Quantification of Wave Reflection in the Human Aorta From Pressure Alone

A Proof of Principle

Berend E. Westerhof, Ilja Guelen, Nico Westerhof, John M. Karemaker, Alberto Avolio

Abstract—Wave reflections affect the proximal aortic pressure and flow waves and play a role in systolic hypertension. A measure of wave reflection, receiving much attention, is the augmentation index (AI), the ratio of the secondary rise in pressure and pulse pressure. AI can be limiting, because it depends not only on the magnitude of wave reflection but also on wave shapes and timing of incident and reflected waves. More accurate measures are obtainable after separation of pressure in its forward (Pf) and reflected (Pb) components. However, this calculation requires measurement of aortic flow. We explore the possibility of replacing the unknown flow by a triangular wave, with duration equal to ejection time, and peak flow at the inflection point of pressure (FtIP) and, for a second analysis, at 30% of ejection time (Ft30). Wave form analysis gave forward and backward pressure waves. Reflection magnitude (RM) and reflection index (RI) were defined as RM=Pb/Pf and RI=Pf/(Pf+Pb), respectively. Healthy subjects, including interventions such as exercise and Valsalva maneuvers, and patients with ischemic heart disease and failure were analyzed. RMs and RIs using FtIP and Ft30 were compared with those using measured flow (Fm). Pressure and flow were recorded with high fidelity pressure and velocity sensors. Relations are: RMFtIP=0.82RMFt30+0.06 (R²=0.79; n=24), RMFtIP=0.79RMFt30+0.08 (R²=0.85; n=29) and RIFtIP=0.89RIFt30+0.02 (R²=0.81; n=24), RIFt30=0.83RFt30+0.05 (R²=0.88; n=29). We suggest that wave reflection can be derived from uncalibrated aortic pressure alone, even when no clear inflection point is distinguishable and AI cannot be obtained. Epidemiological studies should establish its clinical value. (Hypertension. 2006;48:1-7.)

Key Words: aorta ■ blood flow ■ blood flow velocity ■ blood pressure ■ pulse

Aortic pressure, and especially pulse pressure (PP), is now recognized as an important indicator of cardiovascular risk1-4 and can guide pharmaceutical treatment.5,6 Wave reflections affect the pressure and flow wave in the proximal aorta,7 and their contribution depends on their magnitude (determined by the periphery and the large arteries) and time of return (mainly determined by the large, conduit arteries). When the reflected wave arrives in systole, it augments pressure, leading to increased systolic and PP. This augmentation is greater when the heart is hypertrophied.8 In heart failure, wave reflections affect the flow wave negatively, thereby reducing stroke volume and cardiac output.8-10

One way to estimate the amount of reflection is by waveform analysis in which aortic pressure is separated into its forward and backward components.7,11,12 The ratio of the magnitudes of the backward (reflected) wave and the forward (incident) wave, the reflection magnitude (RM), allows for the estimation of the amount of reflection, but this waveform analysis requires measurement of both pressure and flow waves. A method that requires the measurement of pressure only is computation of the augmentation index (AI).13,14 AI gives reproducible results15,16 and is in use in clinical settings.17-20 However, AI is determined by both the magnitude and timing of the reflected wave. This is evident from Figure 1A. In this figure, the original pressure wave is separated into its forward and backward components and then reassembled for different delays of the same backward wave. AI is clearly influenced by the time of return of the reflected wave. Figure 1B gives 2 examples in which AI suggests no wave reflection (left) or a reflected wave that is larger than the forward wave (right). Thus, the magnitude of wave reflection cannot be quantified from AI. This may explain why the AI may not be a good measure of central pulsatile load in patients with congestive heart failure.21

