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Identifying haemodynamic determinants of pulse pressure: a combined numerical and physiological approach

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Abstract

We examined the ability of a simple "reduced" model comprising a proximal characteristic impedance linked to a Windkessel element to accurately predict central pulse pressure from aortic blood flow, verified that parameters of the model corresponded to physical properties, and applied the model to examine pulse pressure dependence on cardiac and vascular properties. Pulse pressure obtained from the reduced model was compared with theoretical values obtained *in silico* and measured values *in vivo*. Theoretical values were obtained using a distributed multi-segment model in a population of "virtual" (computed) subjects in which cardiovascular properties were varied over the pathophysiological range. *In vivo* measurements were in normotensive subjects during modulation of physiology with vasoactive drugs and in hypertensive subjects. Central pulse pressure derived from the reduced model agreed with theoretical values (mean difference±SD, -0.09±1.96 mmHg) and with measured values (mean differencse -1.95±3.74 and -1.18±3.67 mmHg for normotensive and hypertensive subjects respectively). Parameters extracted from the reduced model agreed closely with theoretical and measured physical properties. Central pulse pressure was seen to be determined mainly by total arterial compliance (inversely associated with central arterial stiffness) and ventricular dynamics: the blood volume ejected by the ventricle into the aorta up to time of peak pressure and blood flow into the aorta (corresponding to the rate of ventricular ejection) up to this time point. Increased flow and/or volume accounted for 20.1 mmHg (52%) of the 39.0 mmHg difference in pulse pressure between the upper and lower tertiles of the hypertensive subjects.

Key words: aortic flow, arterial stiffness, hypertension, pulse wave velocity, ventricular ejection.

Introduction

Hypertension, the single most important cause of morbidity and mortality worldwide,[1] arises mainly as a result of an increase in pulse pressure (PP),[2] yet the haemodynamic basis of this increase in PP is still disputed. Simple physical principles dictate that PP is dependent upon the ejection of blood from the left ventricle and the impedance of the arterial tree, particularly the characteristic impedance that relates to the stiffness of large elastic arteries. A detailed understanding requires a mathematical model to describe the coupling of ventricular ejection to impedance of the arterial tree but the complexity of current models limits their use in elucidating the main determinants of PP. We have recently demonstrated that a distributed multi-segment model of the arterial tree can be reduced to a proximal segment of elastic tube representing the aorta coupled to a peripheral compliance and resistance representing the muscular arteries and microvasculature.[3] When subject to identical flow input caused by ventricular contraction, this reduced model describes pressure generation with very little loss of fidelity when compared with a full, distributed model.[3] Theoretical considerations show that, despite the distributed nature and complexity of pressure propagation within the arterial tree, this reduction does not detract from the physical meaning of the model parameters, although these are necessarily average properties of the anatomical and physical properties they represent.

The purpose of the present study was to examine the accuracy with which the 3-element Windkessel model described by Westerhof[4] can predict observed pressure-flow relationships and deduce physical properties of the circulation that determine the usual peak of the central pressure pulse (in young individuals, an early systolic peak may exceed a second systolic peak in central pressure). We examined the agreement between pressure inferred from a reduced model and simulated pressure obtained *in silico* from a full distributed model, and from *in vivo* measurements of pressure and flow in normotensive and

hypertensive subjects. In normotensive subjects, normal physiology was perturbed using vasoactive drugs with divergent effects on the heart and arteries. Having established that parameters extracted from the reduced model corresponded to physical properties of the circulation, we used the model to inform the haemodynamic determinants of PP.

