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A review of wave mechanics in the pulmonary artery with an emphasis on wave intensity analysis

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Abstract

Mean pulmonary arterial pressure and pulmonary vascular resistance remain the most common hemodynamic measures to evaluate the severity and prognosis of pulmonary hypertension. However, pulmonary vascular resistance only captures the non-oscillatory component of the right ventricular hydraulic load and neglects the dynamic compliance of the pulmonary arteries and the contribution of wave transmission. Wave intensity analysis offers an alternative way to assess the pulmonary vasculature in health and disease. Wave speed is a measure of arterial stiffness and the magnitude and timing of wave reflection provide information on the degree of impedance mismatch between the proximal and distal circulation. Studies in the pulmonary artery have demonstrated distinct differences in arterial wave propagation between individuals with and without pulmonary vascular disease. Notably, greater wave speed and greater wave reflection are observed in patients with pulmonary hypertension and in animal models exposed to hypoxia. Studying wave propagation makes a valuable contribution to the assessment of the arterial system in pulmonary hypertension and here, we briefly review the current state of knowledge of the methods used to evaluate arterial waves in the pulmonary artery.

Keywords

pulmonary circulation; pulse wave velocity; wave intensity analysis; wave reflection

Introduction

Mean pulmonary arterial pressure (PAPm) and pulmonary vascular resistance (PVR) are the most common hemodynamic measurements used to assess the progression of pulmonary hypertension (PH, defined as PAPm ≥ 25 mmHg). However, they do not correlate closely with the degree of right ventricular (RV) dysfunction (Champion *et al.* 2009) and although

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pharmacological treatment of PH lowers PAPm and PVR (Galie *et al.* 2009, Macchia *et al.* 2007), a reduction in PVR may not be associated with an improvement in RV function and prognosis (van de Veerdonk *et al.* 2011).

While the importance of wave travel and wave reflection in assessing disease severity and treatment outcome is widely accepted in systemic hypertension (Ghiadoni *et al.* 2009), the significance of travelling waves in the pulmonary circulation is less studied. This review will summarise what is known and what remains to be established, with a particular focus on the potential utility of wave intensity analysis, a time-domain based approach to wave mechanics in the circulation.

Pulmonary hypertension

The underlying pathology in PH is pulmonary vasoconstriction, vascular remodelling, inflammation and thrombosis resulting in increased PVR and arterial stiffness (Chan & Loscalzo 2008). PH is commonly seen secondary to left heart disease (Guazzi & Galie 2012) and lung disease (Ruggiero *et al.* 2012). The most severe forms, however, occur in the forms of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) (Chemla *et al.* 2002), where the main cause of death is right heart failure. RV afterload is determined by the complex relationship between the resistance, the dynamic compliance as well as the magnitude of wave reflection in the pulmonary circulation (Lammers *et al.* 2012). RV failure in PH occurs when adaptive mechanisms such as RV dilatation and hypertrophy cannot compensate for the increased load caused by the altered pulmonary hemodynamics (Chemla *et al.* 2002). The characteristics of travelling waves are determined by ventricular ejection, which in turn is determined by ventricular preload and contractility, as well as the properties of the arterial system it ejects into. Thus, studying wave mechanics makes a distinctive contribution to the assessment of pulmonary hemodynamics.

Travelling Waves

A mechanical wave is a propagated perturbation that transports energy without the need of transport of material (Lighthill 2001). For the purpose of this review we will use the term “waveform” when we refer simply to the undulating shape described by a pressure or flow velocity signal. Wave travel in arteries occurs as a result of the interchange between the kinetic energy of the moving blood and the potential energy stored in the elastic arterial walls (Parker 2009). In large arteries it is assumed that wave propagation occurs with negligible viscous losses, i.e. plug flow (Alastruey 2006). Waves in arteries can be characterized in terms of direction – forward or backward, and their effect on pressure – compression waves increase the pressure while decompression (also termed expansion or rarefaction) waves decrease the pressure (Hughes *et al.* 2008).

The speed at which waves propagate, the wave speed or the pulse wave velocity (PWV), depends on the stiffness and dimensions of the blood vessel (if blood is assumed incompressible and the viscous behaviour of the wall and fluid is neglected). Under these assumptions, PWV can be calculated using the Moens-Korteweg equation (1) or the Bramwell and Hill equation (2) (Mackenzie *et al.* 2002).

