Wave Intensity Analysis Provides Novel Insights into Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension

Running title: Su et al.; WIA in pulmonary artery

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Abstract:

**Background:** In contrast to systemic hypertension, the significance of arterial waves in pulmonary hypertension (PH) is not well-understood. We hypothesized that arterial wave energy and wave reflection are augmented in PH and that wave behavior differs between patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).

**Methods and Results:** Right heart catheterization was performed using a pressure and Doppler flow sensor tipped catheter to obtain simultaneous pressure and flow velocity measurements in the pulmonary artery. Wave intensity analysis was subsequently applied to the acquired data. Ten control subjects, eleven patients with PAH and ten patients with CTEPH were studied. Wave speed and wave power were significantly greater in PH patients compared to controls indicating increased arterial stiffness and right ventricular work, respectively. The ratio of wave power to mean right ventricular power was lower in PAH patients than CTEPH patients and controls. Wave reflection index (WRI) in PH patients (PAH: ~25 %, CTEPH: ~30 %) was significantly greater compared to controls (~4 %) indicative of downstream vascular impedance mismatch. While wave speed was significantly correlated to the disease severity, WRI of patients with mildly and severely elevated pulmonary pressures were similar.

**Conclusions:** Wave reflection in the pulmonary artery increased in pulmonary hypertension and was unrelated to severity, suggesting that vascular impedance mismatch occurs early in the development of pulmonary vascular disease. The lower wave power fraction in PAH compared to CTEPH indicates differences in the intrinsic and/or extrinsic ventricular load between the two diseases.

**Key words:** wave intensity, pulse wave velocity, pulmonary hypertension, pulmonary artery
Clinical Perspective

What Is New?

- Wave intensity analysis applied to the pulmonary artery revealed increased arterial wave speed, power and reflection in pulmonary hypertension patients indicating increased arterial stiffness, right ventricular work and vascular impedance mismatch, respectively.

- In contrast to wave speed, the magnitude of wave reflection was unrelated to pulmonary hypertension severity in established disease suggesting that vascular impedance mismatch occurs early in the development of pulmonary vascular disease.

- The ratio of wave power to mean right ventricular power was lower in PAH patients than CTEPH patients suggestive of differences in the intrinsic and/or extrinsic ventricular load between the two diseases.

What Are the Clinical Implications?

- Wave reflection may be an early marker of disease in the pulmonary vasculature.

- Characterizing the pathophysiological differences between PAH and CTEPH may contribute to our understanding of disease progression and treatment response in pulmonary hypertension.
Pulmonary hypertension (PH), defined as an elevated mean pulmonary arterial pressure (PAPm \( \geq 25 \) mmHg) at rest measured by right heart catheterization\(^1\), is a severe disease that often leads to right heart failure. Clinically, PAPm and pulmonary vascular resistance (PVR) are commonly used hemodynamic measures to evaluate disease severity. However, they only describe the steady-state component of the right ventricular (RV) workload and neglect the dynamic compliance of the pulmonary arteries and magnitude of wave reflection in the circulation. Wave travel is influenced by the working state of the heart under the impact of its workload\(^2\) and therefore, analysis of arterial waves in the pulmonary artery may provide additional information about disease severity and progression in pulmonary vascular disease.

Previous studies that used impedance based methods to investigate arterial waves in the pulmonary artery\(^3-5\) suggested that distal wave reflection plays a significant role in pulmonary hemodynamics. Wave intensity analysis (WIA), as proposed by Parker and Jones\(^6\), uses simultaneous changes in the arterial pressure and flow velocity to determine the energy, origin, type and timing of the traveling waves in a circulation. Unlike the impedance based methods where the results are presented in the frequency domain, WIA is a time domain technique, where the results are presented as a function of time allowing investigators to relate arterial waves to events occurring at specific times in the cardiac cycle. WIA has broadened our knowledge in arterial physiology and pathophysiology in the systemic\(^7,8\) and coronary circulation\(^9,10\) and its clinical utility has been demonstrated in previous studies\(^11-13\). However, it is only very recently that WIA has been applied in the pulmonary circulation in man\(^14,15\).

