in time, using the start of the systolic upstroke in the pressure waveform as the onset of flow, whereas the end of the ejection period was assumed to coincide with the dicrotic notch. In a similar way, a triangular flow waveform was constructed. To estimate the timing of the peak of the triangle, we used the timing of systolic blood pressure for waves with late inflection point (C-type waves), whereas the shoulder point was used for waves with an early inflection point (A-type waves), the shoulder point being identified with an algorithm based on the fourth-order derivative. RM was calculated, using each of these 2 flow waveforms, and compared with RM_{ref} (data not shown). As expected, the levels of agreement with RM_{ref} were markedly lower, with $R^2$ values of 0.26 for the triangular waveform and 0.41 for the averaged waveform.

The main rationale to apply waveform decomposition with an approximated waveform is to find new ways to overcome some of the limitations of the AIx, which is an index related to wave reflection but subject to confounding factors, such as heart rate and body length. As such, it is relevant to see to what extent these approximated methods provide an improvement over AIx in terms of correlation with RM_{ref}. In fact, we found that the correlation between AIx and RM_{ref} ($R^2=0.34$; see Figure 1C) is only slightly worse than the correlation between RM_{ref} and RM_{avg} and still higher than the decomposition based on the triangular approximation using timing info from the pressure waveform. As such, it is questionable whether these more complex methods offer, at this moment, any added value over AIx.

In the second part of this study, we evaluated a method to estimate pulse TTs from the time delay between the forward and backward pressure waveforms, as described previously by Qasem and Avolio. The correlation that we found between estimated and directly measured (carotid-femoral) TTs using approximated flow waveforms was rather limited ($R^2<0.29$) compared with the values reported by Qasem and Avolio ($R^2=0.45$ to 0.64; see Figure 2). Following Qasem and Avolio, we assessed the time delay between the forward and backward waves using a cross-correlation technique. However, because cross-correlation can be problematic when the waveforms are dissimilar (and may, thus, be an underlying factor in the poor correlations that we found), we tried to limit the cross-correlation to a “window” around the peak of the modified forward and backward waveforms. Results, however, did not improve (data not shown). Other techniques to assess timing as foot-to-foot delays and the timing of the inflection and shoulder point did not lead to better results (data not shown).

Unlike Qasem and Avolio, we also estimated pulse TTs using the measured flow waveform instead of an approximated waveform. Interestingly, agreement with ultrasound-derived carotid-femoral TTs did not increase at all when using the measured flow waveform (Figure 2C). Moreover, Bland-Altman plots show a stronger increasing trend for TT_{meas} than for TT_{tri}. This seems to imply that the modification of the forward and backward pressure components is not appropriate when the measured flow waveform is used to separate pressure. Indeed, when calculating TTs without modifying the forward and backward pressure waveforms, mean TT is 71.2 ms (26.6 ms), which is closer to TT_{ref} (67.8 ms) than when using modified pressure components, although the agreement remains rather poor ($R^2=0.22$). This seems to suggest that methods based on wave decomposition generally perform poorly in estimating TT. This is in line with recent work from Westerhof et al. who demonstrated in a theoretical study that methods based on the time delay between the
forward and backward pressure waves should not be used to assess PWV. They showed that the moment of return of the reflected wave is not only determined by the wave speed and distance of travel but also by the time shift at the reflection site. As a result, with an assumed location of the reflection site, the PWV cannot be derived.

TTs derived from wave reflection analysis (TT\textsubscript{enras}, TT\textsubscript{tri}, and TT\textsubscript{syn}) depend on the PWV, the location of reflection, and the nature of the reflection.\textsuperscript{28} On the other hand, TT\textsubscript{ref}, measured along the carotid-femoral pathway, depends only on PWV. With increasing age, PWV increases, but it has also been reported that the reflection sites shift in a direction toward the heart.\textsuperscript{15,27} Therefore, in older people, we expect the TT from wave reflection analysis to become progressively lower than TT\textsuperscript{ref}. This is indeed confirmed by Figure 2E and 2F, and this phenomenon also explains the trend of “overestimation” of TT\textsubscript{ref} for the higher TT values. This shift of the reflection site toward the heart is not reported by Qasem and Avolio,\textsuperscript{19} where the effective length of the arterial tree seemed to increase with age, as also earlier reported by Mitchell et al.\textsuperscript{29} We have suggested previously that this finding is related to the fact that identification of the moment of return of the reflected wave based on pressure waveform information (timing of shoulder or inflection point) alone is not accurate enough.\textsuperscript{27}

Although the mean age of the population in Qasem and Avolio\textsuperscript{19} was slightly higher (56±14 years) than ours, they were also healthy volunteers, making it unlikely that differences could be explained by the different nature of the study population. We used TTs measured with Doppler ultrasound as a reference, whereas Qasem and Avolio\textsuperscript{19} used tonometry to obtain carotid-femoral TTs. Although both techniques are accepted in literature to measure aortic PWV,\textsuperscript{5,30} it is possible that the approximative method based on pressure waves as described by Qasem and Avolio\textsuperscript{19} will correlate better with a pressure-derived reference TT than with a flow-derived TT between the same anatomic locations. A second methodologic difference is the fact that Qasem and Avolio\textsuperscript{19} used synthesized aortic pressure waveforms instead of carotid waveforms. However, when assessing the impact of this methodologic difference, we found the agreement between approximation and reference TT to be even lower, with $R^2$ values <0.13. Similar to RM, the agreement between TT obtained using the carotid on the one hand and synthesized aortic waveforms on the other hand, both using the measured flow waveform, yielded weak correlations (see Figure 3F).

