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Jonathan P. MYNARD^{a,b}

Daniel J. PENNY^{a,b}

Malcolm R. DAVIDSON^c

Joseph J. SMOLICH^{a,b}

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Jonathan P. MYNARD^{a,b}

Daniel J. PENNY^{a,b}

Malcolm R. DAVIDSON^c

Joseph J. SMOLICH^{a,b}

^aHeart Research Group, Murdoch Childrens Research Institute, Melbourne, Australia;

^bDepartment of Paediatrics, University of Melbourne, Australia; ^cDepartment of Chemical and Biomolecular Engineering, University of Melbourne, Australia

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Address for Correspondence:

Jonathan P. Mynard, Biomedical Simulation Laboratory, Mechanical & Industrial Engineering, University of Toronto, Ontario, M5S 3G8, Canada. E-mail: jonathan.mynard@mcri.edu.au

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Abstract

Objectives

Arterial wave reflection has traditionally been quantified from pressure and flow measurements using wave separation and wave intensity (WI) analysis. In the recently proposed reservoir-wave paradigm, these analyses are performed after dividing pressure into ‘reservoir’ and ‘excess’ components, yielding a modified wave intensity (WI^{RW}). This new approach has led to controversial conclusions about the nature and significance of arterial wave reflection. Our aim was to assess whether WI or WI^{RW} more accurately represent wave phenomena.

Methods

We studied two computer models (a simple network and a full model of the systemic arterial tree) in which all systolic forward waves and reflection properties were known *a priori*. Results of these models were compared with haemodynamic measurements in the ascending aorta of five adult sheep at baseline and after incremental arterial constriction.

Results

The key findings of model studies were that the reservoir-wave approach 1) markedly underestimated or eliminated reflected compression waves, 2) overestimated or artefactually introduced forward and backward expansion waves, and 3) displayed non-physical interactions between distal reflection sites and early-systolic waves. These errors arose because, contrary to a key assumption of the reservoir-wave approach, reservoir pressure was not spatially uniform during systole. *In vivo* results were qualitatively similar to model results, with baseline WI and WI^{RW} suggesting that the arterial network was dominated by positive and negative wave reflection respectively, while under all conditions, reflected WI^{RW} compression waves were substantially smaller than corresponding WI waves.

Conclusion

We conclude that the reservoir-wave paradigm introduces error into arterial wave analyses.

Keywords: wave intensity analysis, windkessel, wave propagation, wave reflection, pulse pressure, hypertension

Introduction

Arterial wave analysis is increasingly being used to study the mechanistic origins of clinically-observed haemodynamics, such as the relation of pulse pressure to factors including vessel stiffness, pulse wave velocity and wave reflection [1-3]. Performed mainly to study systolic haemodynamics, wave analysis has shown that at the beginning of systole, a proximal-distal pressure difference produces a wave that propagates towards the periphery and is partially reflected wherever it encounters a change in vessel properties, such as a bifurcation or constriction [4-9]. At a fixed measurement site, the arrival of a wave causes transient changes to local pressure and flow that can be quantified by separating measured signals into forward and backward components [10] and further characterised via wave intensity analysis [3-6, 11, 12].

However, while systolic arterial haemodynamics exhibit both spatial pressure differences and pressure-flow transients, and thus display clear wave effects, doubt has recently been expressed about the validity of using wave analyses to examine diastole, when the decay of pressure is relatively uniform in space and the steadily decaying pressure is accompanied by almost invariant flow [13, 14]. Moreover, classical wave separation [10] predicts the existence of ‘self-cancelling’ (i.e. equal forward and backward) waves during diastole, a notion that has been considered by some to be an artefact of wave analysis with no physiological basis [13-15].

Conventionally, diastolic haemodynamics have been characterised by the 2-element windkessel, a simple hydraulic model consisting of a central reservoir that fills during systole and empties during diastole through a peripheral outflow resistance [16]. This model predicts an exponential decay of diastolic pressure and provides a physically

intuitive explanation of diastolic haemodynamics [17]. However, the 2-element windkessel does not predict important features of the systolic pressure waveform since wave propagation effects are not accounted for [17].

Since wave analysis and the 2-element windkessel appear most suitable for describing systolic and diastolic haemodynamics respectively, Wang et al [13] proposed a unifying reservoir-wave paradigm in which a notionally space-independent reservoir pressure (p_{res}) described the charging and discharging of the arterial windkessel, while the difference between measured pressure (p) and p_{res} , called the excess pressure (p_{ex}), was then considered to govern all wave phenomena. Thus it was proposed that wave intensity, which has traditionally been defined as the product of pressure and velocity differentials, should be derived from p_{ex} rather than p [13]. The reservoir-wave approach remains controversial, however, because while proponents have asserted that it constitutes a ‘correction’ to traditional wave analysis [18-20], others have cautioned its use without further validation [21] and described theoretical limitations in separating pressure into reservoir and wave components [22].