The objective of this study was to employ WIA in the pulmonary artery to characterize wave propagation in individuals without pulmonary vascular disease and patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). Furthermore, we will explore the relationship between WIA parameters and
conventionally used measurements in PH. We postulate that WIA would provide novel insights into pulmonary hemodynamics and RV workload; in particular, we hypothesize that arterial wave energy and wave reflection are augmented in PH and that wave behavior differs between PAH and CTEPH.

Materials and Methods

Study Population

Study subjects were selected among patients undergoing cardiac catheterization for clinical reasons at Hammersmith Hospital, Imperial College Healthcare and Aarhus University Hospital. Patient recruitment and the study protocol were standardized at both centers to avoid measuring bias and the same investigator was present at every patient case at both centers to ensure that the study protocol was performed in the standardized manner. Control subjects were recruited amongst patients without significant cardiovascular or lung disease that were referred for coronary angiography or electrophysiology procedures for supraventricular tachycardias. Only patients whose angiogram and transthoracic echocardiogram showed unobstructed coronary arteries with or without non-flow limiting atheromas and normal biventricular dimensions and function without moderate or severe valvular pathology, respectively, were included. PH patients were recruited amongst patients with confirmed or suspected PAH and CTEPH that were undergoing right heart catheterization as a part of diagnostic investigation or routine follow-up. Patients with normal PAPm and previous history of thromboembolism and patients with elevated pulmonary arterial wedge pressure (PAWP > 15 mmHg) with or without elevated PAPm were excluded as they may not have normal pulmonary hemodynamics in order to be considered as controls.
and they do not fall into the categories of PAH and CTEPH. The study was approved by the London-Fulham Research Ethics Committee and Central Denmark Region Committees on Health Research Ethics, respectively (references13/LO/1305 and M-2013-278-13, respectively), and all of the subjects gave written informed consent.

**Study Protocol**

Following the clinical procedure, a 6 Fr multipurpose catheter or a 6 Fr balloon flotation catheter was advanced into the pulmonary artery via right femoral, brachial or internal jugular vein. A combined dual-tipped pressure and Doppler flow sensor wire (Combowire, Philips Volcano, California, USA) was then advanced approximately 1 cm beyond the end of the catheter. Careful manual catheter and wire manipulation ensured that the Doppler flow velocity signals were optimized in situ. Once stable signals were observed, pressure and velocity data were acquired simultaneously (Combomap, Philips Volcano) at a sampling rate of 200 Hz for 30 – 60 seconds together with electrocardiographic (ECG) monitoring in free breathing state in the main pulmonary artery and subsequently in either the left or right pulmonary artery, hereafter referred to as branch pulmonary artery. In CTEPH patients, data were acquired from both the left and right pulmonary arteries. All subjects were in sinus rhythm at time of data collection. Data from standard transthoracic echocardiography and routine blood test results, both of which were performed within the same week as the cardiac catheterization, were collected.

Cardiac output was determined using the thermodilution, direct Fick or indirect Fick method when direct measurement was not possible. Indexed total pulmonary resistance was calculated as PAPm divided by cardiac index and global pulmonary arterial compliance was calculated as stroke volume divided by pulmonary arterial pulse pressure (PAPp).
In PH patients, indexed PVR was calculated as the transpulmonary pressure gradient (defined as the difference between PAPm and PAWP) divided by cardiac index.

**Right Ventricular Power and Energy Densities**

RV power density and energy density, defined as the power and energy, respectively, delivered by the right ventricle to generate the stroke volume per unit cross sectional area of the artery, were derived from the conventionally used formula for calculating steady flow RV stroke work (RVSW, equation 1)

\[ RVSW = (PAPm - RAP) \cdot RVSV \]

Where RAP is the right atrial pressure and RVSV is the right ventricular stroke volume. RAP was measured in all the PH patients, but not the control subjects and was arbitrarily set to 6 mmHg in controls.

Normalizing RVSW to the cross sectional area (CSA) of the main pulmonary artery yields RV energy density.

\[ \text{RV energy density} = \frac{RVSW}{CSA} = \frac{(PAPm - RAP) \cdot RVSV}{RVSV \cdot HR \cdot U_{mean}} = \frac{(PAPm - RAP)}{HR \cdot U_{mean}} \]

Where \( U_{mean} \) is the mean flow velocity and HR is the heart rate.

Hence,

\[ \text{RV energy density} = (PAPm - RAP) \cdot U_{mean} \cdot CCD \]

Where CCD is the duration of the cardiac cycle.

