SUPPLEMENTAL MATERIAL
Data S1. Supplemental Methods

Input Impedance of Uniform Tube Models

Model A. Uniform Elastic Tube with a Resistive Load

Input impedance of this model is expressed in its most general form as

$$Z_{in,\text{INF}}(j\omega) = Z_c \frac{1+\Gamma_{LA}(j\omega)e^{-j2\omega\tau_A}}{1-\Gamma_{LA}(j\omega)e^{-j2\omega\tau_A}} \quad (1)$$

where $Z_c$ is characteristic impedance of the tube and $\tau_A$ is the one-way wave transit time to the reflection site at the terminal end of the tube.

$\Gamma_{LA}(j\omega)$ is the load reflection coefficient seen at the termination, where $Z_L(j\omega)$ is the terminal load impedance:

$$\Gamma_{LA}(j\omega) = \frac{Z_{LA}(j\omega)-Z_c}{Z_{LA}(j\omega)+Z_c} \quad (2)$$

In the case of a purely resistive load, the load impedance $Z_L(j\omega)$ is frequency-independent and is simply equal to total peripheral resistance $R_p$. This reduces the load reflection coefficient to a purely real number in the mathematical sense (i.e. frequency-independent).

$$\Gamma_{LA} = \frac{R_p-Z_c}{R_p+Z_c} \quad (3)$$

Input impedance can then be expressed in its final form:

$$Z_{in,\text{INF}}(j\omega) = Z_c \frac{1+\Gamma_{LA}e^{-j2\omega\tau_A}}{1-\Gamma_{LA}e^{-j2\omega\tau_A}} \quad (4)$$

With values of three parameters {$R_p$, $Z_c$, $\tau_A$}, a continuous input impedance spectrum can be obtained.

In the case of time to inflection point on the pressure waveform ($T_{\text{INF}}$), $\tau_A$ is one half this value, $\tau_A = 0.5*T_{\text{INF}}$. $Z_c$ is characteristic impedance of the aorta, estimated from pressure-flow data using standard methods, and $R_p$ is the ratio of mean arterial pressure to cardiac output.

Use of the quarter wavelength formula to estimate “effective length” ($L_{\text{eff}}$) of the arterial system or equivalently, “effective reflection distance” (ERD), assumes this particular input impedance model, where PWV is pulse wave velocity and $f_{\text{min}}$ is the frequency at the first minimum of the impedance modulus.²

$$L_{\text{eff,INF}} = ERD_{\text{INF}} = \frac{PWV}{4f_{\text{min}}} \quad (5)$$

In this model, the first zero-crossing of impedance phase occurs at the same frequency ($f_{\infty}$) as $f_{\text{min}}$.

Since use of equation (5) requires both pressure and flow waveforms to determine $f_{\text{min}}$ (impedance analysis), attempts have been made to determine a surrogate of $f_{\text{min}}$ from analysis of the pressure waveform alone (i.e. $T_{\text{INF}}$). It has been reported that $T_{\text{INF}}$ determined from analysis...
of the pressure waveform alone correlates well to \( f_{\text{min}} \) from impedance data, such that the following relation can be substituted for \( f_{\text{min}} \):

\[
f_{\text{min}} = \frac{1}{2T_{\text{INF}}} \]

Upon substitution into equation (5), this leads to the commonly used equation for effective reflection distance, using pressure-waveform-only analysis along with a measurement of PWV:

\[
L_{\text{eff, INF}} = ERD_{\text{INF}} = \frac{\text{PWV}}{2} T_{\text{INF}}
\]

The reported high correlation between \( T_{\text{INF}} \) and \( f_{\text{min}} \) is important so long as the input impedance implied by the underlying model can suitably approximate measured arterial input impedance. Figure S2A shows input impedance implied by this model for each decade of age in the healthy aging sample.