The issue of whether p or p_{ex} should be used in wave analyses is particularly important as the two methods may produce fundamentally different interpretations of arterial haemodynamics. Traditional wave intensity consistently demonstrates the existence of a mid-systolic backward compression (i.e. pressure increasing) wave suggestive of closed-end (i.e. positive) wave reflection [4, 5, 7, 23], whereas the reservoir-wave version of wave intensity displays a backward expansion (i.e. pressure decreasing) wave suggestive of open-end (i.e. negative) wave reflection [15, 18-20]. Moreover, while traditional wave analysis supports the widely-held conception that wave reflection plays

an important role in cardiovascular risk [24-26], reservoir-wave data suggest that the contribution of wave reflection may have been overestimated by up to 70% [15, 27]. Importantly, however, as the reservoir-wave paradigm has never been validated in a system with known vascular and wave reflection properties, it is unclear whether these findings have a sound physiological basis, or are instead a byproduct of methodological factors.

The aims of this study were therefore 1) to assess traditional and reservoir-wave versions of wave separation and wave intensity in model arterial systems in which all wave propagation and reflection properties were known *a priori*, and 2) to test model predictions experimentally using high-fidelity pressure/flow measurements in the ascending aorta of adult sheep under baseline conditions and after increasing arterial pressure and wave reflection by mechanical constriction of distal large conduit arteries.

Methods

The reservoir-wave paradigm

The reservoir-wave paradigm considers measured pressure (p) to be the sum of reservoir (p_{res}) and excess (p_{ex}) pressures [13],

$$p(x,t) = p_{\text{res}}(t) + p_{\text{ex}}(x,t) \quad (1)$$

Here, p_{res} represents the pressure developed when the arterial reservoir, described by compliance (C_{res}), outflow resistance (R_{res}) and downstream pressure (P^∞) parameters, fills with a volume of blood (see Supplemental Digital Content 1 for details regarding calculation of p_{res}). Importantly, both p_{ex} and p are functions of time *and* distance, whereas p_{res} is a function of time only. So when calculated using local pressure and flow

at any site in the reservoir (i.e. any site proximal to R_{res}), in theory p_{res} should be the same regardless of where it is measured, whereas p_{ex} should display spatial differences related to wave propagation. In other words, waves (a one-dimensional, 1D, phenomenon) are considered to ‘ride’ on top of the reservoir (a zero-dimensional, 0D, phenomenon).

Wave Intensity Analysis

The theory of wave intensity has been described in detail elsewhere [4, 7, 11, 12, 28, 29]. Wave intensity (WI) is defined as

$$WI = \frac{dp}{dt} \frac{du}{dt} \quad (2)$$

Four wave types are distinguished: forward and backward compression (i.e. pressure-increasing) waves (FCW and BCW), and forward and backward expansion (i.e. pressure-reducing) waves (FEW and BEW). Forward waves have positive WI and backward waves have negative WI . Wave size is quantified by wave area or ‘cumulative intensity’ (CI), while the pressure effect of a wave is designated Δp .

Given knowledge of wave speed (c), pressure, velocity and wave intensity signals can be separated into forward and backward components [4, 7, 11, 12, 28, 29]. In the reservoir-wave approach, wave intensity (WI^{RW}) is modified by replacing p with p_{ex} in Equation (2) and similarly wave separation is performed with p_{ex} rather than p .

Wave reflection

Wave reflection occurs whenever a propagating wave encounters an impedance mismatch [8-10, 30-33]. The degree of reflection can be quantified with a reflection coefficient and in the model studies described below, we compare the true reflection

coefficient (Γ_y), obtained from known model parameters, with calculated coefficients obtained from traditional or reservoir-wave versions of the forward and backward pressure components ($\Gamma_{\Delta p}^T$ and $\Gamma_{\Delta p}^{RW}$ respectively). Further details are provided in the Supplemental Digital Content 1.

Computer Modelling

The two 1D models employed in this study use previously-described methodology [29, 34, 35]. The input to both models is a forward component of left ventricular pressure (p_{LV+} , Fig. 1), which is imposed at the inlet via a numerical valve that transmits p_{LV+} into the aorta when open. Backward-running aortic waves are absorbed (i.e. not reflected) when the valve is open and reflected completely when it is closed [34, 35]. Three-element windkessels represent the downstream vasculature and consist of a characteristic impedance (Z), compliance (C_d), peripheral resistance (R_d) and outflow pressure (P^∞), with Z matched to the connecting 1D segment [36].