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$$PWV = \sqrt{\frac{Eh}{2r\rho}} \quad (1)$$

$$PWV = \sqrt{\frac{\Delta PV}{\Delta V\rho}} = \sqrt{\frac{1}{D\rho}} \quad (2)$$

where E is the elastic modulus of the vessel wall, h is the thickness, r is the vessel radius, ρ is the density of the blood, ΔP and ΔV are the changes in pressure and volume, respectively, and D is the vessel distensibility.

PWV is often calculated as the distance divided by the transit time of the pressure or flow waveform between two measuring sites, e.g. using the foot-to-foot velocity method. In the systemic circulation, non-invasive PWV is relatively simple to acquire and the clinical value of carotid-femoral PWV in predicting cardiovascular events is well documented (Ben-Shlomo *et al.* 2014, Laurent *et al.* 2001). PWV in the pulmonary artery, though less investigated, has been shown to be increased in patients with PH (Kopec *et al.* 2013, Milnor *et al.* 1969).

Wave speed (i.e. local PWV) can also be calculated from the ratio of the change in pressure and change in flow velocity during early systole when it is assumed that reflected waves are minimal (Hanya 2013, Hughes & Parker 2009). Wave speed or characteristic impedance can be used to separate the measured pressure (P) and flow (Q) waveforms into their forward (P_f, Q_f) and backward (P_b, Q_b) components (Segers *et al.* 2007, Westerhof *et al.* 1972). The forward and backward pressure and flow waves depend on the heart and its load and thus do not give unambiguous information about changes in ventricular function and arterial function.

Forward travelling waves are generally related to changes in the rate of myocardial shortening (e.g. ejection or protodiastole), while backward waves are usually due to reflection. Waves are reflected as a result of a change in energy transmission properties of the artery; when a propagating wave encounters a discontinuity in impedance, e.g. branches, changes in vessel diameter or changes in stiffness, it undergoes reflection. Reflected waves can be compression or decompression waves depending on the nature of the incident wave and the characteristics of the impedance mismatch (Parker 2009). Re-reflection of waves (i.e. backward waves reversing direction and travelling forward) have also been demonstrated in some circumstances (Zambanini *et al.* 2005). Reflected waves have their greatest magnitude close to their site of origin and their intensity diminishes as they travel retrogradely towards the heart (Baksi *et al.* 2016), probably as a result of wave entrapment (Davies *et al.* 2012). Wave entrapment occurs due to the asymmetry in the reflective properties of arterial bifurcations, which facilitates forward wave propagation, but impedes backward travel of discrete waves. Reflected waves may interfere with optimal ventricular ejection performance depending on their intensity and/or timing. For instance, early reflected compression waves associated with high PWV that arrive at the ventricle during

contraction augment pressure and decrease forward flow thereby imposing an additional load on the contracting ventricle (Lammers *et al.* 2012).

The magnitude of wave reflection can be assessed in a number of ways: 1) the ratio of backward to forward pressure (the ratio of backward to forward flow is equivalent but rarely used), 2) the ratio of backward pressure to the total pulse pressure (Westerhof *et al.* 2006). The former is variously termed the reflection magnitude (RM) (Westerhof *et al.* 2005), the reflection factor or reflectance in the literature (Nichols *et al.* 2011):

$$RM = \frac{P_b}{P_f} = -\frac{Q_b}{Q_f} \quad (5)$$

It should be mentioned that this ratio is also sometimes termed the reflection coefficient but this term is more properly reserved for the more general equation describing the complex reflection coefficient (CRC) (Nichols *et al.* 2011). Note that RM is a time domain parameter, while CRC is a frequency domain measure derived from vascular impedance analysis.

$$CRC = \frac{Z_{in} - Z_c}{Z_{in} + Z_c} \quad (6)$$

where Z_{in} is the vascular input impedance and Z_c is an estimate of the characteristic impedance of the system i.e. the relationship between pressure and flow if there were no reflections in the system and is determined principally by the ratio of fluid inertia to arterial compliance (Lammers *et al.* 2008, Wang & Chesler 2011). The local reflection coefficient can also be determined by using the characteristic impedances of the mother (m) and daughter (d) tubes (Segers *et al.* 2006). Hence:

$$\text{Local CRC} = \frac{Z_{c,d} - Z_{c,m}}{Z_{c,d} + Z_{c,m}} \quad (7)$$

When wave intensity is used (see below), wave reflection, 3) denoted as the wave reflection index (WRI), can be quantified as the ratio of the integrals of the backward (BCW) to forward (FCW) compression waves (Manisty *et al.* 2009):

$$WRI = \frac{\sum BCW}{\sum FCW} \quad (8)$$

WRI correlates closely with RM in the systemic circulation (Hughes *et al.* 2013a).

