Towards New Indices of Arterial Stiffness Using Systolic Pulse Contour Analysis: A Theoretical Point of View

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Abstract: Total arterial stiffness plays a contributory role throughout aging and in numerous cardiovascular diseases, including hypertension. Aortic stiffening is responsible for an increased characteristic impedance (ie, the impedance to the left ventricular pulsatile flow), thus increasing the forward pressure-wave amplitude that contributes to pulse pressure elevation. Aortic stiffening also increases pulse wave velocity, and this results in anticipated and enhanced wave reflections, further augmenting central pulse pressure. Unfortunately, there is no simple time-domain estimate of characteristic impedance. Furthermore, recent guidelines have reviewed the limitations of diastolic pulse contour analysis to estimate arterial stiffness in the time domain. The present theoretical article proposes that systolic pulse contour analysis may provide new, simple time-domain indices quantifying pulsatile load in resting humans. Our proposal was mainly based on 2 simple, validated assumptions: (1) a linear aortic pressure-flow relationship in early systole and (2) a triangular aortic flow wave during systole. This allowed us to describe new time-domain estimates of characteristic impedance, pulsatile load (waveguide ratio), total arterial compliance, and total arterial stiffness. It is demonstrated that total arterial stiffness may be estimated by the following formula: 

\[
\frac{[(P_i - DAP) \times ST]}{(SV \times \Delta t)},
\]

where \(P_i\) is the aortic pressure at the inflection point (peak forward pressure wave), \(DAP\) is diastolic aortic pressure, \(ST\) is systolic ejection time, \(SV\) is stroke volume, and \(\Delta t\) is the time-to-\(P_i\). A mathematical relationship among time intervals and indices of pulsatile load is demonstrated, and the clinical implications are discussed in terms of cardiovascular risk and stroke volume prediction.

Key Words: arterial stiffness, pulse pressure, hypertension, left ventricle, afterload, heart rate, cardiovascular risk factors, stroke volume

INTRODUCTION

A growing number of clinical and epidemiological studies use aortic pulse contour analysis to document the role of increased pulsatile load and arterial stiffness throughout aging in subjects exposed to cardiovascular risk factors and in patients with various cardiovascular diseases.\(^1\)\(^-\)\(^6\) Aortic pulse wave may be obtained from invasive catheterization or estimated from noninvasive techniques (eg, applanation tonometry).

In the first part of this article, we will briefly summarize how current hemodynamic theory explains the various components of aortic pressure pulse and arterial load in resting humans. In the second and theoretical part of our article, we will propose that systolic pulse contour analysis may provide new, simple time-domain indices quantifying characteristic impedance (\(Z_c\)), total arterial compliance (\(C\)), total arterial stiffness (\(I/C\)), and the so-called “waveguide” function in humans. Our proposal will be mainly based on 2 simple, validated assumptions: (1) a linear aortic pressure-flow relationship in early systole and (2) a triangular aortic flow wave during systole. The limitations of our approach will be discussed. Finally, the clinical implications of the proposed new indices will be discussed.

ARTERIAL HEMODYNAMICS

Aortic Pressure

Mean aortic pressure (MAP) is the steady component of aortic pressure, while systolic (SAP) and diastolic (DAP) aortic pressures help quantify the pulsatile component of aortic pressure, namely pulse pressure (PP = SAP–DAP) (Figure 1). From the foot of the systolic pressure wave to the peak systolic pressure wave, 2 components can be distinguished: the peak forward pressure wave (dPmax) and the augmentation pressure (Ax) (ie, the amplitude of the reflected pressure wave). An inflection point allows separating these 2 components, and the pressure at the inflection point (\(P_i\)) indicates the beginning upstroke of the reflected wave.\(^2\)\(^,\)\(^8\) The time to the peak/shoulder of the first pressure wave component during systole (\(\Delta t\)) quantifies the timing of the pressure wave reflection.

In healthy young individuals, Ax is low and weakly contributes to PP. The reflected pressure wave is rather diffuse and maintains a relatively high aortic pressure in early diastole, thus boosting coronary artery filling. In elderly individuals, the reflected pressure wave is increased and narrowed, thus significantly contributing to PP (high Ax value) rather than increasing early diastolic pressure. Increased arterial stiffness of the aorta and proximal large arteries is related to the aging process.
The widening of PP is the consequence of alterations of large artery structure and function related to cardiovascular risk factors. Cardiovascular risk factors are known to favor and accelerate the atherosclerotic process, and the widening of PP is involved in the cardiovascular consequences of aging and in the development of cardiovascular diseases, especially hypertension.1–5

**Hydraulic Load**

The hydraulic load opposing to ejection consists of a steady component composed of systemic vascular resistance (Rs) and a pulsatile component consisting of distributed compliant and inertial properties.9–12 The steady and pulsatile components of arterial load are dependent on distal and proximal portions of the systemic vascular tree, respectively, and may be controlled and modified separately.

