Assessment of ventriculo-arterial interaction in pulmonary arterial hypertension using wave intensity analysis

To the Editor:

Wave intensity analysis (WIA) is a recently described haemodynamic analysis methodology which enables assessment of ventriculo-arterial interactions via time-domain analysis of pressure and flow waveforms [1]. It enables quantification of wave energy, separation of waves into forward and backward components, and estimation of wave speed [2]. To date, WIA has not been applied to the pulmonary arterial circulation in humans. As WIA offers a potential novel approach for the study of pulmonary haemodynamics, the present study sought to evaluate the feasibility of invasive WIA of the pulmonary circulation during right heart catheterisation (RHC).

The study was approved by the institutional review board (Sydney Local Health District Ethics Review Committee (RPA Zone)) and consent was obtained from seven controls (mean ± SD age 69 ± 9 years, three females) and six patients (age 56 ± 13 years, four females) with pulmonary arterial hypertension (PAH). Control subjects presented to the cardiac catheterisation laboratory for investigation of possible coronary artery disease. Following standard pulmonary haemodynamic measurements (including thermodilution cardiac output), a combined dual-tipped pressure and Doppler wire (ComboWire; Volcano, Rancho Cordova, CA, USA) was positioned distal to the origin of the right or left lower lobe pulmonary artery via a 6 Fr multipurpose catheter (Mach 1; Boston Scientific, Natick, MA, USA) under angiographic guidance. Pressure and flow measurements were acquired simultaneously at a sampling frequency of 1000 Hz, once stable signals were obtained.

Data were processed offline using customised MatLab software (MathWorks, Natick, MA, USA). Signals were ensemble-averaged with timing gated to the ECG R-wave and smoothed using a Savitzky–Golay filter [3]. Intrinsic hardware processing delays (between pressure and flow signals) were corrected by shifting signals to achieve a linear pressure–flow (P–U) relationship in early systole [4]. Wave speed (c) was derived from the P–U loop method [2]:

\[ c = \frac{(dP/dU)}{\rho} \]

where \( dP/dU \) is the slope of P–U loop in early systole and \( \rho \) is density of blood, assumed to be 1060 kg m\(^{-3}\).

WIA was performed as previously described [3] with separation of waves into forward (\( dI_+ \)) and backward (\( dI_- \)) wave intensities:

\[ dI_+ = +\left(\frac{(dP/dt + \rho c \times dU/dt)^2}{4\rho c}\right) \]
\[ dI_- = -\left(\frac{(dP/dt - \rho c \times dU/dt)^2}{4\rho c}\right) \]

Total wave energy for separated waves was calculated by integration of wave intensities over time. The magnitude of wave reflection (reflection coefficient) was calculated as the ratio of the total forward compression wave intensity to the total backward compression wave intensity [5]. The reflection distance (L) from the measurement site was estimated from the time delay between the peaks of the forward and backward compression waves, together with knowledge of wave speed:

\[ L = c\Delta t/2 \]

Results are presented as mean ± SD, unless otherwise stated. Differences between groups were compared using the Mann–Whitney U-test. Correlation was performed using Pearson’s test. Significance was inferred at a two-sided \( p<0.05 \).

The aetiologies of PAH were idiopathic PAH \((n=3)\), scleroderma PAH \((n=2)\) and portopulmonary hypertension \((n=1)\). Haemodynamics in PAH group revealed a mean pulmonary arterial pressure (PAP) of 41 ± 5 mmHg, pulmonary vascular resistance (PVR) of 6.3 ± 4.4 Wood units and pulmonary capillary wedge pressure (PCWP) of 8 ± 3 mmHg. Controls had normal pulmonary haemodynamics (mean PAP of 16 ± 5 mmHg, PVR of 1.3 ± 0.7 mmHg, and PCWP of 8 ± 3 mmHg).
In both control and PAH groups, three dominant waves were consistently identified: 1) a forward compression wave (FCW) in early systole corresponding to ventricular ejection; 2) a forward expansion wave (FEW) in late systole representing ventricular relaxation and deceleration of blood flow; and 3) a backward compression wave (BCW) related to downstream reflection of the incident FCW (fig. 1).