The first model (see Fig. 1A and Supplemental Digital Content 1) is a simple vascular network containing just three bifurcations. The first and third bifurcations (denoted ‘a’ and ‘c’ respectively) constitute a step increase in impedance, while the second bifurcation (denoted ‘b’) presents a local decrease in impedance. The value of local Γ_y for bifurcations ‘a’, ‘b’ and ‘c’ are initially set to 0.13, -0.12 and 0.12 respectively, but we also alter the diameter of segment 7 to additionally achieve local Γ_y of 0.22 and 0.38 for bifurcation ‘c’. For a unit input pressure pulse, Fig. 1B shows the reflected pressure waves that are predicted from transmission line theory via a wave tracking algorithm (see [37, 38] and Supplemental Digital Content 1). In short, three reflected waves are predicted to arrive at the model inlet, one after the other. Pressure-increasing

waves ‘a’ and ‘c’ in Fig. 1B arise from the closed-end type reflection sites ‘a’ and ‘c’ in Fig. 1A respectively and thus wave intensity analysis at the model inlet should exhibit backward compression waves around these times. Similarly, the pressure-decreasing wave ‘b’ arises from the open-end type reflection site ‘b’ and should therefore produce a backward expansion wave between waves ‘a’ and ‘c’. Note that the terminal windkessels also give rise to reflected waves, but these do not arrive at the inlet until later times than those shown in Fig. 1B.

The second model is an anatomically-based 1D network model of the systemic arteries and is identical to that described in [34], except that 3-element windkessels are used for the downstream vasculature, with resistance and compliance values adapted from [39] for a non-zero P^∞ . Although bifurcations in the systemic arterial model are generally well-matched (average local $\Gamma_Y = 0.01$), vessel tapering is included [34] and is expected to cause distributed closed-end type wave reflection due to a progressive increase in characteristic impedance [40]. Since the wave tracking algorithm cannot be used in tapering vessels, in this case we simply compare $\Gamma_{\Delta p}^T$ and $\Gamma_{\Delta p}^{RW}$. In both models, $\Gamma_{\Delta p}^{RW}$ and associated wave intensity signals for the reservoir-wave approach are obtained after calculation of the reservoir parameters (see Supplemental Digital Content 1).

Experimental Studies

Experiments were approved by the institutional Animal Ethics Committee and conformed to guidelines of the National Health and Medical Research Council of Australia. The surgical preparation was similar to that described previously [7]. Five Border-Leicester cross castrated male sheep were anaesthetized with intramuscular ketamine (5 mg/kg) and xylazine (0.1 mg/kg), followed by 4% isoflurane delivered by

mask. Anaesthesia was maintained with isoflurane (2-3%), nitrous oxide (~30%) and oxygen-enriched air ($\text{FiO}_2 \sim 70\%$) delivered via a mechanical ventilator, supplemented by an intravenous infusion of ketamine (1-1.5 mg/kg/hr) and midazolam (0.1-0.15 mg/kg/hr). Ventilation was adjusted to maintain arterial O_2 tension at 100-120 mmHg and arterial CO_2 at 35-40 mmHg.

The neck was incised in the midline and polyvinyl catheters were advanced through the left external jugular vein to the superior vena cava for fluid and drug infusion. A 5-Fr sheath was then inserted into the left common carotid artery, through which a 2.5-Fr micromanometer catheter (Millar Instruments, Houston, TX) was advanced into the ascending aorta for measurement of high-fidelity pressure. A left thoracotomy was performed in the fourth intercostal space and after incision of the pericardium, a 20 mm diameter “A-series” flow probe was placed around the ascending aorta and connected to a transit-time flowmeter (T206, Transonic Systems, Ithaca, NY). After a 10-15 min period of stabilisation, haemodynamic recordings were taken at baseline. To investigate the effects of stepwise increases in wave reflection and arterial pressure, recordings were also taken after mild and moderate constriction of the brachiocephalic trunk (the only cephalic branch arising from the aorta in sheep) and descending thoracic aorta produced with adjustable polyvinyl snares placed around these vessels. During each recording, an ectopic beat (i.e. a beat with a long diastole) was initiated with a brisk tap to the RV infundibulum using forceps [41]; this beat was then used for analysis.

Signals were filtered using a 48 Hz low-pass filter and flow was converted to velocity using the nominal size of the flow probe [7, 11, 12, 41, 42]. Wave speed (c) was calculated using the *pu*-loop method [28, 43, 44]. Subsequent haemodynamic analysis

was performed as in the systemic arterial model described above and in the Supplemental Digital Content 1.

Specific waves are designated as follows: 1) FCW_{ee} , the early-ejection forward compression wave corresponding with the initial rise in pressure and flow after valve opening; 2) FEW_{pd} , the proto-diastolic forward expansion wave associated with ventricular relaxation; 3) BCW_{sys} , the systolic backward compression wave, i.e. the combination of all backward compression waves occurring between the FCW_{ee} and the onset of the FEW_{pd} ; 4) BEW_{ee} , any early-ejection backward expansion wave preceding the BCW_{sys} ; 5) BEW_{sys} , systolic backward expansion wave, i.e. the addition of BEW_{ee} and any other backward expansion waves occurring before the onset of the FEW_{pd} ; 6) FEW_{ms} , the mid-systolic forward expansion wave.