It can be appreciated that there are strong dissimilarities with patterns of reported arterial input impedance in the literature.\(^2,4,5\) Note the strong oscillation in the impedance modulus plot. This would indicate very strong reflections in the higher frequencies, which is inconsistent with patterns encountered \textit{in vivo}. Furthermore, the phase angle of Figure S2A oscillates strongly between very negative to very positive values.

**Model B. Uniform Elastic Tube with a (Complex) Frequency-Dependent Load**

In order to better match the classical tube models to the complex and frequency-dependent reflection coefficients encountered \textit{in vivo}, a terminal load that accounts for the low-pass filtering features of the distal circulation can be incorporated.\(^6\)

Load impedance can then be expressed in terms of \( R_p \), load compliance (\( C_l \)), and a high-frequency resistive element (\( R_d \)). Input impedance of this model (\( Z_{\text{in,B}} \)) can be made to match aortic \( Z_c \) with increasing frequency, as encountered \textit{in vivo}, if \( R_d \) is expressed as follows:

\[
R_d = \frac{R_p Z_c}{R_p - Z_c}
\]

Load impedance of this model, \( Z_{L,B}(j\omega) \) is expressed as

\[
Z_{L,B}(j\omega) = R_p \frac{1 + j\omega \tau_n}{1 + j\omega \tau_d}
\]

where the time constants (\( \tau_n, \tau_d \)) are defined as

\[
\tau_n = R_d C_l \\
\tau_d = (R_p + R_d) C_l
\]

The reflection coefficient seen at load is thus frequency-dependent

\[
\Gamma_{L,B}(j\omega) = \frac{Z_{L,B}(j\omega) - Z_c}{Z_{L,B}(j\omega) + Z_c}
\]

and input impedance of this model can be fully expressed as

\[
Z_{\text{in,TL}}(j\omega) = Z_c \frac{1 + \Gamma_{L,B}(j\omega)e^{-j\omega \tau_B}}{1 - \Gamma_{L,B}(j\omega)e^{-j\omega \tau_B}}
\]
$\tau_B$ is the one-way wave transit time to the reflection site in this model, equal to one half of $RWTT_{TL}$ used in the current study.

ERD can then be calculated as

$$L_{eff,TL} = ERD_{TL} = PWV \times \tau_B = PWV \frac{RWTT_{TL}}{2} \quad (11)$$

Figure S2B shows input impedance implied by this model for each decade of age in the healthy aging sample. These patterns resemble much more closely the reported arterial input impedance patterns with aging.\textsuperscript{2,4,5,7,8}

**Data S2. Supplemental Discussion**

*Quarter Wavelength Formula Overestimates Effective Reflection Distance*

As clarified by Burattini *et al*\textsuperscript{6,9,10}, when the effective reflection site is more suitably represented by a complex reflection coefficient, the ERD can be computed as

$$ERD = \frac{PWV}{4 f_{zc}} \left(1 + \frac{\varphi(f_{zc})}{\pi}\right),$$

where $f_{zc}$ is the frequency at which the input impedance angle crosses zero and $\varphi(f_{zc})$ is the phase of the effective (load) reflection coefficient at frequency of $f_{zc}$; note that the quarter wavelength formula emerges when $\varphi(f_{zc})$ is set to zero. Because the phase of reflection $[\varphi(f_{zc})]$ is generally negative in vivo\textsuperscript{9,11–13}, ERD calculations that account for the phase of reflection will necessarily be less than values computed by the quarter wavelength formula. This explains why the frequently reported values of ERD employing the quarter wavelength formula\textsuperscript{4,14,15,5,16} are significantly higher than values we report here using tube-load modeling. The general acceptance and frequent reporting of ERD estimates\textsuperscript{5,17} of around 0.5 m computed by the quarter wavelength formula may indeed be consensus-based (since 0.5 m from the heart is close to the terminal aortic bifurcation and apparently plausible) rather than on appropriate use of a suitable reduced model of the arterial system.