In this study, we investigate a new method to calculate pressure wave reflection in the human proximal aorta based on measured pressure alone and derive an index to quantify the magnitude of reflection independent of the time of return of the reflected wave. We assume a triangular shape of the flow wave based on the timing features of the aortic pressure. This is a reasonable assumption in view of the ascending aortic flow patterns obtained by a variety of flow measure-
indications. Of this group, 5 subjects were kindly provided through personal communication with Dr BJ Rubal, Brooke Army Medical Center, Houston, Tex; 6 subjects were taken from the publications of Muro et al., including baseline conditions, exercise, and Valsalva maneuvers; and 1 subject performing a Mueller maneuver was analyzed. Two patients with heart failure with 1 of them before and after nitroprusside infusion (0.50 µg/kg per minute) were analyzed (data from Chiu et al.). In 5 patients, pressure and flow velocity were measured directly after a selective coronary angiographic procedure to evaluate ischemic heart disease and were kindly provided by Blum et al.. In this group of 19 humans, the total number of analyzed beats, including the maneuvers, was 29. All of the participants gave informed consent, and the respective institutional review committees approved the studies.

Catheters equipped with a micromanometer and an electromagnetic flow velocity sensor were used for the measurements (Millar Instruments). All of the signals were sampled at a rate of 100 Hz.

The method to construct a flow wave makes use of the notion that a triangular shape can approximate the flow wave during ejection. The duration, that is, the base, and the time of peak flow of this triangle can be derived from the pressure wave shape as follows (Figure 2). The time of end-diastolic aortic pressure is the time of valve opening and the start of ejection. The incisura of the pressure wave gives the time of valve closure and the end of ejection. These times determine the ejection time and, thus the base of the triangle. In a first analysis, the time of the peak of the triangle is set at the time of the inflection point of the measured pressure wave in systole. The inflection point is derived using higher-order derivatives of pressure as described previously. In a second analysis on the same pressure data, the maximum of the triangular flow is set at 30% of the ejection time, close to the average found from the flow measurements (see Results section). This is done to test the method when an inflection point in the pressure wave cannot be explicitly identified.

The triangular flow with the peak time set at the inflection point of the measured pressure is called F0, and the flow with the peak time fixed at 30% of the ejection time is called F20. In the calculations of forward pressure (Pf) and backward pressure (Pb), the following equations are used: F(t) = (P(t) + Zc · F(t))/2 and P(t) = (P(t) - Zc · F(t))/2. The F(t) in this case is the measured pressure wave, and F(t) is either the measured flow wave or the constructed flow wave with a triangular shape. Zc is the characteristic impedance of the proximal aorta. The arterial input impedance was calculated in the frequency domain, and the characteristic impedance was derived from the averaged value of the 4th to 7th harmonic of the input

Methods
Simultaneous measurements of pressure (Pm) and flow velocity (Fm) in the human ascending aorta recorded for previous studies were used. Twelve healthy subjects were catheterized for various clinical indications. Of this group, 5 subjects were kindly provided through

Figure 1. A. The AM and AI depend not only on the magnitude but also on the time of return of the reflected wave. On the left, the measured pressure and flow and the derived forward and backward pressure waves are shown. On the right, the pressure waves obtained by summation of the forward and backward waves are shown when the backward wave is shifted in time. Thus, with the same magnitude of the reflected wave, but different times of return, the wave shape, the PP, and, consequently, the AM (AM = ΔP/(PP - ΔP)) and AI (AI = ΔP/PP) are different. The RM and RI were 0.35 and 0.54. The AMs from top to bottom were 0.25, 0.27, 0.15, and undefined, and the AIs were 0.20, 0.21, 0.13, and undefined, respectively. B, on the left, the backward wave returns when the forward wave is already falling. AM and AI were found to be 0.03 and 0.03, whereas RM and RI were 0.49 and 0.33, respectively. On the right, the forward wave is still rising when the backward wave returns, resulting in an AM and AI of 1.44 and 0.59, suggesting that the backward wave is larger than the forward wave. The RM and RI in this case were 0.78 and 0.44, respectively.

Figure 2. Principle of method. The flow is approximated by a triangle. End diastole and the incisura (second vertical line) of the measured pressure wave determine the start and end of the triangle. The peak is set at the inflection point (first vertical line) or at 30% of ejection time (arrow). The inflection point is determined by standard method. Calibration of flow is not required (see text).
impedance modulus.\textsuperscript{12} $Z_c$ was determined from each of the 3 flow wave shapes.