Statistical Analysis

Statistical analyses of the experimental data were performed using repeated measures ANOVA, with preceding logarithmic transformation performed where data were non-normally distributed. Specific comparisons were achieved by orthogonal partitioning of the within-animal sums of squares into individual degrees of freedom. Results are expressed as mean $\pm$ SD and significance was taken as $P < 0.05$.

Results

Three-bifurcation model

Fig. 2A shows the results of traditional wave intensity and wave separation from the three-bifurcation model. Three backward waves (labeled a-c) were present during systole, and as predicted by transmission line theory (Fig. 1B), waves 'a' and 'c' were BCWs while wave 'b' was a BEW. As the impedance mismatch at bifurcation 'c' was

increased, so too did the size of wave ‘c’, while the preceding waves were unchanged. In all three simulations, $\Gamma_{\Delta p}^T$ compared well with Γ_Y for waves ‘a’ and ‘b’ (absolute differences all less than 10%), while the differences for wave ‘c’ were somewhat higher (~20%, Table 1). Importantly, traditional wave intensity did not contain a mid-systolic forward wave since the prescribed p_+ was constant between the end of the initial FCW and the start of the proto-diastolic FEW.

In contrast to WI , with $\Gamma_Y = 0.12$ for bifurcation ‘c’, there was a single BEW in WI^{RW} during mid-systole and waves ‘a’ and ‘c’ were essentially absent (solid black line, Fig. 2B). Wave ‘c’ appeared when the impedance mismatch at this site was increased (dashed and grey lines), but $\Gamma_{\Delta p}^{RW}$ was substantially smaller than Γ_Y for both compression waves under all conditions tested (differences of between -42% and -100%), whereas $\Gamma_{\Delta p}^{RW}$ for the BEW was much larger than Γ_Y (differences of 233-294%). In addition, WI^{RW} displayed an FEW during mid-systole that decreased p_{ex+} by 42-51% of the increase caused by the preceding FCW (Fig. 2B), whose CI was also 16% less than for WI . Importantly, although increasing Γ_Y of bifurcation ‘c’ increased wave ‘c’ as expected, this also altered the CI of the main FCW (-5%), wave ‘b’ (32%) and the mid-systolic FEW (40%), even though all of these waves preceded wave ‘c’.

Systemic arterial model

In the systemic arterial model, the FCW_{ee} was 31% smaller in WI^{RW} compared with WI , and while WI contained no subsequent forward waves until the FEW_{pd} , WI^{RW} displayed a relatively large FEW_{ms} following the FCW_{ee} (Fig. 3), with $FEW_{ms} \Delta p^{RW} / FCW_{ee} \Delta p^{RW} = 0.86$. WI displayed a small early BCW followed by a larger BCW

in mid-systole ($BCW_{sys} \Delta p / FCW_{ee} \Delta p = 0.65$), while WI^{RW} contained a BEW_{ee} ($\Delta p^{RW} / FCW_{ee} \Delta p^{RW} = -0.54$) followed by a small BCW_{ms} and then another small BEW . Lumping all pressure-increasing or pressure-decreasing waves together, the CI ratios for BCW_{sys} / FCW_{ee} were -0.22 and -0.05 with WI and WI^{RW} respectively, while corresponding ratios for BEW_{sys} / FCW_{ee} were -0.001 and -0.19 .

Fig. 4A,B shows the evolution of p and p_{res} in space and time, where these variables were obtained from 28 locations starting at the ascending aorta and moving down the descending aorta in 3 cm steps. Corresponding surface plots (Fig. 4C,D) show marked spatial variation in both p and p_{res} throughout systole and early diastole but little variation during most of diastole, when pressure declined exponentially and uniformly. Fig. 4C also reveals the propagation of the FCW_{ee} , which advanced distally with a wave speed equal to the local slope of the contour line. Importantly, the contour plot of p_{res} also reveals similar wave propagation behaviour during systole (Fig. 4D). Thus, both p and p_{res} exhibited substantial spatial pressure differences, as seen in plots of the instantaneous maximum pressure difference (Fig. 4E).

In-vivo experiments

A representative *in vivo* recording under baseline conditions is shown in Fig. 5 and includes the measured p and q_{in} , calculated p_{res} and p_{ex} and the respective forward- and backward-running components of pressure and wave intensity. WI contained a number of BCWs (black arrows) that together caused a substantial rise in p_- throughout mid-systole, during which time forward waves were negligible. By contrast, WI^{RW} exhibited a BEW that reduced p_{ex-} and an accompanying FEW_{ms} that reduced p_{ex+} substantially (open arrows).