Physicians are familiar with the concept of Rs, which is a measure of the extent to which the systemic circulation “resists” to mean cardiac output. The driving pressure is the MAP minus the mean downstream pressure. The driving pressure is related to the viscous (frictional) resistance of the blood when flow is induced. The Rs is calculated by dividing the driving pressure by cardiac output. The architecture and function of the microvascular network are the primary determinants of Rs.

In hydraulic circuit when the flow is pulsatile, the relationship between pulsatile flow and pulsatile pressure includes not only the opposition to flow afforded by friction but also due to both the vascular elasticity and the inertia of blood mass. Because blood is incompressible and given that the proximal aorta and its major branches are viscoelastic vessels, the blood volume ejected by the left ventricle and entering the circuit is accommodated thanks to aortic dilatation during systole. The compliance of the proximal aorta and large arteries mainly depends on the relative contribution of elastin and collagen.1–5

Total arterial compliance (C) is a measure of the capacity of the arterial system to accommodate this sudden increase in volume. The major part of the stroke volume is stored in the compliant proximal aorta, which is equivalent to charging a capacitor in electronics, and then released during diastole.13

In cases where the measurement of stroke volume is available, various estimates of C may be obtained by diastolic pulse contour analysis using analogies with electrical models of the systemic circulation. Various methods have been proposed to estimate C in diastole, including the time decay method, the area method, and other methods using a modified windkessel analog.13–17 Recent guidelines have reviewed the theoretical, technical, and practical limitations of such methods.6 From a theoretical point of view, the pure RC windkessel model is zero-dimensional, and implies infinite pulse wave velocity. Because the windkessel model does not take into account the finite pulse wave velocity and the phenomena of blood propagation and wave reflections, the model does not apply at high frequency and during the systolic period. However, it must be noted that the windkessel model applies in diastole whatever the model chosen for the overall systemic circulation, namely pure windkessel model, distributed linear model, or nonlinear model.9–12

In fact, pulse wave velocity has finite values, and this implies finite values of travel times (forward and backward) such that a more realistic propagative model must be used in systole.9–12 According to the transmission line theory, the distributed linear model emphasizes the importance of pulse wave velocity, wave reflections, and characteristic impedance (ie, the input impedance in the absence of wave reflection). The distributed linear model takes into account the fact that pressure waves travel along the aorta with finite velocity and may suffer attenuation and experience reflection, resulting in backward propagating waves that in turn influence the aortic pressure and flow curve. Although the windkessel model assumes that all the reflections occur immediately, the distributed linear model takes into account the time delay of the reflections with respect to the initial wavefront.
Characteristic Impedance (Zc) and the Waveguide Function

Characteristic impedance governs the pressure-flow relationship in the proximal aorta until the arrival of the first pressure wave reflection. Characteristic impedance may be expressed as the square root of the L/C ratio, where L is blood inerterance. Decreased C (ie, stiffening of the aorta) is thus a major cause of increased Zc.

In a normal aorta, Zc is a small fraction (5% to 10%) of Rs, and this “impedance mismatch” has 2 main consequences. First, the heart and vessels are thus properly matched or coupled, and the aorta functions as a low impedance interface or waveguide that serves to isolate pulsatile output of the heart at one end from the high resistance vessels at the other. Second, the impedance mismatch together with multiple bifurcation and finite length of the network is responsible for wave reflections.

Indeed, pressure and flow measured in the aorta result from waves traveling simultaneously from heart to periphery (forward wave) and in the retrograde direction (backward wave) with finite velocity. It is widely admitted that pressure increases when forward pressure wave from the heart collides with the backward (reflected) pressure wave. Conversely, when forward flow wave collides with the backward-traveling flow wave, flow decreases. Because forward and backward waves have either the same (positive) sign (pressure) or have opposite signs (flow), the result of more wave reflections is decreased resemblance of measured aortic flow and measured aortic pressure. Conversely, in cases where wave reflections are negligible (eg, as observed in the pulmonary artery of healthy subjects), central pressure and flow waves look alike. Wave reflections explain why the modulus magnitude and phase shift of the impedance spectra varies with frequency. The timing and extent of wave reflections mainly depend on reflection coefficient (determined by Zc and Rs), functional length of the arterial network, pulse wave velocity, and heart rate.