*Early-Systolic (Before Peak Flow) Reflections*

In regards to the apparent reflection-free early-systole implied by $T_{INF}$, the hemodynamic literature provides support for the existence of early-systolic effects of wave reflections. In a study of seven mongrel dogs in which invasive and simultaneous measurements of aortic pressure and flow were analyzed\textsuperscript{6}, Burattini and Di Carlo found that one-way wave transit times (to an effective reflection site) averaged 14 msec (calculated as $\sqrt{(ld)(cd)}$ from their Table I), giving a $RWTT_{TL}$ of 28 msec. This timing precedes time of peak flow and the inflection point observed on the aortic pressure waveforms, which occurred around 50 msec. In another study combining a large-scale model of the systemic arterial tree based on Womersley’s theory and dog experiments, $RWTT_{TL}$ averaged 37.2 msec.\textsuperscript{18} Although the studies employed the same tube-load model we use in the present study (for estimating $RWTT_{TL}$), it can be appreciated that both their invasive and numerical and our noninvasive studies agree that significant effects of reflection can precede time of peak flow (and $T_{INF}$).
With the additional measurement of descending thoracic aortic flow, studies of wave reflection can be extended to the modified asymmetric T-tube model. Applying this model to dogs, Shroff et al. found one-way transit times to effective reflection sites in the head-end and body-end circulations of approximately 25 msec and 55 msec, respectively, during control conditions; peak flow occurred around 60 msec and calculated RWTT from the head-end circulation (~50 msec) preceded peak flow. Burattini and Campbell, applying the same model, similarly found times of 26.5 msec and 68.5 msec for head-end and body-end circulations, with peak flow similarly occurring at around 60 msec. Consistent with these invasive studies, when the timing of arterial wave reflections is assessed using both pressure and flow measurements (as opposed to pressure-only analysis), along with a suitable arterial system model, there is no theoretical support for a reflection-less state until the time of peak, nor there is a need to make this assumption.

Reports evaluating time-domain techniques to estimate aortic characteristic impedance from early-systolic pressure-flow relationships also lend support for reflections that can occur prior to time of peak flow. Estimations of aortic Zc vary depending on the region chosen on the early-systolic pressure-flow waveforms, with various authors invoking different criteria to minimize the effects of reflections (e.g. first 60 msec of ejection, period up to 95% of peak flow, peak derivatives, etc.). Evidence of early-systolic wave reflections have also been found when estimating local pulse wave velocity in both in vivo and in 3D fluid-structure interaction simulation studies. It was shown that an apparent linear early-systolic relation between pressure and flow (velocity) is insufficient to conclude a reflection-free period in early-systole; wave reflections can cause under- and over-estimation of local pulse wave velocity. Therefore, applying methods that purportedly track timing of wave reflections but are apparently blind to early-systolic wave reflections should be discouraged, since they lead to artificial asymptotes when studied across a large range of age.

Modeling Study: RWTT_{WSA}/ERD_{WSA} Confounded by the Phase of Reflection

We note that the pattern of changes in RWTT_{WSA} with aging roughly parallels that of RWTT_{TL} across the age spectrum studied. We conducted a modeling study (below), which confirmed that the apparent discrepancy in absolute RWTT values is due to the fact that RWTT_{WSA} does not account for complex nature of the reflection coefficient (i.e. frequency-dependent in magnitude and phase) encountered in vivo, whereas tube-load modeling implicitly does. Therefore, time delay measures between P_f and P_b represent an accurate estimate of RWTT if phase shifts at the reflection site are assumed to be absent. RWTT_{TL} emerges as the most logically consistent and theoretically justifiable measure of RWTT.

A model of the left ventricle (LV) coupled to the aorta terminating in a complex load was used to demonstrate the effects of the phase of reflection on RWTT_{WSA} and ERD_{WSA}. This model incorporates a single (complex) reflecting site at a known distance from the heart (28 cm).