Other parameters include the ratio of backward pressure to the total pulse pressure (i.e. sum of backward and forward pressure) – termed the reflection index (RI), which is comparable in formulation to the augmentation index (AI_x) (Hirata *et al.* 2006):

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$$RI = \frac{P_b}{P_f + P_b} \quad (9)$$

$$AI_x = \frac{\Delta P}{pP} \quad (10)$$

where ΔP is the augmentation pressure (the difference in pressure between the shoulder or peak of pressure waveform in early systole, and the second peak, or shoulder of the pressure waveform in late systole), and pP is the pulse pressure. AI_x has been used as an approximate estimate of wave reflection in the pulmonary circulation, where AI_x was found to be higher and the inflection time shorter in patients with CTEPH, a proximal artery disease, than in patients with PAH, a distal artery disease (Castelain *et al.* 2001, Nakayama *et al.* 2001). The use of AI_x as a measure of wave reflection in the systemic circulation has been criticized (Hughes *et al.* 2013b) and there appear to be no validation studies comparing AI_x to other measures of reflection in the pulmonary vasculature.

Wave Intensity Analysis

Wave intensity analysis (WIA) is a time-domain based approach to hemodyanmics that offers an alternative approach to the widely-used vascular impedance analysis for the study of wave propagation. WIA was formulated by Parker *et al*. over 25 years ago (Parker *et al.* 1988, Parker & Jones 1990) based on the incremental temporal changes in pressure and flow velocity. The major differences between vascular impedance analysis and WIA are outlined in Table 1. WIA analyses measured pressure and flow velocity in terms of successive "wavefronts" and uses the method of characteristics to solve the one-dimensional wave equations (Parker 2009). In contrast, vascular impedance analysis uses Fourier transforms to decompose signals into sinusoidal "wavetrains". WIA (in the absence of wave separation) does not assume linearity or periodicity, which enables analysis of beat to beat changes of blood pressure and flow even when the cardiac cycle is irregular, e.g. during extrasystoles (Smolich *et al.* 2009). The mathematical background may seem complex, but the results are easy to interpret in physiological terms.

The net wave intensity (*dI*) has the units Wm^{-2} and measures the instantaneous power per unit cross sectional area (CSA) of the tube, i.e. the artery (energy flux density) transported by the "wavefront" as it propagates and is the product of the measured change in pressure (*dP*) and flow velocity (*dU*) over a small time interval. By convention it is positive for forward waves and negative for backward waves.

$$dI = dP \cdot dU \quad (11)$$

If waves are assumed to be linearly additive, then they can be separated into forward and backward components by use of the waterhammer (or Joukowsky) equation. Hence:

$$dP_+ = \rho \cdot c \cdot dU_+ \text{ , for forward waves} \quad (12)$$

$$dP_- = -\rho \cdot c \cdot dU_- \text{ , for backward waves} \quad (13)$$

where ρ is the density of blood and c is the local wave speed.

Integration of the forward and backward pressure wavefronts (dP_+ and dP_-) yield forward and backward pressure waves (P_f and P_b). If the local wave speed (or alternatively the characteristic impedance) is known, pressure separation into P_f and P_b by WIA or vascular impedance analysis give almost identical results (Hughes & Parker 2009, Westerhof *et al.* 2015). A simple way to estimate wave speed is by plotting instantaneous measurements of pressure versus velocity, the PU-loop (Khir *et al.* 2001). In very early systole it is assumed that only forward travelling waves are present in the pulmonary artery, hence the PU-curve is expected to be linear (Figure 1), with the slope of the curve equal to ρc.

$$c = \frac{1}{\rho} \cdot (slope\ of\ PU - curve) \quad (14)$$

If the PU-loop does not display an initial linear segment (a circumstance where forward and backward travelling waves are present at the same time in early systole), e.g. in the coronary arteries, the local wave speed can be determined by the sum of squares method (Davies *et al.* 2006b),

$$c = \frac{1}{\rho} \cdot \sqrt{\frac{\sum dP^2}{\sum dU^2}} \quad (15)$$

although concerns have been raised regarding the accuracy of this approach in the coronary circulation (Siebes *et al.* 2009). In practise, in the absence of early wave reflection, the wave speed derived from both methods should be similar (Dwyer *et al.* 2012, Quail *et al.* 2015) and the impact of any errors in wave speed estimates by the sum of squares technique, even in the coronary circulation, is small (Rolandi *et al.* 2014).