The Zc is most often calculated in the frequency domain, which requires simultaneous high-fidelity pressure and flow recordings, sophisticated mathematical calculations, and a number of theoretical assumptions (including hemodynamic stability) that are not always fulfilled in clinics. However, thanks to a number of reasonable approximations, it has been assumed that Zc may be considered as real and frequency-independent. Simpler, time-domain calculation methods of Zc have been validated in previous invasive studies and have proved useful in pathophysiological, noninvasive studies. It is accepted that the ratio of the peak forward pulsatile pressure to the peak flow is a reliable estimate of Zc, but precise flow velocity recordings are still required and this limits a more widespread use of the method.

Functional Measures of Arterial Stiffness: Zc and Pulse Wave Velocity (PWV)

Aortic stiffening is responsible for an increased impedance to the left ventricular pulsatile flow (Zc), increasing the forward pressure-wave amplitude (dPmax) that contributes to PP elevation. Aortic stiffening also increases PWV, and higher PWV results in anticipated and enhanced wave reflections, further augmenting central systolic pressure and PP by increasing the contribution of Ax.

A number of papers and guidelines have previously addressed the theoretical, methodological, and practical issues related to the estimation of arterial stiffness. Theory indicates that both Zc and PWV are dependent on the caliber and compliant properties of the aorta and first large arterial branches. Zc and PWV are thus viewed as functional measures of large artery stiffness. Calculating Zc requires simultaneous pressure-flow recordings and clinically relevant indices, allowing the simple quantification of Zc are still lacking. Although PWV is fast and easy to obtain, several limitations have been underlined, including difficulties and inaccuracies in the measurement of the distance covered by the pulse waves. Furthermore, Zc is 5 times as sensitive to changes in vessel radius as PWV. It has been suggested that Zc is more sensitive to the endothelium-mediated changes in vessel diameter; therefore, is more amenable than PWV to short-term regulation. As a result, simple method allowing Zc estimation is especially needed in practice.

NEW ESTIMATES OF PULSATILE ARTERIAL LOAD BY USING SYSTOLIC PULSE CONTOUR ANALYSIS

Characteristic Impedance

As previously discussed, the peak amplitude (dPmax) of the forward aortic pressure wave may be approximated as follows (Figure 1):

\[ dP_{max} = Pi - DAP \]  

The concept of characteristic impedance implies that the pressure-flow relationship is linear in the proximal aorta when aortic pressure is measured before the arrival of the first reflected wave. Previous studies have taken advantage of such an assumption to calculate Zc in the time-domain as the ratio of the peak amplitude of the forward aortic pressure wave (dPmax) divided by the peak pulsatile flow (Qmax):

\[ Zc = dP_{max}/Q_{max} \]  

On the other hand, the left ventricular pulsatile outflow results in a systolic flow wave in the proximal aorta that may be described by using a triangular shape. The accuracy of such an approximation has been recently discussed and has proved useful to provide a reasonable estimate of pulsatile flow. Because there is flow in the proximal aorta only during the systolic period, we obtain:

\[ Q = (Q_{max} \times ST)/(2T) \]  

where Q is the mean cardiac output, T is the heart period, and ST is systolic time (ejection duration or left ventricular ejection time). Finally, Q may be expressed as follows:

\[ Q = SV/T \]  

where SV is stroke volume. By combining equations 1–4 we obtain:

\[ Zc = [(Pi - DAP) \times ST]/(2SV) \]
It is therefore suggested that pulse contour analysis may provide a valuable estimate of $Z_c$ (Figure 2). As compared to previous time-domain methods for $Z_c$ calculation, solving equation 5 does not require continuous flow velocity recordings and is thus applicable to patients whose mean cardiac output is monitored by using either invasive (eg, thermodilution) or noninvasive (eg, Doppler echocardiography) validated techniques. The present approach is a theoretical one and therefore it remains to be validated by further experiments.