Limitations

The main limitation of this study is that it is entirely based on noninvasively measured data, which implies an approximation of the central aortic pressure waveform. Ideally, also, pressure and flow are measured simultaneously and at the same anatomic location. For this study, pressure was measured noninvasively using applanation tonometry at the common carotid artery, whereas flow was measured at the level of the left ventricular outflow tract with Doppler ultrasound. Although carotid pressure is commonly used as a surrogate for central aortic pressure, both curves are not entirely equal, differing from each other in timing and in waveform. The time delay between aortic and carotid pressure waveform is corrected for by visual time alignment. The difference in waveform persists, and may have an effect on the accuracy of timing approximations for the beginning, peak, and end of flow used for the flow reconstructions. One could, therefore, expect better correlations between approximated and actual RM when using invasively measured aortic pressure and flow waveforms, which might also contribute to the better results reported by Westerhof et al.\textsuperscript{8} In addition, the fact that the results based on the carotid waveforms and synthesized aortic waveforms correlate rather poorly, underlines the need for invasive data. Furthermore, the age range of our study population is rather narrow. This might be a reason why no significant age effects were noticed in the different RM approximation methods. It is also expected that the physiological flow waveform, as assessed from this data set, will be less representative for subjects with age or clinical characteristics far beyond those of our Asklepios population.

Perspectives

Quantification of wave reflection by using a triangular flow wave approximation shows limited accuracy when applied to noninvasively measured pressure and flow data from our Asklepios population database. A newly proposed method making use of a more physiological flow waveform yields a significantly better agreement between approximated and actual RM, but considerable deviations still persist. Unlike the findings of Qasem and Avolio,\textsuperscript{19} assessment of pulse TT and, hence, of PWV from a single pulse recording shows a rather limited correlation with the pulse TT measured over the carotid-femoral pathway when tested on our middle-aged population. It cannot be totally excluded that these relatively poor results are, to a certain extent, attributable to the noninvasive nature of our study, where the approximation of central aortic pressure by the carotid pressure waveform might introduce some scatter in the data. Another factor that might play a role is the limited age range in our population, testing the methods over a limited range of possible parameter values. However, if the techniques are to be applied clinically, PWV (and wave RM) will be determined on an individual basis and based on noninvasive data and not on a large population with a wide age range. Also, the age range of the Asklepios population, 35 to 55 years, might be the range of age to start screening for cardiovascular disease and where sensitive methods are required to identify subjects at increased risk.

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Disclosures

None.

References

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EVALUATION OF NON-INVASIVE METHODS TO ASSESS WAVE REFLECTION AND PULSE TRANSIT TIME FROM THE PRESSURE WAVEFORM ALONE

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The Asklepios population
Non-invasive aortic flow and carotid artery pressure measurements recorded within the framework of the Asklepios Study\(^1\) are used. From the 2524 subjects included in the Asklepios study, 2325 complete data-sets were used in this study. Carotid pressure waveforms were obtained using applanation tonometry at the left common carotid artery, following an earlier described calibration scheme based on brachial artery tonometry\(^1,2\). The aortic flow waveform was assessed using pulse Doppler ultrasound (Vivid7, GE Vingmed Ultrasound) in the left ventricular outflow tract (LVOT). Carotid-femoral pulse wave velocity (PWV) was measured by Doppler ultrasound flow measurements in the femoral and carotid artery, respectively. Details on the study protocol and specifications of the measurement techniques and pressure and flow wave processing are found elsewhere\(^3\).

Triangular waveform construction
Following Westerhof et al.\(^4\), a triangular flow waveform (\(Q^{tri}\)) was constructed, see also Figure 1. Whereas the authors of that study obtained timing information from the pressure waveform, we approximated the flow using timing information for start, peak and end of flow from the measured flow waveform itself. By doing so, we can evaluate the isolated effect of the triangular shape approximation, independent of errors introduced via the assessment of the timing from the pressure waveform. As such, these results can be considered as the best possible results that can be obtained with a triangular approximation of the flow waveform.

The root mean square error (RMSE) between the approximated flow waveform and the measured one is calculated and expressed as mean (SD).

\[ S1: \text{(A) Triangular and averaged flow waveform approximation principle. The triangular flow waveform is constructed based on timing of begin, peak and end of the measured flow} \]
waveform. The averaged physiological flow waveform is constructed using measured flows of 74 subjects and stretched in time based on timing of the begin and end of the measured flow waveform. (B) Pulse transit time (TT) approximation principle, applied with triangular flow waveform. Forward and backward pressure components are modified (see text for modification criteria). Cross-correlation is performed on normalised pressure components. Aortic TT is estimated as half of the time lag at maximum correlation.