Methods

Reduced model

The reduced model is a 3-element Windkessel model as described by Westerhof,[4] and a further simplification of that previously described by ourselves[3] in which the aorta is represented by a characteristic impedance (Z_c) coupled to a Windkessel element characterising peripheral resistance (R) and total compliance (C). Under normal physiological conditions, this links pressure, *P(t)*, and flow rate, *Q(t)*, at the aortic root by Eq. (1), and yields the analytical solution for *P(t)* given by Eq. (2):

$$\frac{dP(t)}{dt} + \frac{1}{RC}P(t) = Z_c\frac{dQ(t)}{dt} + \frac{R+Z_c}{RC}Q(t) + \frac{1}{RC}P_{out} \quad (1)$$

$$P(t) = Z_cQ(t) + \frac{1}{C}e^{-\frac{t}{RC}}\int_0^t e^{\frac{t'}{RC}}Q(t')dt' + (DBP - P_{out})e^{-\frac{t}{RC}} + P_{out} \quad (2)$$

where *DBP* is the diastolic blood pressure. P_{out} is the asymptotic pressure equal to pressure in the arterial system in the absence of ventricular ejection, which is related to capillary and venous pressure. Z_c, the characteristic impedance is related to aortic pulse wave velocity (PWV) and cross-sectional area (A) by: $Z_c = \rho.PWV/A$, where ρ is blood density. Z_c relates pressure changes to flow changes without involving any dissipation of energy, just the transfer of wave energy from potential to kinetic form. In the frequency domain, Z_c is defined as the modulus of high-frequency components of the impedance[4] when compliance predominates. The first term in Eq. (2) dominates at high flow early in systole and is equal to

the Water Hammer pressure.[5] Subsequent terms dominate later in systole/diastole when flow is low/zero and represent the pressure generated by the volume of blood injected into the compliance and peripheral resistance of the arterial tree. In the absence of mitral regurgitation, aortic flow corresponds to the rate of ventricular ejection and the integral of aortic flow corresponds to the blood volume ejected from the ventricle into the aorta (referred to as "volume" hereafter). The derivation of these equations and of the parameters Z_c, C and R from simulated or experimental data is provided in the on-line supplement.

In silico "virtual population"

A population of virtual subjects similar to that previously described was used.[6] For each virtual subject, an aortic pressure wave, $P(t)$, was computed from a simulated aortic flow waveform, $Q(t)$, and from a multi-segment distributed model with physical arterial properties including cross-sectional area and PWV specified for each arterial segment. Characteristics of the flow waveform and physical characteristics of the arterial tree (including the terminal values of compliance, contributing to total compliance) were varied over the pathophysiological range[6] to produce a combination of 3,095 virtual subjects in total. All post-processing calculations were performed using customized Matlab software (The MathWorks, MA, USA).

In vivo data

In vivo data was that previously obtained in a group of normotensive healthy volunteers (n=13, 10 men, age 49±8 years, BP 110±16/69±10 mmHg, means±SD) and in hypertensive subjects (n=156, 83 men, age 46±17 years, BP 130±23/83±13 mmHg).[7,8] Characteristics of the hypertensive subjects are given in table S1. Healthy volunteers took part in cross-over studies to investigate the change in pulsatile haemodynamics during administration of drugs with different inotropic and vasopressor/vasodilator properties: dobutamine (2.5, 5 and 7.5

μg/kg/min, a positive inotrope with some vasodilator actions), noradrenaline (12.5, 25, 50 ng/kg/min, a vasoconstrictor with some inotropic actions), phentolamine (1 mg bolus + 25 μg/min, 2mg + 50 μg/min and 4 mg + 100 μg/min, a small artery dilator) and nitroglycerin (3, 10, 30 μg/min, a large artery dilator with some action on ventricular dynamics and also venodilation). Each subject received at least 2 comparator drugs: either the vasopressor agents dobutamine and noradrenaline or the vasodilators phentolamine and nitroglycerin, and data for each drug was obtained on at least 10 subjects. Each drug was given on a different occasion separated by at least 7 days and the order was randomised. Haemodynamic measurements were made as detailed below during saline vehicle infusion and during each dose of vasoactive drug. In hypertensive patients, measurements were made at baseline only.