The Waveguide Ratio

In most clinical situations, Q is not available, making it impossible to calculate $Z_c$. Nevertheless, in such conditions, the waveguide function of the aorta may still be calculated. Indeed, the systemic vascular resistance is calculated as:

$$Rs = \frac{(MAP - Po)}{Q}$$  \hspace{1cm} (6)

where MAP is mean aortic pressure and Po is the mean downstream pressure. Thus, the pulsatile arterial load relative to steady load (waveguide ratio) is obtained as follows:

$$Zc/Rs = \frac{[(Pi - DAP) \times ST]/[(MAP - Po) \times 2T]}{[(Pi - DAP)/(MAP - Po)] \times [(ST)/(2T)]}$$  \hspace{1cm} (7)

Put differently we obtain

$$Zc/Rs = \frac{[(Pi - DAP)/(MAP - Po)] \times [(ST)/(2T)]}{[(Pi - DAP) \times ST]/[(MAP - Po) \times 2T]}$$  \hspace{1cm} (8)

Thus the waveguide ratio may be simply calculated as the product of a pressure ratio and a time ratio.

It must be noted that the waveguide ratio is critically related to the ejection time over heart period ratio (ST/T), namely the “duty cycle” (or “duty ratio”). By analogy with engines, the duty cycle may be viewed as the fraction of time the “system” (ie, the left ventricle) is actually employed in performing its systolic function (ie, ejection). To the best of our knowledge, the duty cycle has not been extensively studied so far in humans. It has been recently demonstrated that prolonged ejection duration after beta-adrenergic blocking agents and in patients with diastolic dysfunction may compromise the left ventricle-vascular coupling by allowing more time for the reflected pressure wave to peak during systole at the aortic level and to increase the afterload of the still-ejecting left ventricle.

One result of the waveguide ratio is that it provides a physiological estimate of the relative pulsatile load put on the heart, as reflected in the $Zc/Rs$ ratio. Another is that it does not require any measurement of cardiac output and thus may be derived from aortic pressure recordings only. Further studies are needed to test this ratio and its correlates in both health and disease.

Total Arterial Compliance (C) and Stiffness (1/C)

In an attempt to obtain a clinically usable estimate of total arterial stiffness (1/C), a distributed linear model of the systemic circulation may be used together with a number of reasonable and simplified assumptions including: (1) that Rs, L, and C are constant and independent of the frequency, (2) that the aorta may be described as 1 uniform tube of effective length $L$, thereby neglecting the effects of tapering and bifurcation, (3) that the phase and group wave propagation velocities are identical, constant (PWV), and independent of the frequency (ie, there is no dispersion). The PWV may be expressed as a function of L and C and the time from systolic pressure upstroke to the pressure inflection point indicating pressure reflection ($\Delta t$) may be expressed as a function of the effective forward and backward travelling distance. Thus we obtain:

$$PWV = \frac{l}{\sqrt{LC}}$$  \hspace{1cm} (9)

$$\Delta t = \frac{2l}{PWV} = 2\sqrt{LC}$$  \hspace{1cm} (10)

On the other hand, $Z_c$ may be expressed as a function of L and C:

$$Zc = \sqrt{\frac{L}{C}}$$  \hspace{1cm} (11)

By combining equations 10 and 11 we obtain

$$C = \frac{\Delta t}{2Zc}$$  \hspace{1cm} (12)

By combining equations 5 and 12 we obtain...
Thus, from a theoretical point of view, equations 13 and 14 provide new, simple estimates of total arterial compliance and stiffness in the time domain using systolic pulse contour analysis (Figures 3 and 4). Some authors have suggested that a fixed 30% to 33% Δt/ST value may be on average correct in most resting subjects.\textsuperscript{24,27} Other authors have highlighted the importance of considering subtle differences in the Δt/ST value in clinical studies performed in both health (eg, throughout aging) and disease.\textsuperscript{7,8,11,23} Further experimental studies are needed to test the validity of these formulae.

**Limitations**

The main limitation of our study is that the new formulae are mainly applicable for invasive methods, and this impacts on their clinical application. The precise calculation of time and pressure variables, especially aortic Pi, is a prerequisite to our formulae. The systolic aortic pressure and PP reconstructed from radial artery applanation tonometry have been satisfactorily validated against pressure simultaneously recorded by micromanometers,\textsuperscript{11,28} but the high-frequency components of the pulse-wave, including Pi and thus time-to-Pi (Δt), appear less reliable.\textsuperscript{29} Thus, the validation or the use of our formulae may be ideally restricted to invasive, high-fidelity pressure recordings rather than to radial applanation tonometric devices. A clinical study aimed at comparing the new pulsatile load indices estimated by using invasive and noninvasive methods should be important to develop.