Constriction of the descending aorta and brachiocephalic trunk had no effect on heart rate or cardiac output, but was associated with an increase in aortic root mean and pulse pressures (Table 2). The constrictions caused no change to the windkessel parameters R_{res} or P^{∞} but a progressive fall in C_{res} (Table 2). With the rise in pressure, wave speed tended to increase ($P = 0.15$), while values did not differ significantly if calculated from p_{ex} rather than p (Table 3). There was a trend for the FCW_{ee} to increase with the constriction (WI , $P = 0.06$; WI^{RW} , $P = 0.13$), while the CI and Δp of this wave were consistently smaller in WI^{RW} compared with WI ($P = 0.04$ and 0.004 respectively). Similarly, there was an increase in the size of the BCW_{sys} with constriction for both techniques ($P < 0.05$), but this wave was smaller when using the reservoir-wave approach ($P < 0.001$, Fig. 6A and Table 3). Conversely, although the BEW_{ee} decreased with the constriction using both approaches ($P < 0.05$), this wave and its pressure effects were smaller in WI compared with WI^{RW} ($P \leq 0.05$, Fig. 6B and Table 3). Finally, the pressure effect of the WI FEW_{ms} was negligible, whereas the effect of the WI^{RW} FEW_{ms} was substantial ($P < 0.001$), the latter decreasing progressively with the constriction ($P < 0.01$, Fig. 6C and Table 3). Comparing the CI ratios for $\text{BCW}_{\text{sys}}/\text{FCW}_{\text{ee}}$ and $\text{BEW}_{\text{sys}}/\text{FCW}_{\text{ee}}$, WI suggested that the arterial system was dominated by positive wave reflection at baseline and both levels of constriction (Fig. 7A), while WI^{RW} suggested that the arterial system was dominated by negative wave reflection at baseline, relatively equal amounts of positive and negative reflection with mild constriction, and predominant positive reflection with moderate constriction (Fig. 7B).

Discussion

This study has provided the first detailed assessment of the modified wave analysis proposed in the reservoir-wave paradigm [13]. Results from our computer models indicate that the separation of pressure into reservoir and excess components introduces error into arterial wave analysis, with the main effect being underestimation or elimination of compression waves and overestimation or artefactual introduction of expansion waves. These results were further supported by *in vivo* studies, which showed qualitatively similar differences between traditional and reservoir-wave approaches.

Although windkessel and wave descriptions of arterial haemodynamics have been used for many years, the ‘reservoir-wave’ paradigm is a relatively recent attempt at unifying these previously separate approaches [13]. A key result of the reservoir-wave approach has been a reduced prominence of the BCW compared with traditional wave analysis [14, 18, 45]. On this basis, it has recently been concluded that the increase in pulse pressure and augmentation index evident with aging is mainly due to an increase in reservoir pressure [15, 27], rather than an increase in or earlier arrival time of reflected waves [24-26]. Whilst the subject of less attention, published $p_{\text{ex-}}$ waveforms also contain a pronounced negative dip in early systole [15, 18], suggestive of proximal negative wave reflection. A pivotal question, however, is whether these findings arising from the reservoir-wave approach have a sound physiological basis, or are instead a byproduct of methodological factors.

To address this question, we compared the traditional and reservoir-wave approaches using a simple three-bifurcation network model and an anatomically-based model of the systemic arteries. In both, systolic forward waves were prescribed and arterial properties (and thus wave reflection properties) were known *a priori*. Results of these models

revealed substantial differences between the reservoir-wave (WT^{RW}) and traditional approach (WI) in four key areas.

First, the reservoir-wave separation markedly attenuated or eliminated backward compression waves. In the three-bifurcation model, the first BCW was not present in WT^{RW} and thus the first impedance mismatch went undetected. This was also true for the third bifurcation, and although the BCW appeared and increased as the true reflection coefficient (Γ_Y) was increased, $\Gamma_{\Delta p}^{RW}$ underestimated Γ_Y by approximately 50%, whereas traditional wave separation more closely matched the predicted Γ_Y for all cases tested. Similarly, in the systemic arterial model, the systolic BCW was substantially smaller in WT^{RW} than WI . These findings are consistent with prior observations [14, 18, 45], although this is the first study to show that the smaller degree of positive wave reflection apparent in WT^{RW} is an underestimation rather than a correction, noting that the widely-accepted definition of reflection coefficient is based on transmission line theory [8-10, 30-33].

Second, model data suggested that the reservoir-wave approach overestimates or artefactually introduces backward expansion waves. In the three-bifurcation model, traditional wave separation displayed a BEW of a similar size to that predicted by transmission line theory (differences <10%, Table 1), whereas the reservoir-wave technique led to a 2 to 3-fold overestimation of the BEW reflection coefficient. Moreover, while WI contained only backward compression waves in the systemic arterial model, WT^{RW} was dominated by backward expansion waves (Fig. 3). However, there were no sites in the model where such negative wave reflection could have occurred; these backward expansion waves were therefore artefactual.