**Linear wave separation analysis and derived parameters**

Forward ($P_f$) and backward ($P_b$) pressure waveforms were calculated using the linear wave separation equations as first described by Westerhof et al. \(^5\):

$$P_f = \frac{P + Z_c * Q}{2}; \quad P_b = \frac{P - Z_c * Q}{2}$$

In these formulas, $P$ and $Q$ denote harmonics derived from the measured pressure and flow waveform, using Fourier decomposition \(^5\). The characteristic impedance, $Z_c$, was calculated by averaging the modulus of the 3rd to 10th harmonic of the input impedance. $Z_c$ was recalculated for each of the (measured and approximated) flow waveforms. To obtain the total forward and backward wave, forward and backward harmonics were summated. As explained by Westerhof et al. \(^4\), flow calibration is not required for wave separation calculations, since the product $Z_c * Q$ is independent of flow amplitude.

The forward and backward pressure waveforms derived using the measured flow serve as a reference. Agreement between the approximated (derived using approximated flow) and reference forward (and backward) pressure waveform is assessed by calculating the RMSE between the two waveforms. The amplitudes of the approximated forward ($|P_f^{\text{approx}}|$) and backward ($|P_b^{\text{approx}}|$) pressure waves are compared to the reference forward ($|P_f^{\text{ref}}|$) and backward ($|P_b^{\text{ref}}|$) pressure wave amplitudes via linear regression analysis ($R^2$-values) and their mean difference is displayed as mean (SD).

**Reflection magnitude assessment**

Reference (RM\(^{\text{ref}}\)) and approximated reflection magnitude (RM\(^{\text{approx}}\)) are calculated as the ratio of the amplitudes of backward over forward pressure wave: $RM^* = |P_b^*/|P_f^*|$, with $^*$ referring to either the reference, either the approximation. Agreement between reference and approximation was studied via linear regression analysis ($R^2$ values) and Bland-Altman analysis. In addition, we also calculated the augmentation index (AIx) as a measure of wave reflection. We refer to previous work \(^3\) for a description of how AIx was derived.

**Pulse wave velocity assessment: time delay between $P_f$ and $P_b$**

To assess the time delay between $P_f$ and $P_b$, Qasem et al. proposed to first modify the pressure waveforms using three criteria \(^6\):

- $dP_b(t)/dt = 0 \quad 0 \leq t \leq \text{peak flow}$
- $dP_f(t)/dt < 0 \quad \text{peak flow} \leq t \leq \text{end ejection}$
- $P_f + P_b = P \quad \text{at all times}$

We refer to Qasem et al. for details on these assumptions \(^6\). Basically, it is assumed that the forward pressure wave reaches its peak at the moment of peak flow. The backward pressure wave arrives at the moment of peak flow and only plays a role from that moment on (Figure 1).

After normalization of the modified forward and backward pressure waveforms, the time lag between $P_f$ and $P_b$ was obtained using cross-correlation techniques, assuming that the correct time-lag is the value for which there is maximum cross-correlation \(^7\) between the two waveforms.
normalized waveforms. Following Qasem et al.\textsuperscript{6}, the pulse transit time (TT) is obtained as half of the time lag.

This method was applied using either the measured flow waveform (Q\textsuperscript{meas}), either the approximated waveform (Q\textsuperscript{fit}). Transit-times obtained from these approaches are indicated as TT*, with * referring to either the measured approach, either the approximative approach. TT's were also compared to the carotid-femoral pulse transit times measured by Doppler ultrasound (TT\textsuperscript{ref}), which serve as a reference here.

**Averaged physiological flow waveform**

In a third part of this study, approximation via triangular flow waveform profiles was left aside, and the analysis (assessment of RM and TT) was repeated by using a more physiological flow waveform (Q\textsuperscript{avg}) obtained from normalizing and averaging measured flow waveforms. using data from 74 subjects (32 women, 42 men; 3.1 % of the total database). The average flow waveform was calculated after normalising each individual flow curve in time and amplitude. The physiological waveform is mathematically described as a Fourier-series using the first 20 harmonics. A description of the systolic part of the waveform, both graphical (Figure 2) and by its first 10 harmonics (Table 1) is given. The subjects used to construct the physiological flow waveform were subjects where aortic flow was available, but where other data were missing for various technical reasons. To approximate the actual flow waveform, the averaged and normalized waveform was scaled in time using the timing of begin and end of each individual measured flow waveform.

**S2:** Systolic phase of the normalised physiological flow waveform, constructed after normalising each of 74 measured flow curves in time and amplitude. Time and flow are expressed in arbitrary units (AU).
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S3: Harmonic content of the averaged and normalised flow waveform (only systolic phase)

**Synthesized aortic pressure**

The analysis (assessment of RM and TT) was repeated by using synthesized aortic instead of carotid pressure, obtained from radial tonometry via a generalized pressure transfer function.
Reference List