And

\[ \text{RV power density} = (PAPm - RAP) \cdot U_{mean} \]

**Wave Intensity Analysis**
Pressure (P) and velocity (U) data were processed offline using customized Matlab software (MathWorks, Massachusetts, USA). Signals were ensemble-averaged with timing gated to the R-wave of ECG and smoothed using a Savitzky-Golay differentiating filter (2\textsuperscript{nd} order polynomial fit, window size 11). An automatic procedure for eliminating particular noisy velocity waveforms from the ensemble was applied by calculating and ranking the cross-correlation of each beat with the global ensemble average. Beats with the lowest correlation coefficient were eliminated iteratively until the integral of the standard error of the ensemble average velocity waveform over the cardiac period was minimized. The ensemble average pressure waveform was then calculated for the same beats. Hardware-related delay between pressure and velocity signals was corrected by shifting the velocity data until the beginning of the upslope of the velocity and pressure waveforms were aligned.

The local wave speed (c) was calculated using the sum of squares method (equation 5)\textsuperscript{18}.

\begin{equation}
    c = \frac{1}{\rho} \sqrt{\frac{\sum P^2}{\sum U^2}}
\end{equation}

where $\rho$ is the blood density, assumed to be 1040 kg/m$^3$ and the sum is taken over one cardiac period.

The sum of squares method was used here to calculate wave speed rather than the PU-loop method. In the latter method, the instantaneous measurement of pressure is plotted against velocity and the slope of the early linear portion of the PU-curve is expected to be equal to the product of blood density and wave speed\textsuperscript{19}. PU-loop method is only valid under the assumption that there is no wave reflection in early systole, i.e. that there is an early linear segment on the PU-curve. In many of our subjects, the PU-loop did not display a perfectly linear initial segment and as wave propagation in the pulmonary artery is not well-
understood, we could not rule out early wave reflection, especially in pulmonary hypertension patients.

A wave originating from the proximal part of the artery can be a forward compression wave (FCW) that increases the pressure and flow or a forward decompression wave (FDW) that decreases the pressure and flow. Likewise, a wave originating from the distal part of the artery can be a backward compression wave (BCW) that increases the pressure while decreasing the flow or a backward decompression wave (BDW) that decreases the pressure while increasing the flow. Wave intensity is positive for forward travelling waves and negative for backward travelling waves. WIA was performed essentially as previously described\(^2\), but values were normalized to cardiac cycle length to make it independent of sampling rate\(^20\). With the knowledge of the local wave speed, waves were separated into their forward (WI\(_f\)) and backward (WI\(_b\)) components (equation 6).

\[
WI_{\pm} = \pm \left( \frac{dP \cdot CCD}{dt} \pm \rho c \cdot \frac{dU \cdot CCD}{dt} \right)^2 / (4 \rho c)
\]

Separated waves were quantified by the peak intensity of the individual waves (Wm\(^2\)) and by the cumulative area under each wave corresponding to the wave energy density (Jm\(^2\)) over a cardiac cycle squared. The magnitude of wave reflection, denoted as the wave reflection index (WRI), was calculated as the ratio of the energy of the backward traveling wave in systole to the energy of the incident wave related to ventricular ejection.

**Statistical Analysis**

Data were analyzed for normality using the Q-Q plot. Results are expressed as mean ± standard deviation (SD) when normally distributed or median (25 % – 75 % quartile) when
non-normally distributed. Proportions are expressed as percentages. Differences between the three study groups were compared using one-way analysis of variance (ANOVA) followed by a Bonferroni test. Kruskal Wallis test followed by Dunn’s test was used for non-normally distributed data and for normally distributed data with unequal variances as tested by Bartlett’s test. Fisher’s exact test was used for categorical variables. Differences between data from the main and branch artery within each group were compared using paired t-test or the Wilcoxon signed-rank test. Spearman’s correlation analysis was performed to examine simple relationships between variables. Area under the receiver operating characteristics curve (AUROC) was used to assess the accuracy of FCW to RV power and energy density ratios to discriminate between PAH and CTEPH patients. The level of significance in all tests was set at $p < 0.05$. All statistical analyses were performed using Stata 13 (StataCorp, Texas, USA).