In addition to direction, WIA also characterizes the waves by their effect on pressure and flow. Accordingly, in a vessel with increased impedance distally (“close ended” vessel), the incident wave reflects back as a backward compression wave (BCW) that increases pressure and decelerates flow. In a vessel with decreased impedance (“open ended” vessel) the reflected wave returns as a backward decompression wave (BDW) that decreases pressure and accelerates the flow (Figure 2). One of the strengths of WIA is its ability to differentiate between compression and decompression waves, which has provided novel insights into vascular physiology. The finding of a forward decompression wave (FDW) in the aorta in late systole indicated that aortic flow deceleration is principally determined by a reduced

rate of myocardial shortening and not wave reflection from the periphery as previously thought (Parker *et al.* 1988); while a BDW likely caused by myocardial relaxation is shown to play a dominant role for the filling of coronary arteries during diastole (Davies *et al.* 2006a).

Application of WIA to the pulmonary circulation is limited and measurements are typically obtained invasively (Lau *et al.* 2014). However, acquiring measurements using magnetic resonance imaging (MRI) is clearly feasible (Quail *et al.* 2015), where simultaneous changes in volumetric flow (Q) and area (A) are used as surrogates for velocity and pressure and the local wave speed can be calculated using the QA-loop (Segers *et al.* 2014). This approach, however, gives estimates of wave intensity (dI_a) in cm^5s^{-1} and is not directly comparable with wave intensity calculated from pressure and flow velocity. Whether it is possible to use ultrasound based flow velocity combined with wall tracking in the pulmonary circulation, as in the systemic circulation (Fujimoto *et al.* 2004, Niki *et al.* 1999), remains to be established.

Interpreting the results

In the original description of WIA the values of wave intensity depended on the sampling time of data acquisition. Doubling the sampling time doubled the value of *dP* and *dU* and consequently increased *dI* by 2^2 (i.e. 4 fold). This complicates performing a direct quantitative comparison between studies carried out with different sampling rates. To circumvent this problem, it has been proposed to use a "time-normalised" wave intensity, abbreviated as WI to distinguish it from non-time normalized *dI*. This quantity is made independent of the sampling rate by calculating the corresponding time derivatives *dP/dt* and *dU/dt* (Niki *et al.* 1999, Ohte *et al.* 2003). However, the resulting units of WI ($Wm^{-2}s^{-2}$) and the integral of WI ($Wm^{-2}s^{-1}$) do not have a straightforward physiological meaning. An alternative resolution to this problem would be to express *dP* and *dU* "per cardiac cycle" i.e. to multiply instantaneous value of *dP* and *dU* by the number of samples in the cardiac cycle, but we are unaware of such an approach having been used in any study.

Comparison of WIA and pressure separation can lead to differences in interpretation regarding waves: in WIA, high intensity waves are largely restricted to systole; in contrast, pressure separation shows that a substantial part (~50 %) of the declining pressure in diastole is due to backward pressure (P_b). It has be proposed that this apparent discrepancy can be resolved by considering backward pressure in diastole to be composed of multiple waves, individually of very small intensity, but together making up substantial backward pressure (Davies *et al.* 2012). Further consideration of this contentious issue can be found elsewhere (Hughes *et al.* 2013a, Westerhof *et al.* 2015).

If the arterial tree is conceptualised as a single tube, the approximate location of reflection sites, i.e. sites of impedance mismatch, can be estimated by multiplying the wave speed by one-half of the time from the peak of the incident wave to the peak of the reflective wave. However, the validity of this approach is dubious (Westerhof *et al.* 2008) and exact determination of reflection sites would require detailed knowledge of the anatomy and the local wave speeds at all intervening locations in pulmonary circulation. It is generally believed that the wave speed increases towards the peripheral pulmonary arteries (Caro &

Saffman 1965), though due to the relative inaccessibility of the peripheral pulmonary vasculature *in vivo*, experimental data on pulse wave propagation through the pulmonary artery tree is limited.