Haemodynamic measurements

Haemodynamic measurements of aortic flow and pressure were performed as previously described.[7] Radial and carotid pressure waveforms were obtained by applanation tonometry performed by an experienced operator using the SphygmoCor system (AtCor, Australia). Approximately 10 cardiac cycles were obtained and ensemble averaged. Ensemble averaged carotid pressure was used as surrogate for ascending aortic pressure.[9] Waveforms that did not meet the in-built quality control criteria in the SphygmoCor system were rejected. Brachial blood pressure was measured in triplicate by a validated oscillometric method (Omron 705CP, Omron Health Care, Japan) and used to calibrate radial waveforms and thus to obtain a mean arterial pressure (MAP) through integration of the radial waveform. Carotid waveforms were calibrated from MAP and diastolic brachial blood pressures on the assumption of equality of these pressures at central and peripheral sites.[10] Ultrasound imaging was performed by an experienced operator using the Vivid-7 ultrasound platform (General Electric Healthcare, UK). This provided a measurement of the velocity above the aortic valve

using pulsed wave Doppler obtained from an apical 5-chamber view. All ultrasound measurements were averaged over at least 3 cardiac cycles.

Results

Accuracy of reduced model in predicting pressure waveforms and pulse pressure

Examples of pressure waveforms obtained from the reduced model together with simulated waveforms obtained from the full model in the virtual population, and measured waveforms in normotensive and hypertensive subjects are shown in Figure 1. Corresponding waveforms for a larger proportion of the virtual population and all of the *in vivo* data are shown in supplementary material (see online supplement, Figures S1, S2 and S3). Waveforms obtained from the reduced model are seen to lack the fine detail of measured waveforms and those simulated from the full model. However, values of PP obtained from the reduced model agreed closely with simulated and measured values. In the virtual population, optimisation of the scaling factor for estimating Z_c (see supplementary material) ensured that the mean error between values of PP extracted from the reduced and full models was zero, but there was good agreement across the virtual population with the standard deviation (SD) of the error < 2 mmHg (Figure 2A). For normotensive subjects, using data at rest and during modulation of cardiac and vascular properties with drugs, the mean±SD error was -1.95±3.74 mmHg (Figure 2B) and for the hypertensive subjects the mean error was -1.18±3.67 mmHg (Figure 2C). There was no trend for the mean error or SD of the error to vary with PP in any of the groups (Figure 2). Agreement between PP obtained from the reduced model and measured values was much closer than that between PP estimated from the ratio of stroke volume to compliance for which mean errors were 3.89±4.95, -2.05±6.49 and -8.41±13.53 mmHg for the virtual population, normotensive and hypertensive subjects, respectively.

Relation between parameters of the reduced model and physical properties

In the virtual population, total compliance C obtained by fitting an exponential to the pressure waveform in diastole and used in the reduced model (Equation (xi) in supplementary material) was closely correlated with theoretical total compliance computed through summation of the compliances of all segments of the full model (R=0.90 for the virtual population). The characteristic admittance $1/Z_c$ was linearly related to total compliance within the virtual population and a similar relation was seen between $1/Z_c$ and total compliance extracted using the reduced model from *in vivo* measurements in normotensive and hypertensive subjects (R=0.83 and R=0.82 respectively for the virtual population and the combined *in vivo* groups, Figure 3).

Further simplification of the model to ventricular flow/volume and arterial compliance

The inverse relationship between Z_c and total compliance means that Z_c can be expressed in terms of C and, hence, Equation (2) used to obtain PP as a function of only Q, R, C, P_{out} and DBP. Estimates of PP obtained using this simplification agreed with simulated / measured values to within -0.02±2.04, -3.95±4.88 and -5.44±5.75 mmHg for the virtual population, normotensive and hypertensive groups respectively (Figure S4). Using this further reduction, the model accounted for 88% of the variance in PP in the normotensive and hypertensive groups combined as opposed to 93% when Z_c was derived independent of compliance.