Results

Patient Characteristics

A total of 36 subjects were recruited (Figure 1). Eleven subjects had no significant cardiovascular disease or lung disease and served as control subjects and technically satisfactory data were obtained from 10 of them (59 ± 14 yrs, 8 male). Eleven patients (56 ± 21 yrs, 2 male) had confirmed PAH – 6 with idiopathic PAH, 4 with PAH associated with connective tissue disease and one with pulmonary veno-occlusive disease. Of the remaining 14 patients, 10 of them were diagnosed to have CTEPH (66 ± 9 yrs, 2 male). Satisfactory velocity data from the left pulmonary artery could not be obtained from several of the CTEPH patients, therefore, only data from the right pulmonary artery were included in this
study. Satisfactory data from the main pulmonary artery were obtained from 10 of the PAH patients and 9 of the CTEPH patients, while satisfactory data from the branch pulmonary artery were obtained from all of the PAH patients and 9 of the CTEPH patients. All PH patients had normal left heart function on transthoracic echocardiography and no significant mitral or aortic valve disease.

Baseline characteristics and hemodynamic parameters of all patients studied are shown in Table 1. The PH patients had higher PAPm and total pulmonary resistance and lower flow velocity and global pulmonary compliance compared to controls. The cardiac index was highest in the control group, though the difference was not statistically significant compared to the PH groups. There were no significant differences in the conventionally used hemodynamic parameters between the PAH group and CTEPH group.

Wave Intensity Parameters

A representative original recording trace for a PAH patient is shown in Figure 2. A mid-systolic notch was observed in the Doppler velocity signal in the majority of the PH patients. Ensemble averaged pressure and velocity waveforms in the main pulmonary artery and the corresponding wave intensity patterns from a representative subject in each group are shown in Figure 3 and wave intensity parameters are summarized in Table 2. Wave speed (Figure 4) in the main pulmonary artery was ~3 m/s in control subjects and significantly higher in PAH patients at ~12 m/s indicating increased local arterial stiffness. Wave speed in CTEPH patients was ~15 m/s, which was significantly higher compared to controls, but not to PAH patients.

During systole, two distinct forward traveling waves were consistently identified in all three groups. A FCW, the incident wave, was observed in early systole, which is generally
attributed to right ventricular ejection and a FDW was observed in late systole just before the
dicrotic notch on the pressure waveform. The FDW decreased the pressure and flow and is
assumed to correspond to ventricular relaxation prior to the closure of the pulmonary valve.
The magnitude of the FCW (both peak wave intensity and wave energy) in the main
pulmonary artery was significantly greater in PH patients compared to controls indicating
increased RV work, while there was no significant difference between the PAH and CTEPH
patients (Table 2).

Backward waves were observed in mid-systole. In control subjects, an identifiable BCW
was present in mid-systole in 7 cases, while BDW was present in 3 cases in the main
pulmonary artery. WRI, which expresses the fraction of the FCW energy that is reflected,
was ~4 %. In PH patients, a substantial BCW in mid-systole was observed in all the patients
indicating vascular impedance mismatch. BDW was not observed in systole in any of the
patients. WRI in the main pulmonary artery was ~25 % and ~30 % in PAH and CTEPH
patients, respectively, which was significantly higher compared to controls. The arrival time
of the BCW was not significantly different between PAH (63 ms [55 – 85 ms]) and CTEPH
(70 ms [60 – 100 ms]) patients.

Similar findings were observed in the branch pulmonary arteries (Table 2). The observed
differences in wave propagation between the three study groups persisted when non-
normalized WIA data were examined (data not shown). Moreover, WIA parameters of PAH
patients treated with specific PAH drugs (N =7) were comparable to patients not on PAH
treatment (data not shown).

**RV Wave Power to Stroke Power Ratios**
RV stroke power and energy densities are defined as the steady flow power and energy, respectively, delivered by the right ventricle to generate the stroke volume per unit cross sectional area of the artery. They were significantly higher in PH patients compared to controls, while there were no significant differences between PAH and CTEPH (Table 2).

FCW to RV power and energy density ratios were significantly lower in the PAH group than both the control and CTEPH groups, while there were no significant differences between the two latter groups (Figure 5A & 5B). Moreover, FCW to RV power/energy density ratios showed significant discriminatory capacity between CTEPH and PAH patients (Figure 5C & 5D).