WIA cannot intrinsically distinguish how waves of the same direction and type are generated. The most plausible mechanism that explains the wave patterns must be based on interpretations of cardiovascular physiology. For instance, a BCW is observed shortly after the initial FCW in the coronary artery. This is most likely a combination of reflected waves due to impedance mismatch and waves generated distally by compression of the coronary microcirculation (Davies *et al.* 2006a). Their relative contribution is impossible to determine. Another excellent example is demonstrated in the pulmonary artery in dogs, where it was not possible to determine whether the detected BCW was generated by reflection at distal sites or by retrograde transmission caused by increased left atrial pressure (Hollander *et al.* 2004). Moreover, there is evidence that not only changes in the pulmonary vasculature, but also changes in the properties of blood impact wave travelling (Schreier *et al.* 2016). Thus, for instance in patients with pulmonary hypertension caused by sickle cell disease, it would be challenging to distinguish whether the presence of any wave reflection is a result of stiffened red blood cells or vascular remodelling or both.

Pulmonary WIA in canine and ovine models

While the clinical implication of WIA in the systemic circulation is becoming more apparent, only a few studies have applied WIA in the pulmonary circulation and these have mainly been in animal models. In close chested dogs, the net wave intensity profile in normoxia was characterized by the presence of forward travelling waves mainly in early and late systole, while the wave intensity was minimal in diastole (Nie *et al.* 2001). The initial and dominant wave was a forward compression wave (FCW) as a result of RV contraction. In late systole, there was a forward decompression wave (FDW) that was a result of a decreased rate of ventricular contraction and consequent deceleration of blood flow before closure of the pulmonary valve. There were no net backward travelling waves present in normoxic dogs. Other studies in open chested dogs have also used wave separation and have reported a BDW which is almost coincident with the FCW. This wave was attributed to an "open-ended" type reflector (Bouwmeester *et al.* 2014, Hollander *et al.* 2001), possibly due to increased vessel CSA at the first or second bifurcation (Caro & Saffman 1965). This is plausible but the difficulties of assessing wave speed so close to a reflection site raise concerns about the robustness of wave separation under these conditions. A mid-systolic BDW was also observed in sheep, but its magnitude was negligible (WRI ~1 %) (Dwyer *et al.* 2012).

In dogs, pulmonary vasoconstriction induced by acute exposure to hypoxia increased the wave speed and introduced BCW in mid-systole attributed to wave reflection (Hollander *et al.* 2001, Nie *et al.* 2001) resulting in augmented RV afterload. The intensity of the FCW was also increased consistent with increased contractile performance of the RV to maintain the cardiac output in the face of increased ventricular afterload.

WIA in the pulmonary trunk and pulmonary artery has also been used to study *in utero* pulmonary vascular physiology in foetal lambs, where a prominent BCW in mid-systole is

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observed. The BCW is associated with the mid-systolic flow attenuation and can be attributed to reflection of the FCW at the highly constricted distal pulmonary vasculature due to the hypoxic fluid-filled lungs and waves generated by impulsive myogenic contraction in the foetal pulmonary microvasculature (Grant *et al.* 1999, Smolich *et al.* 2008). One can speculate whether continued presence of the BCW is a contributing factor in the pathophysiology behind persistent PH of the newborn.

Pulmonary WIA in man

Recently, the feasibility of applying WIA in the human pulmonary artery has been demonstrated (Lau *et al.* 2014, Quail *et al.* 2015). In individuals without pulmonary vascular disease, a pilot study applying WIA invasively using intravascular catheters in the lower lobe pulmonary artery showed the anticipated FCW and FDW with a wave speed of ~4 m/s (Lau *et al.* 2014). Unlike some studies in canine models, no BDW was observed. In 6 subjects with PAH, WIA revealed increased wave speed indicating increased arterial stiffness. Also, the intensity of all three waves as well as the WRI (~35 %) were increased; this is analogous to what was found in animal models after exposure to hypoxia (Hollander *et al.* 2001, Nie *et al.* 2001). The investigators estimated the reflection site to be ~15 cm downstream of the measurement site, which, assuming constant wave speed, would correspond to the terminal branches (Singhal *et al.* 1973); however, as discussed above, the underlying assumptions of this calculation are questionable. Recent unpublished studies performed by our group have shown similar wave intensity profiles and differences between individuals with and without PH (Figure 3).