The parameters characterizing the LV model: E_{max} = 1.53 mmHg•mL^{-1}; E_{min} = 0.08 mmHg•mL^{-1}; EDV = 157 mL; HR = 75 bpm; k = 0.0005 s•mL^{-1}.
The parameters used in the arterial system model: \( PWV = 700 \text{ cm/s} \); \( d = 28 \text{ cm} \); \( Z_0 = 0.079 \text{ mmHg s mL}^{-1} \); \( R_p = 0.85 \text{ mmHg s mL}^{-1} \); \( C = 1.21 \text{ mL mmHg}^{-1} \).

Aortic input impedance of the model is shown in Figure S4. The vertical red line indicates the frequency of the impedance modulus minimum. The vertical purple line indicates the frequency at which the phase crosses zero. Consistent with impedance patterns observed \textit{in vivo}, these two frequencies are not identical.\textsuperscript{6,30}

Aortic pressure and flow waveforms from the model are shown in Figure S5A. After wave separation analysis, the forward and backward pressure waves are shown in Figure S5B. The dashed vertical red and green lines indicate the zero-crossings of the backward and forward pressure waves, respectively.

\( \text{RWTT}_{\text{WSA}} \) was calculated as 160 msec and with use of the known \( PWV=700 \text{ cm/s} \), \( \text{ERD}_{\text{WSA}} \) is estimated as 56 cm. In this case, length of the aorta is overestimated by 100\% (known length of the aorta is 28 cm), due to the phase shift caused by reflection at the complex load. This is the same limitation encountered by using \( T_{\text{INF}} \) as reflection timing; \( \text{RWTT}_{\text{WSA}} \) and \( T_{\text{INF}} \) will provide accurate estimates of reflection timing only if reflection coefficients encountered \textit{in vivo} are purely real (e.g. that vascular compliance and wave transmission phenomena are non-existent outside the aorta). It is interesting to note that the overestimation of \( \text{ERD} \) by \( \text{ERD}_{\text{WSA}} \) of this example is on the same order of magnitude observed in the younger adults of the present study (Figure 2); accounting for the different phases of reflection for each subject, as implicit in the \( \text{RWTT}_{\text{TL}} \) and \( \text{ERD}_{\text{TL}} \) procedure used in the present study, resolves the overestimation.
Figure S1. Example of a case in which the zero-crossing of $P_b$ is poorly defined. Due to the presence of noise, particularly on high-frequency features of pressure and flow waveforms, single-point landmarks (e.g. zero-crossing, ‘foot’) may be ambiguous. Note that there is no apparent ‘foot’ to the backward wave (due to the presence of multiple reflection sites in vivo). Empirically imposing a ‘foot’ to $P_b$ may amplify the significance of high-frequency artefacts (e.g. due to pressure-flow alignment processes, use of surrogate waveforms, etc.).
Figure S2. Arterial input impedance implied by (A) $T_{\text{INF}}$ and the quarter wavelength formula, and (B) tube-load modeling with a complex and frequency-dependent load for each decade of age in the clinical sample. Vertical lines correspond to the frequencies of impedance modulus minimum and phase angle zero-crossings.
**Figure S3.** Arterial input impedance implied by (A) $T_{\text{INF}}$ and the quarter wavelength formula, and (B) tube-load modeling with a complex and frequency-dependent load for each decade of age in the general sample. Vertical lines correspond to the frequencies of impedance modulus minimum and phase angle zero-crossings.
Figure S4. Aortic input impedance from the model-based study. The vertical red and purple lines correspond to the frequencies at which the impedance modulus is minimum and the phase angle crosses zero degrees, respectively. As generally encountered in vivo, these two frequencies are not identical.
Figure S5. (A) Aortic pressure and flow waveform from the model-based study. (B) Aortic pressure separated into its forward and backward traveling components. The vertical dashed green and red lines correspond to the zero-crossings of the forward and backward waves, respectively.
Figure S6. Carotid-radial PWV measurements were available in the clinical population sample. The reported\textsuperscript{15} trend of carotid-femoral PWV surpassing muscular artery PWV is reproduced in our clinical sample. Contrary to the age-related impedance-matching interpretation of this PWV-gradient cross-over, pressure-flow analyses reveal earlier effects of reflection.
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