Correlation Analyses

Correlation analyses between wave intensity indices from the main pulmonary artery and conventionally used clinical parameters to evaluate PH were performed by pooling together the data from all PH patients (Table 3). The association of wave speed, magnitude of the waves and wave reflection with conventionally used hemodynamic measurements, echocardiographic parameters reflecting RV function and B-type natriuretic peptide (BNP), was investigated. As the data from the controls were very different in comparison to the data from PH patients, they were excluded from the correlation analysis to avoid bias.

There was a significant association between wave speed and the dynamic parameters of the RV workload: global pulmonary compliance (rho = -0.62, p < 0.01) and PAPp (rho = 0.78, p < 0.01); with the steady flow parameters: PAPm (rho = 0.62, p < 0.01) and PVR (rho = 0.46, p = 0.05); as well as a significant association with the tricuspid annular plane systolic
excursion (TAPSE, rho = -0.58, p < 0.01 ). Also, there was a significant correlation between the magnitude of FCW – both peak wave intensity and wave energy – and PAPp.

In contrast to wave speed, there was no significant association between the magnitude of BCW and WRI and any of the conventionally used hemodynamic, echocardiographic and biochemical parameters. In fact, patients with mildly elevated PAPm had similar WRI compared to patients with moderately and severely elevated PAPm (Figure 6).

**Discussion**

In the present study, we applied WIA in the main and branch pulmonary arteries to characterize the interaction between the right ventricle and pulmonary artery in subjects with and without pulmonary hypertension. We observed similar wave intensity pattern in the main and branch pulmonary arteries within each group. Consistent with a previous short report\(^\text{14}\), we observed that the wave speed, magnitude of waves and WRI were significantly greater in PH patients compared to control subjects demonstrating increased arterial stiffness, RV work and vascular impedance mismatch, respectively. Furthermore, FCW to RV power and energy density ratios were significantly reduced in PAH patients compared to CTEPH patients and controls. Finally, we observed that there was no strong association between WRI and the conventionally used hemodynamic measurements, echocardiographic parameters, BNP or PH severity. Thus, this study revealed distinct differences in arterial wave propagation between individuals with and without pulmonary hypertension.

**RV Hydraulic Power**

PH is a progressive disease of the pulmonary vasculature that often leads to right heart failure\(^\text{21}\); therefore, it is important to understand the interaction between the right ventricle
and the pulmonary circulation. Consistent with the low-pressure, low-resistance and high-compliance nature of the right-sided system, the magnitude of the waves and wave speed were low in the control subjects. As PH develops, the pulmonary artery becomes a high-pressure, high-resistance and low-compliance system resembling the hemodynamic properties of the systemic arterial system. This is reflected not only in the pulmonary pressures and resistance, but also in the wave characteristics\textsuperscript{22, 23}. Wave speed, i.e. local arterial stiffness, increased 4 – 5 fold in PH patients and the increase in wave speed was related to decreased global pulmonary compliance and cardiac function. The magnitude of FCW increased \(\approx 1.5\) fold in PH patients indicating greater RV work to accommodate increased workload. However, it might not always be the case to find increased FCW intensity in PH patients; for instance, as the disease advances and the ventricular performance and cardiac output decrease, the magnitude of FCW may be reduced\textsuperscript{15}.

The conventional calculation of RV work accounts for the steady flow fraction of RV stroke work\textsuperscript{16}. We described RV stroke power and energy densities, which are useful dimensions for comparison with WIA parameters. It may seem strange that wave power/energy exceed the total steady hydraulic power/energy. However, this is the result of the definition of normalized wave intensity, where the number of samples is squared. We have demonstrated that the fraction of wave power/energy relative to the mean hydraulic power/energy, as expressed by FCW to RV power and energy density ratios, reduced in PAH. The oscillatory power fraction of total RV power has been shown to be reduced in PH in previous studies\textsuperscript{24, 25} and this has been interpreted as an efficient RV adaption to increased afterload, as the oscillatory power is considered an unavoidable “waste”\textsuperscript{26}. This may explain the reduced wave power fraction in PAH. Although not directly related to RV oscillatory power, wave power is associated with the generation of pulse waves and was significantly correlated to the pulmonary pulse pressure. However, there is also evidence suggesting
conserved\textsuperscript{27} or increased\textsuperscript{28} ratio of oscillatory power to mean hydraulic power in PAH. It is unclear why these studies differ, but may relate to methodological differences.