Non-invasive WIA using MRI has been performed in the branch pulmonary artery of healthy controls and patients with PAH and CTEPH (Quail *et al.* 2015). The wave speed was estimated to be ~1 m/s in control subjects, which is substantially lower than the wave speed reported by Lau *et al*. Interestingly, after wave separation, the investigators observed an early systolic BDW (WRI ~10 %) that accompanied the FCW in control subjects, with no BCW. In patients with PH, wave speed doubled, the intensity of FCW decreased and an early systolic BCW (WRI ~13 %) was evident. The reduced intensity of FCW was interpreted as indicating decreased ventricular performance in the face of increased workload. The reflection site in PH was estimated to be 2 – 3 cm distant, i.e. the next generation of branches. The discrepancies between the studies of Lau *et al* and Quail *et al* may be explained by differences in anatomical measurement sites, methodology (including the definitions of *dI* as opposed to *dIa*) and study subjects. The more distal measurement site and older control group in Lau's study would be expected to be associated with a greater arterial stiffness (Gozna *et al.* 1974) and therefore could contribute to the observation of a higher local wave speed. However, methodological differences between the two studies must also be taken into consideration. For instance, it has been shown that in the presence of wave reflection, the PU-loop method (Lau *et al.* 2014) overestimates wave speed while the QA-loop method (Quail *et al.* 2015) underestimates it (Segers *et al.* 2014). A systematic comparison between invasive and non-invasive WIA is warranted.

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Technical Limiations

Like all analytical tools, there are limitations associated with WIA. Simultaneous data acquisition of pressure and flow velocity at the same site is challenging; particular issues relate to temporal alignment of signals, signal quality and signal processing.

Care is needed to ensure that sensors are correctly aligned and that signal processing delays do not give rise to a time lag between the two measurements. External Doppler devices and intravascular pressure sensors should be aligned precisely. Incorrect angling of the external Doppler gives an underestimation of flow velocity. Use of a multisensor catheter tip-manometer minimises the uncertainty of alignment, but the time-offset between pressure and velocity sensors can differ between wires of different models (Volcano Corp 2015). Delays of ~43 ms between pressure and flow velocity signals attributed to signal processing have been reported (Hadjiloizou 2010) and possible delays need to be quantified and corrected for.

Wave intensity calculations depend on derivatives of both pressure and flow velocity and therefore errors in either signal, e.g. due to noises or other artefacts, compromise wave intensity estimates. Obtaining invasive measurements in the pulmonary artery can be technically challenging. Motion artefact, vibration and axial movements of the catheter with each ventricular contraction as well as occasional positioning of the catheter against the vessel wall can introduce artefacts (Ragosta 2008). The relative signal-to-noise ratio of the velocity sensor on the catheter tip-manometer is often poor, particularly in regions of disturbed blood flow. Once *in situ*, small rotational movements of the intravascular catheter can be made to optimize Doppler signals. During post-hoc data processing it is nearly always necessary to ensemble average and apply signal processing to the raw data. A Savitzky-Golay filter is particularly suitable for this purpose (Parker 2009), as it has the advantage of preserving the morphology of the signal better than many other types of filtering approaches, but care should be taken to optimise filter properties.

Separation of travelling waves into forward and backward waves requires accurate determination of wave speed (Khir *et al.* 2001). Errors in wave speed estimation can lead to miscalculation of reflection sites, incorrect separated wave intensities and generation of artefactual waves in the pulmonary artery (Dwyer *et al.* 2012). The usual approach is to adjust alignment of the pressure and velocity data until the first portion of PU-loop appears most linear “by eye”. This is evidently subjective and an objective approach using a Bayesian statistical approach has been described (Aguado-Sierra *et al.* 2006). Nevertheless, the impact of small imprecision in wave speed estimates may be minor: in the aorta at least, < 20 % miscalculation of the wave speed does not lead to major changes in wave intensity patterns (Khir *et al.* 2001). As discussed above, determination of wave speed from the initial portion of the PU-loop is realistic only under the assumption that there are no reflected waves in this period (Segers *et al.* 2014), however, there is no direct evidence for this.

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Clinical Implications

The clinical usefulness of WIA in the systemic circulation is well attested (Bleasdale *et al.* 2003, Manisty *et al.* 2010, Ohte *et al.* 2003, Sen *et al.* 2012). It is therefore credible that WIA could also provide valuable information in the pulmonary circulation.