Cardiac and vascular determinants of pulse pressure

For the virtual population in which cardiac and vascular properties were varied independently around mean values, PP derived from both the reduced model and from the full model showed almost identical trends in relation to cardiac and vascular parameters. PP increased with increasing flow and volume of blood ejected into the aorta up to the time of peak

pressure (V_{pp}); PP increased with increasing Z_c and P_{out}, and decreased with greater compliance (Figure S5). To determine the relative dependence of PP on cardiac and vascular properties *in vivo* (where properties are likely to be interdependent), we examined variation of PP with V_{pp}, whilst total compliance remained constant and vice versa (Figure 4). Because of the close inverse relationship between compliance and Z_c, Z_c also remained approximately constant when compliance was held constant. PP was seen to increase with increasing V_{pp} and with a decrease in compliance. The relationship between PP and C was similar to that predicted by Equation (2), with coefficients of 30 and 34 mmHg increase in PP per ml/mmHg increase in C for the normotensive and hypertensive subjects respectively compared to a theoretical value derived from Equation (2) of 35 mmHg per ml/mmHg change in total compliance (Figure 5). Change in PP per ml change in V_{pp} was 0.54 and 0.53 mmHg per ml for normotensive and hypertensive subjects respectively compared to a theoretical value derived from Equation (2) of 0.66 mmHg per ml change in V_{pp}. Mean PP in the upper and lower tertiles of the distribution of PP in hypertensive subjects was 30.8±5.7 mmHg and 69.8±12.8 mmHg respectively. Increased flow and/or V_{pp} accounted for 20.1 mmHg (52%) of the difference in pulse pressure between the upper and lower tertiles of the hypertensive subjects. V_{pp} was closely correlated with stroke volume (R=0.86, P<0.001).

Discussion

The focus of numerical modelling in understanding the haemodynamics of hypertension has been largely to develop ever more detailed distributed models of the circulation.[11] Although these models provide an in-depth understanding of how pressure-flow relationships can potentially be influenced by the arterial tree, they are of limited value when seeking to determine to what extent a given pressure component depends upon properties of the heart, and arterial tree. This is because the redundancy of parameters means that any given pressure

waveform can be described by a variety of cardiac and/or arterial properties. To infer properties of the circulation a model that contains a small number of parameters that can be robustly determined from observed measures of pressure and flow is required. The model must describe pressure-flow relationships and the parameters fitted to the experimental measurements must relate to physical characteristics of the arterial tree.

In the present study we have demonstrated that a simple model comprising proximal impedance characterised by PWV, linked to a Windkessel component providing peripheral resistance and compliance is adequate in estimating central pulse pressure. Importantly, the parameters of this model are not simply "fitting parameters" but correspond to physical properties of the arterial tree. Testing the model against simulated data from a virtual population and against *in vivo* data obtained across a wide pathophysiological range including that induced by vasoactive drugs provided a rigorous test of the model. Although accuracy against *in vivo* data is critical, the simulated data allows parameters of the reduced model to be compared to those of a theoretical model without experimental error.

That such a simple model can explain pressure-flow relationships without invoking the complexities of pressure wave propagation and reflection can be explained by backward pressure waves maintaining an approximately constant relationship to forward waves,[8,12] particularly around the time of PP and hence summating to form an effective total pressure captured by the reduced model or by reflection having minimal effects on central PP.[13] Our study does not distinguish between these possibilities (which are not mutually exclusive). It is notable, that the reduced model is less accurate in predicting pressure early in systole around the time of the first peak in pressure. This is likely to be due to omission of effects due to pressure propagation/reflection since pressure is changing rapidly at this time. By contrast at the time of PP, rate of change of pressure is low, variation in pressure along the arterial tree is correspondingly low and thus, to a reasonable approximation, effects of pressure propagation