From the above equations, it can be seen that the product $Z_c \cdot F$ appears in the calculation of the forward and backward waves. $Z_c$ is a ratio of pressure and flow ($P/F$) (more explicitly; $Z_c = P/F_e = -P/F_e$). Thus, by multiplication of $Z_c$ and $F$, the amplitude of flow is eliminated, and $Z_c \cdot F$ is independent of the flow calibration. When flow is twice as large, the calculated $Z_c$ is twice as small, but the product remains the same. A similar reasoning holds whether flow velocity or volume flow is used in the calculations. Thus, calibration of the flow wave is not required, the shape is of importance only, and so stroke volume does not have to be determined. In the remaining text, flow velocity will simply be called “flow.”

Using the above equations, we calculated forward and backward pressure waves on the basis of the measured pressure ($P_m$) in combination with the measured flow ($F_m$) and each of the 2 triangular flows ($F^{\text{tp}}$ and $F^{\text{tn}}$). The amplitudes (peak-trough) of the forward waves obtained by the triangular flows ($P^{\text{tp}}$) and ($P^{\text{tn}}$) were compared with the amplitude of the forward pressure wave derived from the measured flow ($P^{\text{m}}$). Similarly, the backward waves ($P^{\text{bp}}$) and ($P^{\text{bn}}$) were compared with ($P^{\text{m}}$). $\Delta P$ and ($P^{\text{m}} - \Delta P$) represented forward and backward waves directly derived from measured pressure by the inflection point (see Figure 1).

The accuracy of the shapes of the forward and backward pressure waves were determined by calculating the root mean square error (RMSE) between the waves derived from triangular and measured flow waves. The RM is calculated as the ratio of the amplitudes (peak-trough) of the backward and forward pressure waves derived from measured flow ($P^{\text{m}}$ and $P^{\text{m}}$). The reflection index (RI) is defined as:

$$ RI = \frac{(P^{\text{m}} - \Delta P)}{(P^{\text{m}})} $$

P and ($PP^{\text{m}}$) were compared with ($PP^{\text{m}}$). $\Delta P$ and ($PP^{\text{m}} - \Delta P$) represented forward and backward waves directly derived from measured pressure by the inflection point (see Figure 1).

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the figure. The intercepts of the relations do not contribute, implying that the relations are proportional. The relations between AM and RMmf and between AI and RImf are also given in Figure 4. Both intercept and slope contribute to the model, meaning that the relations are not proportional. The range of the AM and AI is much larger than that of the RM and RI, respectively. The data are also presented as a Bland–Altman plot in Figure 5. AM and AI (Figure 5C and 5F) are given in a modified Bland–Altman plot, because the difference is not well described by a mean value, and a
features of the pressure wave, an accurate estimate of the RM and the RI can be obtained. The results are based on a wide range of patients and interventions and, thus, differences in flow wave shapes. The extremes of flow are shown in Figure 6, and the results obtained from these extremes are indicated in Figure 4 and fit the relations. As shown in the Methods section, both flow calibration and pressure calibration are not required. This implies that derivation of the RM and the RI can be based on the same data as used to derive the AI, namely, that pressure information alone suffices, and calibration of pressure is not necessary.

The use of the triangular flow tends to overestimate the amplitude of the forward wave and underestimate the amplitude of the backward wave, but the differences are small and not significant. The RMSE between the waves calculated from measured flows and from triangular flows are small as well, indicating that the wave shapes are well predicted by triangular flow. The RM and RI quantify the amount of reflection, whereas the AM and AI strongly depend on the time that the reflected wave returns.

Whereas for the calculation of AM and AI, an inflection point in the pressure wave is required, the use of the triangular flow with its maximum at 30% of ejection time \((F^{30})\), allows waveform analysis, calculation of forward and backward waves, and derivation of RM and RI without a distinguishable inflection point. The RM and RI derived from a triangular waveform are proportional to those derived from measured flow. Thus, multiplying the reflection parameters derived using a triangular flow with a factor of 1.2 results in estimates of RM and RI that are very close to their true values.