The shape of the aortic flow wave may deviate from the triangular hypothesis in clinical situations such as low flow states and heart failure. It is also likely that the triangular hypothesis is not met in cases of atrial fibrillation or other significant rhythm disturbances. The formulae proposed here strictly apply to steady state conditions in resting humans. The equations remain to be validated in patients studied during daily activity. Finally, our approach was a theoretical one, and further studies are needed to confirm our hypotheses.
Potential implications

The new formulae proposed here may furnish valuable and rapid estimates of pulsatile load in various populations, both at baseline and after therapeutic interventions. The formulae clearly illustrate the fact that time indices (systolic time, heart period, and time to the first reflection wave) and the indices quantifying arterial stiffness and pulsatile load are intrinsically related.

Numerous studies performed during the past 3 decades have documented that the resting heart rate is an independent cardiovascular risk factor in patients with cardiovascular diseases, heart failure, diabetes mellitus, and hypertension. The resting heart rate (HR, in beats/min) is related to the resting heart period T (in seconds) according to the following formula:

\[
HR = \frac{60}{T}
\]

(15)

The positive association frequently observed between increased heart rate and increased systolic and pulse pressure has been mainly attributed to an increased sympathetic drive. It is intuitive that both an increased pulsatile pressure and a high heart rate may be especially deleterious and contribute to both the increased pulsatile stretch put on the large arteries and the increased load put on the left ventricle. However, to the best of our knowledge, there has been no useful analytical formula relating pulsatile load and time intervals. One implication of our study is that only the waveguide ratio (equation 8) is mathematically related to heart rate. Conversely, equations 5, 13, and 14 indicate that Zc, C, and 1/C are mathematically dependent upon ST, not heart rate. The heart rate-independence of the mathematical formalisms of Zc, C, and 1/C we documented here is consistent with basic hemodynamical grounds.

Finally, the new indices we propose here may be also valuable in the specific area of the intensive care unit, where rapid changes in cardiac output must be monitored. In the critically ill patient and following an initial calibration set with calculation of the reference, calibrated value of C (C_cal), systolic pulse contour analysis may help predict stroke volume changes assuming an essentially unchanged C_cal after dynamic events. Rearranging equation 13 led to the following equation:

\[
SV = C_{\text{cal}} \times \left[ (\Pi - \text{DAP}) \times \frac{\text{ST}}{\Delta t} \right]
\]

(16)

Provided that a reliable estimation of aortic pressure, and especially Pi, is available, the formula may help track SV changes after fluid infusion, vasoactive drugs, and hemofiltration. The formula may not apply in cases where pressure-dependent changes in C are observed (e.g., after severe hemorrhage). The proposed formula 16 is theoretical and thus deserves further experimental evaluation and confirmation.

CONCLUSION

Here we have proposed 4 new hemodynamical formulae (equations 5, 8, 13, and 14) derived from systolic pulse contour analysis and relating the characteristic impedance (Zc), the waveguide ratio (Zc/Rs), total arterial compliance (C), and total arterial stiffness (1/C) to simple aortic pressure indices and time indices. The mathematical relationship between pulsatile load indices and time intervals was stressed, with Zc being mathematically related to ST, the waveguide ratio being related to the duty cycle (ST/T), and 1/C being related to the ST/Δt ratio. Further experimental studies are needed to test the validity of our theoretical approach.

Unlike previous studies performed on the basis of diastolic pulse contour analysis, our systolic pulse contour analysis relies on the propagative model, not the windkessel model, and thus avoids the theoretical limitations related to the latter model. Our proposal incorporates the potential influences of wave propagation and reflections on the indices of pulsatile load. The present viewpoint is mainly based on 2 validated hypotheses: (1) a linear aortic pressure-flow relationship in early systole, (ie, before the arrival of the first reflected wave) and (2) a triangular aortic flow wave during systole. While the former hypothesis intrinsically belongs to the characteristic impedance concept, the latter may be inaccurate in low flow states or in arrhythmic patients. The main limitation of our study is that the new formulae are mainly applicable for invasive methods, and this affects on their clinical application. However, in the near future, it may be expected that improved tonometric devices may well furnish more reliable estimates of the high-frequency components of the pulse wave, allowing a more reliable, noninvasive estimation of pulsatile load.

REFERENCES