can be ignored. However, prediction of central pulse pressure to within 2±4 mmHg of measured pressure means that the model can reliably be used to infer the major determinants of central pulse pressure. These comprise the flow and ejection volume up to the time of PP, the proximal impedance, and total arterial compliance. Thus for a given ventricular input, pulse pressure relates to PWV, inversely to aortic cross-sectional area and for a given PWV and aortic area will be reduced by greater peripheral compliance. However, there is a close inverse relationship between characteristic impedance and compliance such that PP can be described by blood flow, volume and a single arterial parameter: total compliance. This highlights the importance of ventricular dynamics in determining PP, an observation that has been noted in previous studies.[14-16] Much of the dependence on ventricular dynamics is captured by the volume ejected up to the time of peak pressure, which in turn approximates stroke volume. However, PP is not only dependent on volume up to the time of PP but on the ventricular dynamics in early systole that determine the preceding flow (since, if there is no mitral incompetence, flow is closely correlated with the rate of ventricular contraction). This explains modification of pressure in the absence of a change in stroke volume and the rate of ventricular contraction is thus an important determinant of PP. We also demonstrate dependence of PP on asymptotic pressure P_{out}, which was higher in hypertensive compared to normotensive subjects compatible with capillary rarefaction[17] and/or increased venous pressure due to sodium and volume overload.[18]

The model we have applied should be distinguished from previous simple models incorporating a network of elements representing compliances, resistances and inertances.[19] These have usually been applied without direct measurement of flow and volume (stroke volume often being estimated from nomograms relating this to body size) and the physical meaning of parameters obtained by fitting such models to experimentally derived pressure is uncertain. The present study shows the critical importance of measuring flow and volume.

This study is subject to a number of limitations. Our non-invasive measurements of pressure and flow, were subject to experimental error. Carotid pressure is also an imperfect surrogate of aortic pressure and subject to calibration errors. This could have influenced absolute but not relative values of parameters extracted from the reduced model. These errors may explain the increased discrepancy between values derived from the reduced model and measured values, compared to the closer agreement with simulated values. Further validation using more accurate methods for measuring flow such as magnetic resonance would be valuable. We tested the reduced model only in healthy normotensive subjects and in otherwise healthy hypertensive subjects. Although comparison with the virtual population across a larger range of pathophysiological parameters and modulation of normal physiology with vasoactive drugs suggests that the model would be equally valid in other pathological conditions, such as systolic hypertension in older subjects and in heart failure, this needs testing prospectively. Our model relates only to the prediction of the usual peak of central pulse pressure and will not provide accurate values of central pulse pressure in young subjects in whom an early systolic peak may be of higher amplitude (i.e. negative augmentation index).[20] However, previous work suggests that pulse pressure can then be estimated from the water hammer equation.[21]

Perspectives

An increase in pulse pressure is the major cause of incident hypertension in middle-aged to older persons and in older persons (and probably at all ages when measured centrally) is more closely related to cardiac events and mortality than other blood pressure components. It is, therefore, essential to understand the haemodynamic determinants of pulse pressure. The simple model of pressure generation in response to ventricular ejection that we have verified and applied to a group of hypertensive subjects, demonstrates that ventricular ejection is a key determinant of central pulse pressure. To what degree altered ventricular ejection is due

to ventricular remodelling, a compensatory response to hypertension, is secondary to increased pre-load or increased sympathetic drive is likely to vary between individuals. Partitioning pulse pressure into components due to arterial stiffness and ventricular ejection provides the potential for a haemodynamically orientated stratified approach to hypertension.

Conclusions

In conclusion, we present a simple model, verified numerically and against physiological data, that defines the relationship between central aortic pulse pressure, aortic flow and blood volume ejected into the aorta and arterial properties. Total arterial compliance inversely related to aortic *PWV* dominates in determining the contribution of the arterial tree. Volume ejected from the ventricle up to the time of peak pressure dominates in determining the contribution of ventricle, but there is an important component of rate of ventricular ejection (corresponding to aortic flow) that influences pulse pressure. Ventricular ejection and rate of ejection account for a relatively large proportion of central pulse pressure in young to middle-aged subjects with hypertension.