PAH patients displayed an increase in the total intensity in all of the identified waves (total FCW of $164.5 \pm 39.7 \times 10^2 \text{W} \cdot \text{m}^{-2} \cdot \text{s}^{-1}$ versus $88.3 \pm 20.7 \times 10^2 \text{W} \cdot \text{m}^{-2} \cdot \text{s}^{-1}$ in controls; total FEW of $85.1 \pm 36.0 \times 10^2 \text{W} \cdot \text{m}^{-2} \cdot \text{s}^{-1}$ versus $32.5 \pm 13.7 \times 10^2 \text{W} \cdot \text{m}^{-2} \cdot \text{s}^{-1}$ in controls; all $p<0.01$), with the most notable difference being a five-fold increase in the total BCW wave intensity (total BCW of $56.9 \pm 14.6 \text{W} \cdot \text{m}^{-2} \cdot \text{s}^{-1}$ versus $10.7 \pm 5.6 \text{W} \cdot \text{m}^{-2} \cdot \text{s}^{-1}$ in controls; $p<0.01$). Importantly, the total BCW intensity was proportionally larger relative to the total FCW intensity in PAH patients, resulting in a higher reflection coefficient ($0.35 \pm 0.05$ versus $0.11 \pm 0.06$; $p<0.01$). Wave speed was significantly faster in PAH patients ($6.9 \pm 1.3 \text{m} \cdot \text{s}^{-1}$ versus $3.8 \pm 1.0 \text{m} \cdot \text{s}^{-1}$; $p<0.01$), leading to earlier arrival ($45 \pm 20 \text{ms}$ versus $89 \pm 30 \text{ms}$; $p<0.01$) of the reflected BCW in mid-systole. The estimated reflection site in PAH patients was $15 \pm 5$ cm downstream from the measurement site in the proximal lower lobe artery. Wave speed correlated significantly with pulmonary capacitance ($r=0.7$, $p<0.01$).

To the best of our knowledge, this is the first study to apply WIA for the evaluation of pulsatile wave travel in the human pulmonary arterial circulation. WIA was feasible during routine RHC using a commercially available dual-tipped pressure and Doppler wire, and revealed relevant pathophysiological changes in PAH subjects characterised by: 1) increased wave reflections due to distal closed-end reflection sites; 2) increased energies of travelling waves indicating increased right ventricular workload; and 3) higher wave speed due to arterial stiffening resulting in earlier arrival of large reflected waves, augmenting afterload unfavourably in the still-ejecting right ventricle. The potential appeal of WIA is that these pathophysiological changes can be quantified in an integrative time-domain approach.

Time-domain analysis of pulmonary artery waveforms using invasive high-fidelity measurements has previously been limited to pressure waveforms only [6]. It has been suggested that pulmonary artery pressure waveform analysis can assess the timing, extent and magnitude of wave reflections [7]. However, time-domain pressure waveform analysis is critically dependent on the accurate determination of the inflection point, which may not be identifiable in all patients [8] and may, thus, result in erroneous estimation of wave reflection indices [9]. By combining pressure and flow waveforms, WIA overcomes such limitations of isolated pulmonary artery pressure waveform analysis, and potentially provides an improved

![Wave intensity analysis](image_url)
assessment of wave reflection. Furthermore, WIA enables determination of local wave speed, allowing estimation of reflection site distances. However, it is unknown, at present, whether WIA can discriminate differences in reflection sites in chronic thromboembolic pulmonary hypertension (CTEPH) versus PAH, and whether it can aid in the partitioning of predominately proximal versus distal disease in CTEPH.

Pulmonary artery impedance analysis has been the traditional method used to fully characterise pulsatile right ventricular afterload [10, 11]. As the impedance spectrum is presented in the frequency-domain, interpretation is not straightforward and is unintuitive for most clinicians. WIA offers an alternate approach to impedance analysis, and it has been demonstrated that both impedance and WIA can provide similar results for the separation of forward and backward waveforms [12], with WIA having the distinct advantage of data presentation in the time-domain. However, impedance and WIA are not interchangeable in other aspects. WIA describes wave energy which is a function of both the pump and the vasculature, whereas impedance provides information regarding right ventricular afterload (or the arterial system).

Some methodological limitations need to be acknowledged. Obtaining high quality in vivo measurements was challenging and it was technically difficult to achieve a stable catheter position in the main pulmonary artery (the ideal anatomical position as the entire circulation is “seen”); therefore, the lower lobe vessels were studied. It is unknown whether WIA (or impedance) will differ between the upper or lower lobe pulmonary artery in healthy and PAH subjects in the supine posture, as we are not aware of any previous literature on this subject. Numbers of subjects were small in this preliminary study, but the differences between groups were very marked.

In conclusion, we demonstrate, in this preliminary “proof of principle” study, that WIA of the pulmonary circulation is feasible during RHC and may offer a novel time-domain based approach for the assessment of ventriculo-arterial interactions in pulmonary vascular disease. Further validation studies are required to determine whether parameters derived from WIA provide incremental clinical information, additional to conventional haemodynamics, regarding prognosis and response to therapy.

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Demonstration that wave intensity analysis of the pulmonary circulation is feasible during right heart catheterisation http://ow.ly/rH5bE

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References