Contrary to PAH, we observed that the fraction of wave power/energy in CTEPH patients was not significantly different compared to controls. The lower FCW to RV power/energy ratios in PAH compared to CTEPH suggests differences in the intrinsic and/or extrinsic components of the RV load. RV remodeling is triggered by pressure overload in both CTEPH and PAH, but the disease mechanism differs. CTEPH is characterized by elevated pressure after an episode (or multiple episodes) of pulmonary embolism in the proximal pulmonary arterial segments\textsuperscript{29}, while PAH is caused by gradual changes in the distal pulmonary vasculature\textsuperscript{30}. Although not statistically significant, the wave speed, i.e. proximal arterial stiffness, was greater and yet the total pulmonary vascular resistance and PAPm were lower in the CTEPH group in comparison to the PAH group. The differences in the fraction of wave power/energy may therefore reveal subtle dissimilarities in the altered RV afterload between the two diseases. Though less likely, another possibility is that it reflects differences in RV adaptation. RV remodeling in response to pressure overload is complex\textsuperscript{31}, for instance, pressure overload states such as Eisenmenger syndrome and congenital pulmonary stenosis are better tolerated than other causes of PAH and RV failure occurs late in the course of disease demonstrating different RV adaptation\textsuperscript{32}. Whether the mechanism of RV remodeling in CTEPH differs from PAH is unclear. Our findings may reflect a more rapid (in most cases) RV adaptation to a sudden change in pressure load as it is in CTEPH versus gradual alteration over time in PAH.

**Wave Reflection**
Reflected waves are generated when there are changes in the energy transmission properties of the vessels, e.g. altered cross sectional area or arterial stiffening, causing impedance mismatch between the proximal and distal vasculature. In the control subjects, wave reflection was practically negligible (WRI of 3 – 6 %). This suggests that there is no single distinct reflection site in the normal pulmonary vasculature, supporting the theory that the pulmonary arterial tree is constructed in a way that facilitates the propagation of forward traveling waves optimally whilst minimizing wave reflection and thereby minimizing the ventricular workload. In contrast to previous studies in open-chested canine models and a recent magnetic resonance imaging (MRI) based study in man, we did not consistently observe a BDW in mid-systole that accelerates pulmonary flow in control subjects. One subject of 46 years and another subject of 55 years did show an evident BDW (WRI > 5 %). It has been shown that the pulmonary artery stiffens with age, therefore, it is not inconceivable that a more prominent BDW may be present in younger healthy individuals.

In PH patients, there was a large BCW, i.e. a reflection wave, present in mid-systole, indicating a mismatch in pulmonary vascular impedance. Previous studies in animal models and man have used the local wave speed and half the traveling time between the peak of FCW to BCW to give an estimate of the reflection site. However, this calculation is based on the assumption that the local wave speed is constant throughout the circulation, which is unlikely. For instance, applying the calculation in the PAH group and CTEPH group in this study would give a reflection site of ~40 cm and ~56 cm downstream of the main pulmonary artery, respectively, both of which are anatomically implausible.

We found no significant differences in the wave reflection pattern between the PAH and CTEPH patients, and the differences remained insignificant even after excluding the two non-operable CTEPH patients. As discussed above, PAH is considered a disease of the distal pulmonary artery, while CTEPH is regarded as a disease of the more proximal segments.
Previous studies have suggested that earlier and larger wave reflection, as assessed by inflection time and augmentation index, respectively, applied to the pressure waveform, is present in CTEPH patients and may be used as an additional marker to differentiate between the two diseases. However, the use of this method to evaluate wave reflection in the systemic circulation has been questioned. A recent study suggests that the energy of BCW is increased in CTEPH patients with proximal clots compared to PAH patients. However, we did not observe any significant differences in reflection time, the magnitude of the reflective wave or WRI between the two groups suggesting that the main apparent reflection site is similar in the two types of pulmonary hypertension. CTEPH patients are characterized by chronic thrombi in the pulmonary artery and wave behavior in the vicinity of the thrombi is unknown. As CTEPH advances, progressive pulmonary vascular remodeling in the small vessels and changes in pulmonary microcirculation including plexiform lesions occur, much like the pathology of PAH, which may explain the similarity in the wave reflection pattern between the two groups of patients.