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Novelty and Significance

1. **What's new:** Development of a reduced model of the arterial tree that allows the major determinants of central pulse pressure to be partitioned into those due to arterial stiffness and those due to ventricular flow and volume.
2. **What's relevant:** The most important determinants of central pulse pressure, other than arterial stiffness, are the characteristics of ventricular ejection: flow and volume up to the time of peak pulse pressure. Increased flow and/or peak pressure volume accounted for 20.1 mmHg (52%) of the 39.0 mmHg difference in pulse pressure between the upper and lower tertiles of the hypertensive subjects.
3. **Summary:** A reduced model of the arterial tree that defines the relationship between central aortic pulse pressure, arterial properties and ventricular dynamics has been verified numerically and against physiological data. Total arterial compliance closely related to aortic PWV dominates in determining the contribution of arterial tree but ventricular dynamics account for a relatively large proportion of the increased pulse pressure in hypertension.

Figure Legends

Figure 1. Examples of pressure waveforms simulated *in silico* from the virtual population (left panels, blue) or measured *in vivo* (right panels, blue) and waveforms obtained from the reduced model (red) incorporating characteristic impedance Z_c, total compliance C, aortic flow and volume. Examples are shown for normotensive (upper panels) and hypertensive cases (lower panels). A larger subset of waveforms obtained in the virtual population and all the waveforms for the *in vivo* cases are shown in supplementary Figures S1, S2 and S3. Whilst the reduced model does not accurately reproduce fine detail in the waveform, pulse pressure (PP) is reproduced accurately (see figure 2)

Figure 2. Bland-Altman plots comparing pulse pressure (PP) derived from the reduced model (upper row) and further-reduced model (lower row) with simulated values obtained *in silico* (left panels) and with measured values *in vivo* in normotensive subjects (including during treatment with rising dose infusions of dobutamine, nitroglycerin, noradrenaline and phentolamine, see text for details, middle panels) and hypertensive subjects (right panels). The reduced model represented by Equation (2) (see text) incorporates characteristic impedance (Z_c) and total compliance (C) as well as measured flow and volume. In the further-reduced model, Z_c is derived assuming a reciprocal relationship with C (see figure 3).

Figure 3. Scatter plots showing the inverse relationship between the characteristic admittance ($1/Z_c$) and total compliance (C): (A) *in silico* data (Pearson correlation coefficient R=0.83); (B) *in vivo* data in normotensive (including during treatment with rising dose infusions of dobutamine, nitroglycerin, noradrenaline and phentolamine, see text for details) and hypertensive groups (R=0.82).

Figure 4. Variation of pulse pressure (PP) obtained from the reduced model with ejection volume up to the time of PP and total arterial compliance for *in silico* (virtual population) and *in vivo* (normotensive and hypertensive groups) data. Upper panels show variation with volume when compliance is approximately constant (solid line, 0.5–1 ml/mmHg; dashed line, 0.1-0.5 ml/mmHg; dotted line, 1-1.5 ml/mmHg). Lower panels show variation with compliance when volume is approximately constant (solid line, 60–70 ml; dashed line, 80-90 ml; dotted line, 40-90 ml).

Figure 5. Theoretical variation of pulse pressure (PP) with (A) arterial and (B) cardiac parameters according to the reduced model (Equation (2), see text). Parameters are varied over the range -50% to 100% from average values (for the *in vivo* data): total compliance C = 0.71 mL/mmHg; asymptotic pressure P_{out} = 56.9 mmHg; stroke volume SV = 62.3 mL; peak flow = 1.17 m/s; Z_c = 4.97 mmHg.s/mL.