The RM and the RI derived from the triangular flow \(F^{30}\), with maximal flow at 30% of ejection, show the strongest correlations with their measured counterparts (Figure 4B and 4E, respectively). These correlations, however, are based on more data, including very low values occurring during Valsalva maneuvers and during one of the exercise recordings. In these data, no inflection point was found, and, therefore, RM\(^{30}\), RI\(^{30}\), AM, and AI could not be determined. When these 5 points are also excluded from the analysis of RM\(^{30}\) and RI\(^{30}\), the correlations become slightly weaker. Thus, the presence of an inflection point in the pressure wave to determine the flow wave shape is only marginally better than using the 30% value of ejection time for the peak time of the flow.

Wave reflection is usually quantified as the ratio \(|P_f|/|P_b|\), which we here call RM. The RM can be compared with the frequency-dependent Reflection Coefficient\(^{7}\). This is akin to the AM, being the ratio of secondary pressure rise and initial pressure rise. We defined RI as the ratio \(|P_f|/(|P_f|+|P_b|)\), that is, the backward wave, \(|P_b|\), with respect to the summed waves, \(|P_f|+|P_b|\). The summation of the amplitudes \(|P_f|+|P_b|\) is well defined, because timing is excluded from the calculation. The RI is conceptually comparable with the AI, where the secondary pressure increase, related to the backward wave, with respect to total wave (PP) is calculated. The RM and RI as used in the present study can be converted into each other without loss of information: \(RM = RI/(1-RI)\) and

Discussion

We found that from aortic pressure measurement alone and an assumed triangular flow wave derived from the timing regression line should be used (AM: difference = 1.04 average \(-0.76, R^2=0.80, n=24\), and AI: difference = 1.11 average \(-0.48, R^2=0.86, n=24\).

In 5 cases, no inflection point was found in the pressure, explaining the different number of data points. When the 5 points in which no inflection point could be determined are excluded, the relation for the RM is RM\(^{30}\) = 0.74 RM\(^{30}\)+0.12 \((R^2=0.73; n=24)\) and for the RI is RI\(^{30}\) = 0.79 RI\(^{30}\)+0.07 \((R^2=0.75; n=24)\).

Figure 6 shows the extreme cases of convex and concave flow in our study population. On the left, the measured pressure and measured, convex flow give an RM and RI of 0.50 and 0.33, respectively. With a triangular flow \(F^{30}\) this is 0.39 and 0.28, and with \(F^{30}\), we find 0.48 and 0.32, respectively. With the quadrangular flow, RM is 0.49 and RI is 0.33. In the case of concavity (Figure 6, right), measured pressure and flow give 0.96 and 0.49 for RM and RI. With a triangular flow \(F^{30}\), 0.81 and 0.45 are found, and with \(F^{30}\), 0.79 and 0.44 are found, respectively. With the quadrangular flow, RM is 0.92 and RI is 0.48.

The triangular flow wave introduces rather sharp peaks, especially at the maximum of flow. When a 5-point running average filter was applied to the triangular flow wave and this smoother flow curve was used, the improvements were small.

![Figure 6](image-url). The 2 most extreme cases of convexity (left) and concavity (right). A quadrangular flow approximates the measured flow and gives better estimates of RM and RI (for calculated values, see text). The triangular flow can be based on measured pressure, but a quadrangular flow wave cannot. The calculated reflection parameters using the triangular flow wave are indicated with a square (convex flow wave) and circle (concave flow wave) in Figure 4.
RI = RM/(1 + RM). Similarly, AI = AM/(1 + AM) and AM = AI/(1 − AI).