Current clinical measurements to evaluate PH severity, such as increased PAPm and PVR and decreased cardiac output, detect relatively late manifestations of pulmonary vascular disease (Lau *et al.* 2011) and, possibly as a consequence, the mortality rate remains high in PH despite recent advances in treatment (Seferian & Simonneau 2013). Indices derived from wave intensity analysis – such as the intensity and integral of the forward compression wave (indicative of right ventricular power and work), wave speed (local arterial stiffness) and wave reflection (vascular impedance mismatch) – could supplement conventionally used clinical measurements. For example, the magnitude of FCW correlates with RV ejection fraction and the magnitude of BCW may help to differentiate between proximal and distal clots in patients with CTEPH, and evaluation of local wave speed and reflection may be useful when asymmetrical disease is suspected (Quail *et al.* 2015).

There appears to be little or no association between PVR (conventional measure of the RV afterload in PH) and the magnitude of the BCW and wave speed (Quail *et al.* 2015). In addition, one study has shown a significant decrease in the complex reflection coefficient in PH patients during exercise despite no change in PVR (Laskey *et al.* 1993), while another study (Brin & Yin 1984) showed no changes in wave reflection despite decreased PVR after vasodilator challenge. Thus, wave reflection may provide distinct information from PVR regarding pulmonary vascular disease severity. It will be important to assess wave behaviour throughout the progression of pulmonary vascular disease and it would be interesting to compare wave characteristics before and after initiating PH treatment. Recent advances in multisensor catheters and advanced MRI technologies should facilitate future use of pulmonary WIA in a clinical setting. Much is to be learned about waves in the pulmonary artery.

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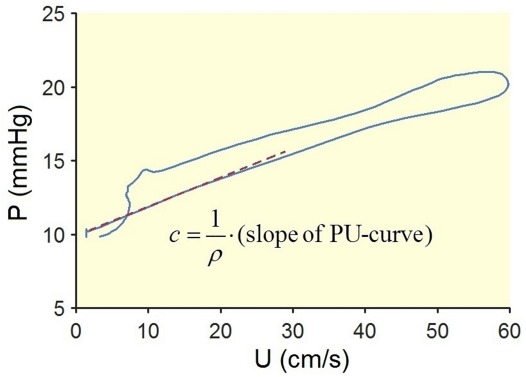

Figure 1. PU-loop

The local wave speed, c, can be calculated from PU-loop. P: pressure, U: velocity, ρ: blood density.

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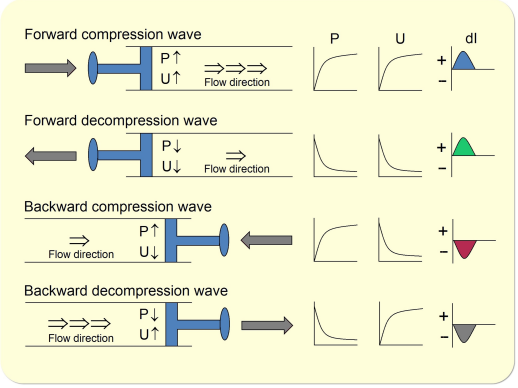

Figure 2. Wave intensity analysis

Wave intensity analysis distinguishes between waves of different origins – forward (proximal) versus backward (distal) waves, and their effects on pressure – compression versus decompression waves. Wave intensity is positive for forward waves and negative for backward waves. P: pressure, U: velocity, dI: wave intensity.