Third, consistent with published figures [13, 18], both models predicted a mid-systolic FEW in WI^{RW} immediately following the initial FCW, resulting in a 40-80% fall in the forward component of pressure. However, in these models, the forward-running pressure component was prescribed to be invariant during mid-systole. Since the open valve was also prescribed to be reflectionless, it was known *a priori* that no forward waves were present between the initial FCW and the proto-diastolic FEW. We have previously shown that the aortic WI profile may contain a mid-systolic FEW arising from inertial effects, and although this wave plays a significant role in the context of inotropic stimulation, it is very small or absent under baseline conditions [7]. Thus, although a mid-systolic FEW may exist under some circumstances, our model data indicates that the reservoir-wave approach can introduce an artefactual FEW into the wave intensity profile.

Fourth, use of the three-bifurcation model indicated that altering the properties of a distal reflection site can change the amplitude of both forward and backward WI^{RW} waves that occur well before the arrival of the distally-reflected wave. This is not physically possible since it would require propagation of information at a speed greater than wave speed. With traditional WI , however, all waves occurring before the arrival of the distally-reflected wave were unchanged in amplitude.

The foregoing modelling results were corroborated by qualitatively similar differences between WI and WI^{RW} in baseline *in vivo* data, with WI^{RW} displaying 1) smaller backward compression waves, 2) larger backward expansion waves and 3) a mid-systolic forward expansion wave with substantial pressure effects. With progressive partial constriction of the descending aorta and brachiocephalic trunk, the BCW_{sys} increased in both WI and WI^{RW} (Fig. 7), analogous to the changes in wave ‘c’ for the

three-bifurcation model when the distal impedance was increased (Fig. 2). Thus, although the BCW_{sys} size may be underestimated by the reservoir-wave approach, the trend of changes appears to be similar regardless of the approach used. In addition, since the WT^{RW} BEW_{sys} and FEW_{ms} decreased as the arterial impedance increased, WT^{RW} may not always contain artefactual expansion waves, particularly in the context of high pulse pressure where positive wave reflection is probably more pronounced [15]. In all cases, however, the reservoir-wave separation appears to underestimate positive wave reflection.

In accord with previous findings [14, 18, 45], we have shown that traditional and reservoir-wave approaches to wave analysis can yield profoundly different conclusions regarding the overall design of the proximal arterial network. The predominance of backward compression waves using the traditional approach suggested that characteristic impedance increases when travelling away from the heart, whereas the predominance of backward expansion waves using the reservoir-wave approach suggested that this impedance decreases. Although the vascular properties of the adult sheep were not specifically determined, information from the modelling studies strongly suggest that the traditional approach yielded a more accurate view of the wave reflection properties of the arterial system.

A likely explanation for the underestimation of compression waves and overestimation of expansion waves observed with the reservoir-wave paradigm is that this approach does not account for the spatial non-uniformity of the reservoir pressure during systole. Calculation of reservoir pressure at multiple points along the aorta in the systemic arterial model indicated that this pressure is relatively uniform during diastole, as concluded previously [13], but not during systole. Our contour plot of model pressure

(Fig. 4C) is very similar to the *in vivo* plot presented by Wang et al [13], while our plot of p_{res} (Fig. 4D) shows that the reservoir pressure does not change uniformly during systole, a conclusion supported by previous model [22] and experimental data [20]. If the initial rise in p_{res} begins at the aortic valve and propagates distally, p_{res} exhibits wave propagation behaviour, suggesting that systolic wave effects cannot be wholly assigned to p_{ex} . Given that p_{res} increases during systole, its removal prior to wave analysis would therefore attenuate compression waves and introduce or amplify expansion waves.

Our findings and those of others [22] provide caution in considering wave and reservoir phenomena to be mutually exclusive as expressed in Equation (1). For example, it has been shown [22] that if there were no peripheral wave reflections, there would be no diastolic pressure decay and the reservoir pressure would be invariant over the whole cardiac cycle. However, if traditional wave analysis is the most appropriate approach, as our data suggests, how can the ‘self-cancelling’ diastolic waves, which have been considered an “artefact of events that occur outside the one-dimensional domain considered by the wave analysis” [14], be explained?