We found that the AI and AM vary over a much larger range than the RI and the RM (Figure 4C and 4F). Theoretically, the magnitude of the backward wave is always smaller (or equal) than the magnitude of the forward wave. This implies that the RM and the AM are < 1, and the RI and AI are < 0.5. From Figure 4C and 4F, we see that this requirement is not fulfilled. This results from the contribution to wave shapes of incident and reflected waves and on the timing of the reflected wave, as can be seen from Figure 1. Even when a reflected wave of similar amplitude returns, the time of reflection has a strong effect on the AI. When the reflected wave returns in diastole (right bottom curve in Figure 1A), the AI does not give a good estimate of the amount of reflection. This can be seen in the Bland–Altman plot (Figure 5C and 5F), where differences between AM and AI and their references are too small for small values and too large for large values. The differences, however, can be described accurately by regression models, as can be appreciated from the high coefficients of determination ($R^2=0.80$ and 0.86, respectively) and the acceptable CIs (see Figure 5).

By using the information contained in the flow wave, even in the simplified form of a triangle, wave analysis can be carried out, and the forward and backward pressure waves can be obtained. From the amplitudes of these waves, RI and RM can be calculated without the confounding effects of timing.

The triangular flow, using the assumption that its time of maximum is 30% of the ejection time, is, on average, correct. To obtain some insight into the errors, we calculated the RM and RI as a function of peak time, whereas the ejection period and heart rate were kept constant. We found that a 10% error in peak flow results in an 8% error in the RM and a 5% error in the RI.

The wave shape of pressure and flow depend on the pump function of the heart and the arterial load. In a strong heart, which approximates a flow source, the flow wave will be concave. In a weak heart, which approximates a flow source, the flow wave will be scalloped or concave. We found that convexity of the flow wave shape leads to underestimation, and concavity leads to underestimation of the RM and RI. We have calculated the RM and RI for the most extreme cases of convexity and concavity using a triangular flow and a quadrangular flow to mimic convexity or concavity (Figure 6). This better approximation of the flow wave results in better estimations of the RM and RI. The data points obtained with the triangular flow are highlighted in Figure 4: the convex flow (Figure 6, left) is indicated with a square and the concave flow (Figure 6, right) with a circle. The data points are on the tight relation, suggesting a triangular flow to be an acceptable approximation. In practice, we do not have the information to construct a quadrangular flow wave shape.

In waveform analysis, the characteristic impedance of the proximal aorta is required. The characteristic impedance derived from triangular flow wave is close to that one derived from measured pressure and flow. The relations between characteristic impedance calculated from measured pressure and flow and from the triangular flows $F_{TP}$ and $F_{to}$ are given by the following correlation coefficients: $R^2=0.86$ for $F_{TP}$ and $R^2=0.89$ for $F_{to}$. Thus, there is a good relation between the characteristic impedances. We also found that a factor 2 change in $Zc$ results in $\approx 16\%$ error in RI. This is a substantial change, and any real changes in $Zc$ would be much smaller than that.

Limitations

The triangular wave shape that is assumed for the flow is an approximation that may differ from the actual flow wave shape. In the present study, however, this approximation gave results close to those obtained with high-fidelity measured flows even during the Valsalva maneuver and exercise. We, therefore, believe that the approximation of flow with a triangular shape to calculate the amount of reflection is a useful one. Although the number of data is limited, the range of RMs that we studied is large, namely from 0.16 to 0.82 (see Figure 4 horizontal axis of the 3 top panels).

Perspectives

Our method requires the same uncalibrated pressure information as is used to derive the AI. We suggest that the calculations to quantify wave reflection can also be performed using the carotid pressure wave as a surrogate for the aortic pressure and obtained noninvasively, as, for instance, by applanation tonometry or by using a transfer function on finger arterial pressure or radial artery pressure. The entire calculation then may be based on the noninvasive measurement of the pressure wave shape only. For instance, the effects of pharmacological interventions on reflection could be studied without measurement of aortic flow. Also, accurate estimation of the amount of reflection as a function of age in large epidemiological studies is considerably more practical when flow measurement is not required. The calculations to find peak flow from the timing features of the pressure waves, the separation of the waves, and the subsequent calculation of the RM and the RI are straightforward and can be automated. When automated, the derivation is as easy as the derivation of the AI with improved quantitative information on the magnitude of wave reflection. However, epidemiological or clinical trials are necessary to investigate whether the proposed calculation of RI is a good predictor of cardiovascular morbidity or mortality.

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Disclosures

None.

References


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