There was no strong association between pulmonary WRI and conventionally used hemodynamic, echocardiographic or biochemical parameters, i.e. the degree of vascular impedance mismatch (as expressed by WRI) was not related with the dynamic and steady flow components of the RV workload, nor was it associated with measures of RV function. The lack of correlation between WRI, pulmonary artery compliance and resistance suggests that these parameters represent different manifestations of pulmonary vascular disease and thus different components of the RV workload. The normal adult pulmonary circulation is a low-pressure, high-compliance system with a large vascular reserve in the form of non-perfused vessels. As a result, increased PAPm (≥ 25 mmHg) occurs relatively late in the progression of disease when damage to the vasculature is advanced, i.e. PAPm may not reveal the true severity of pulmonary vascular disease. Early diagnosis of pulmonary vascular...
disease prior to an increase in resting PAPm may be advantageous in patients at high risk of PH, for example patients with systemic sclerosis, patients with persistent symptoms after acute pulmonary embolism or first degree family members of patients with heritable PAH. Early detection of pulmonary vascular disease remains a great challenge. Potential clinical techniques for early detection such as stress Doppler echocardiography, MRI adenosine stress test and invasive cardiopulmonary exercise test still lack validation. The current study showed that in individuals without pulmonary vascular disease, there was minimal wave reflection, while in patients with mildly elevated PAPm, WRI was ~30%; similar to patients with severely elevated PAPm. Furthermore, WRI of patients treated with specific PAH drugs was comparable to patients not on PAH treatment. Thus, progressive vascular impedance mismatch in the pulmonary artery must occur in the initial phase of pulmonary vascular disease, maybe even before a rise in PAPm is detectable. While WRI does not serve as an indicator of the degree of PH or RV dysfunction in established disease, it may be possible that increased WRI, in the presence of normal PAPm and RV function, is an early marker of disease in the pulmonary vasculature. WIA as a technique for early detection of disease does not require exposing patients to additional stress in the form of hypoxia or exercise as it is the case with stress echocardiography and invasive cardiopulmonary exercise. On the other hand, it would be interesting to apply WIA during interventions that are likely to alter the RV workload, such as cardiopulmonary exercise and nitric oxide inhalation. However, this is beyond the scope of this paper and further studies are required to determine the clinical usefulness of pulmonary WIA.

**Study Limitations**
The number of study subjects was small and therefore, some of the statistical comparisons may be underpowered. For the same reason, we have abstained from performing multivariable analysis. Although unlikely, we cannot exclude that the uneven distribution in of men and women may have a small influence on the observed differences in wave characteristics between the three groups. However, the aim of this study was to apply WIA in health and disease and the wave intensity pattern was consistent for all the subjects in each group. The number of patients recruited from the two centers was not equally distributed. Therefore, care was taken to avoid measurement bias as mentioned above. To recruit completely healthy control subjects in a catheterization laboratory was not feasible. However, we only included individuals without any risk factors for pulmonary vascular disease in the form of lung diseases, left ventricular dysfunction or valvular diseases. Likewise, PAH and CTEPH are both rare diseases, therefore to recruit PH patients without other cardiovascular or respiratory morbidities was challenging.

We do not have simultaneous recordings from the right ventricle and therefore, interpretation of the forward traveling waves in relation to the temporal RV function are assumptions based on knowledge of physiological events. Acquiring high quality velocity measurements was challenging. This is especially the case for PH patients, where the pulmonary flow may be highly disturbed\textsuperscript{49}, which induces signal noises and artefacts on the Doppler flow tracings. Vibration and axial movements of the catheter as well as occasional positioning of the catheter against the vessel wall also introduce signal artefacts. Thus, careful manipulation of the catheter during the procedure and meticulous post hoc data processing were necessary. Rather than making measurements in both branch pulmonary arteries of each control subject and PAH patient, we acquired data from either the left or right pulmonary artery, depending on which artery the catheter most easily advanced into, consistent with common clinical practice. However, we do not expect asymmetric
hemodynamics in these subjects. In CTEPH patients, it would be ideal to obtain data from both pulmonary branches to assess whether there is asymmetry in wave characteristics. However, good quality velocity data were not obtainable from the left pulmonary artery from several of the patients, and as all the patients either had bilateral thrombi or solely right-sided thrombi, we chose to focus our data analyses on the main and right pulmonary arteries.