As a starting point, we note that mathematically, windkessel models are an approximation (or reduction) of 1D models [38, 46]. Thus all phenomena accounted for by the windkessel model must also lie within the explanatory power of the 1D model. Indeed, a wave-based explanation for the quasi-exponential decay of diastolic pressure has recently been proposed [22, 38], and relies on three main tenets. First, wave reflection in the arterial circulation is of a dispersed nature due to the tree-like vascular structure and tapering of the aorta. Second, since waves are not transmitted as efficiently in the backward direction as in the forward direction [32], multiple re-reflections lead to further wave incoherence and a degree of wave ‘trapping’. Third,

during diastole the aortic valve is closed and any backward-running waves are reflected almost completely, thus explaining why forward and backward components of the pressure/velocity change are equal/opposite during diastole. Since the magnitude of waves decreases exponentially and these waves become increasingly incoherent (i.e. spread out in space and time), the diastolic pressure decay tends to an exponential and spatial pressure differences disappear. Given that the reservoir pressure is generated by peripheral wave reflection, the mechanism underlying increases in pulse pressure with aging cannot be validly separated into independent ‘reservoir-related’ and ‘wave-related’ factors [15, 27].

Finally, several methodological issues require comment. First, transmission line theory is a linear technique. Thus, non-linearities in our 1D model, while physiologically realistic, were probably a factor underlying differences between Γ_Y and $\Gamma_{\Delta p}^T$ in the three-bifurcation model. Indeed, we found that running a quasi-linear simulation (by using a very small input pulse [29]) reduced all differences to less than 6%. Remaining differences were probably due to a combination of viscous losses [29] and minor overlap between adjacent waves. Second, while constriction of the descending aorta and brachiocephalic trunk in the sheep was an effective means of increasing the BCW_{sys} , the increase in pulse pressure with aging is probably associated with more spatially-distributed reflections [26].

In conclusion, results of our modelling studies suggest that the reservoir-wave paradigm introduces error into arterial wave analysis, with attenuation or elimination of compression waves and augmentation or artefactual introduction of expansion waves. These findings were consistent with *in vivo* data, provide an explanation for previous

observations and support the use of traditional wave analysis for investigating wave propagation and reflection.

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Table 1. Percentage difference between reflection coefficients calculated from transmission line theory (Γ_Y) and traditional ($\Gamma_{\Delta p}^T$) or reservoir-wave ($\Gamma_{\Delta p}^{RW}$) approaches for waves ‘a’, ‘b’ and ‘c’ in the three bifurcation model.

	$\Gamma_{\Delta p}^T$	$\Gamma_{\Delta p}^{RW}$
Wave	%	%
a ₁	8.7	-84.9
a ₂	8.8	-94.9
a ₃	7.4	-100.0
b ₁	-6.0	232.5
b ₂	-6.6	253.1
b ₃	-7.2	294.2
c ₁	-22.0	-86.7
c ₂	-17.0	-54.0
c ₃	-22.6	-42.6

Referring to Fig. 2, a₁,b₁,c₁ correspond to the solid black line, a₂,b₂,c₂ to the dashed black line, and a₃,b₃,c₃ to the solid grey line.

Table 2. Haemodynamics and two-element windkessel parameters (R_{res} , C_{res} and P^{∞}) in the adult sheep at baseline (BL) and after two levels of incremental arterial constriction (C1 and C2).

	HR	CO	MAP	PP	R_{res}	C_{res}	P^{∞}
	bpm	L/min	mmHg	mmHg	mmHg.s/mL	mL/mmHg	mmHg
BL	93±20	2.6±0.5	77±9 ^a	17±3 ^b	1.1±0.3	1.3±0.2 ^a	26±17
C1	93±21	2.6±0.4	81±11 ^c	26±2 ^c	1.2±0.7	1.1±0.2	31±22
C2	93±21	2.5±0.5	88±10	33±6	1.2±0.7	0.9±0.2	38±20

Abbreviations: heart rate (HR), cardiac output (CO), mean arterial pressure (MAP), pulse pressure (PP). ^a

$P \leq 0.01$; ^b $P < 0.001$, BL vs C1 and C2; ^c $P < 0.05$ C1 vs C2

Table 3. In vivo wave analysis using the traditional and reservoir-wave approaches.