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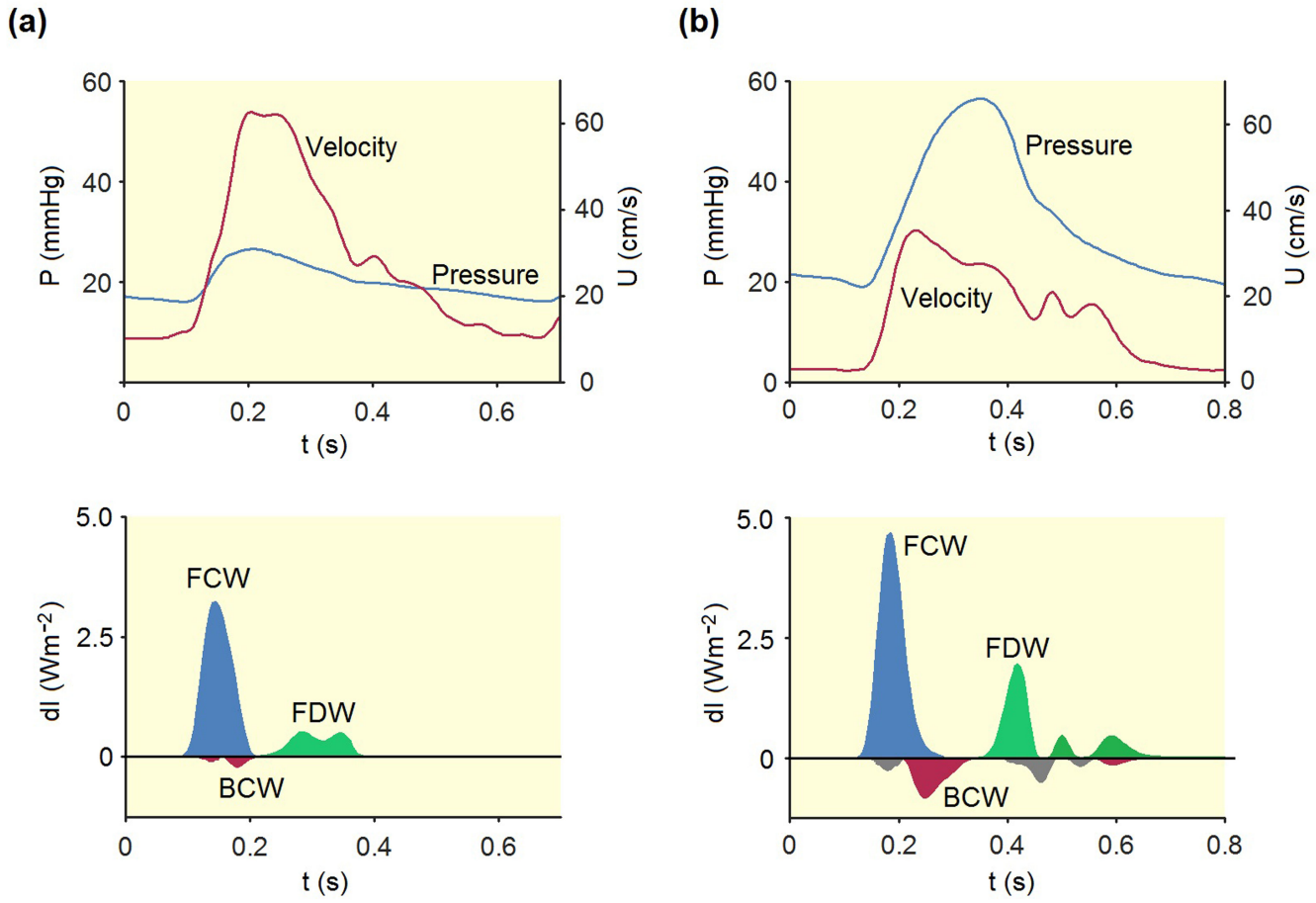

Figure 3. WIA in the pulmonary artery

Wave intensity analysis (WIA) in the main pulmonary artery of an individual without pulmonary vascular disease (a) and a patient with pulmonary arterial hypertension (b) are shown with the same scaling factor. Upper panel shows the pressure and flow velocity profiles and the lower panel shows the wave intensity profiles. Sampling rate was 200 Hz. In patients with pulmonary hypertension, the magnitude of backward compression wave, wave reflection index as well as wave speed increased significantly. P: pressure, U, flow velocity, dI: wave intensity, FCW: forward compression wave, FDW: forward decompression wave, BCW: backward compression wave.

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Table 1

Schematic overview of the vascular impedance analysis and wave intensity analysis

	PVR & PAPm	Impedance analysis	WIA
Widely used in clinic	Yes	No	No
Easy to measure	Yes	No	No
Describes the steady state afterload	Yes	Yes	Not directly
Describes the pulsatile afterload	No	Yes	Yes
Information about the ventricle	No	No	Yes
Describes travelling waves	No	Yes	Yes
Valid in non-linear and non-periodic state	--	No	Yes
Wave separation possible	--	Yes	Yes
Allows decompression waves	--	No	Yes
Results presented in	--	Frequency domain	Time domain
Depiction of waves	--	Sinusoidal waves	Wavefronts