	Traditional WIA			Reservoir-Wave WIA			<i>P</i>
	BL	C1	C2	BL	C1	C2	
<i>c</i> (m/s)	2.7±0.7	3.1±1.1	3.3±0.8	2.5±0.6	3.0±1.1	2.8±0.6	NS
<i>CI</i> (Wm ⁻² s ⁻¹ x10 ⁴)							
FCW _{ee}	2.39±0.45	2.41±0.59	2.75±0.84	2.04±0.45	1.99±0.43	2.11±0.70	0.04
FEW _{ms}	0.01±0.01 ^b	0.00±0.01	0.00±0.00	0.16±0.06 ^b	0.09±0.11	0.02±0.05	< 0.001
FEW _{pd}	1.64±0.51 ^b	2.12±0.58	2.60±0.64	1.56±0.61 ^c	2.07±0.53	2.51±0.62	NS
BCW _{sys}	-0.26±0.11 ^a	-0.40±0.23 ^d	-0.72±0.38	-0.04±0.05 ^a	-0.11±0.11	-0.22±0.20	< 0.001
BEW _{ee}	-0.04±0.04 ^a	-0.00±0.00	-0.01±0.01	-0.16±0.17 ^a	-0.03±0.05	-0.03±0.04	0.05
Δp (mmHg)							
FCW _{ee}	12.7±2.6	14.6±1.4	16.4±2.7	10.5±2.2	12.5±2.1	12.8±2.6	0.004
FEW _{ms}	-0.5±0.6 ^a	-0.2±0.4	0.0±0.0	-4.1±1.8 ^b	-2.2±2.7	-0.6±1.2	< 0.001
FEW _{pd}	-10.2±2.3 ^b	-12.9±1.0	-15.1±1.9	-10.2±3.0 ^b	-13.6±1.0	-14.7±1.8	NS
BCW _{sys}	6.2±1.1 ^b	8.2±1.5	11.5±3.0	1.2±1.0 ^a	3.2±2.8	4.6±3.0	< 0.001
BEW _{ee}	-1.0±0.8 ^a	-0.2±0.1	-0.3±0.4	-2.7±1.9 ^b	-1.1±1.6	-0.9±1.2	0.02

Abbreviations and symbols: wave speed (*c*), cumulative intensity (*CI*), wave-related pressure change

(Δp), recordings taken at baseline (BL) and at two levels of incremental arterial constriction (C1, C2).

Right-hand column compares traditional vs reservoir-wave approaches: ^a*P* < 0.05, ^b*P* ≤ 0.01, ^c*P* ≤ 0.002,

BL vs C1 and C2; ^d*P* < 0.05, C1 vs C2

Figure Legends

Fig. 1. (A) Schematic of the 1D model containing three bifurcations (denoted 'a', 'b' and 'c'). Compression and expansion waves are indicated by solid and outlined arrows respectively. Terminal 1D segments are longer than drawn (indicated by broken lines). (B) The unit pressure impulse response at the inlet of the model, predicted via transmission line theory. The input is a forward pressure-increasing wave, while backward-running pressure waves 'a', 'b' and 'c' arise from the corresponding reflection sites in (A). Abbreviations: IC, isovolumic contraction; E, ejection; IR, isovolumic relaxation; DF, diastolic filling.

Fig. 2. (A) Forward and backward components of pressure (p) and wave intensity (WI) at the inlet of the three-bifurcation model (Fig. 1). (B) Corresponding components of excess pressure (p_{ex}) and the reservoir-wave version of wave intensity (WI^{RW}). See text for explanation of waves labelled a-c.

Fig. 3. Forward and backward components of p (A) and p_{ex} (B) in the aortic root of the systemic arterial circulation model, with corresponding components of WI and WI^{RW} . Filled and outlined arrows identify compression and expansion waves respectively.

Fig. 4. Pressure-distance-time plots of (A) pressure, p , and (B) the reservoir pressure, p_{res} , along the aorta of the systemic arterial circulation model. Corresponding contour plots of (C) p and (D) p_{res} , where the arrows indicate a propagating wave front whose local slope is equal to local wave speed. (E) Maximum spatial difference of p and p_{res} at each time point.

Fig. 5. Aortic root flow (q_{in}), measured and reservoir pressures (p and p_{res}) and their forward and backward-running components ($p_{\pm}$ and $p_{\text{ex}\pm}$) in an adult sheep. During mid-systole, traditional wave intensity ($WI_{\pm}$) displayed backward compression waves (solid arrows) and negligible forward waves, while the reservoir-wave version of wave intensity ($WI_{\pm}^{\text{RW}}$) displayed a predominance of backward expansion waves and a forward expansion wave (open arrows). See text for wave abbreviations.

Fig. 6. The ratios of the pressure effects of (A) the mid-systolic backward compression wave (BCW_{ms}), (B) the early-ejection backward expansion wave (BEW_{ee}) and (C) the mid-systolic forward expansion wave (FEW_{ms}) to the pressure effect of the early-ejection forward compression wave (FCW_{ee}), using traditional and reservoir-wave pressure separation (solid squares and open circles respectively) at baseline (BL) and at the two levels of constriction (C1 and C2). Traditional vs. reservoir-wave: * $P < 0.01$, † $P < 0.001$; Baseline vs C1 & C2: ^a $P = 0.08$ (trend), ^b $P \leq 0.02$, ^c $P = 0.002$; ^d $P = 0.03$.

Fig. 7. Traditional (A) and reservoir-wave (B) cumulative intensity ratios of all systolic backward compression waves (BCW_{sys}) or all systolic backward expansion waves (BEW_{sys}) and the early-ejection forward compression wave (FCW_{ee}). * $P < 0.03$, † $P < 0.001$, BCW_{sys} vs BEW_{sys} ratio.