**Conclusion**

In conclusion, wave intensity analysis in the pulmonary artery revealed distinct differences in arterial wave propagation between individuals with and without pulmonary hypertension. Wave reflection was minimal in individuals without pulmonary vascular disease, while large wave reflection was observed in patients with pulmonary hypertension indicating downstream vascular impedance mismatch. In contrast to wave speed, the magnitude of wave reflection was unrelated to disease severity. Thus, while WRI does not serve as an indicator of the degree of PH or RV dysfunction in established disease, it may be possible that increased WRI, in the presence of normal PAPm and RV function, is an early marker of disease in the pulmonary vasculature.

In addition, FCW to RV power/energy density ratios differ between PAH and CTEPH patients suggestive of differences in the intrinsic and/or extrinsic RV load. Differentiation between PAH and CTEPH in clinical practice is mainly based on medical history and imaging. While this is unlikely to change, we have demonstrated that FCW to RV power/energy ratios display significant discriminatory capacity to distinguish between CTEPH and PAH. Characterizing the pathophysiological differences between the two diseases may contribute to our understanding of disease progression and treatment responses, be they in terms of the pulmonary vasculature or right ventricle.
The complex nature of data acquisition and processing may limit the use of WIA in clinical setting at present, however, recent advances in multisensor catheters, MRI technologies and automated data processing could facilitate future use of pulmonary WIA.

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Table 1. Patient Characteristics and Hemodynamic Values.

|                        | Control (n = 10) | PAH (n = 11) | CTEPH (n = 10) | p     |
|------------------------|-----------------|--------------|----------------|-------|
| **Demographics**       |                 |              |                |       |
| Age, yrs               | *59 ± 14        | *56 ± 21     | 66 ± 9         | 0.36  |
| Male, n (%)            | *8 (80)         | *2 (18)      | 2 (20)         | 0.009†|
| BMI, kg/m²             | 27.9 ± 5.2      | 26.5 ± 4.6   | 27.4 ± 6.3     | 0.82  |
| **Drugs, n (%)**       |                 |              |                |       |
| α-/β-adrenoceptor antagonist | 4 (40)       | 3 (27)       | 0 (0)          | 0.11  |
| Calcium antagonist     | 3 (30)          | 3 (27)       | 0 (0)          | 0.20  |
| ACE inhibitor/Angiotensin II antagonist | 2 (20)       | 0 (0)        | 3 (30)         | 0.16  |
| Diuretic               | 1 (0)           | 6 (55)       | 7 (70)         | 0.022†|
| Phosphodiesterase-5 inhibitor | 0            | 6 (55)       | 1 (10)         | 0.007‡|
| Endothelin receptor antagonist | 0             | 5 (45)       | 0 (0)          | 0.006‡|
| Prostanoid             | 0               | 1 (9)        | 0 (0)          | 1.0   |
| **Hemodynamics**       |                 |              |                |       |
| Heart rate             | *73 ± 8         | *81 ± 8      | 80 ± 15        | 0.21  |
| SBP, mmHg              | 129 ± 19        | 116 ± 14     | 125 ± 20       | 0.19  |
| DBP, mmHg              | 73 ± 19         | 71 ± 10      | 86 ± 16        | 0.080 |
| Right atrial pressure, mmHg | --             | 8 ± 2        | 9 ± 5          | 0.36  |
| PAPs, mmHg             | *26 ± 3         | *76 ± 16     | 72 ± 17        | <0.001†|
| PAPd, mmHg             | *12 ± 3         | *33 ± 9      | 27 ± 5         | <0.001†|
| PAPm, mmHg             | *17 ± 3         | *47 ± 11     | 42 ± 8         | <0.001†|
| Mean velocity in main PA, cm/s | 27.8 ± 10.2 | 20.5 ± 5.9  | 20.0 ± 6.4    | 0.065 |
| Max velocity in main PA, cm/s | 53.1 ± 14.6 | 37.3 ± 11.2 | 36.9 ± 11.2  | 0.011†|
| Mean velocity in branch PA, cm/s | *33.8 ± 13.1§| *21.0 ± 9.5 | 17.5 ± 6.2   | 0.003†|
| Max velocity in branch PA, cm/s | *63.0 ± 21.1§| *40.9 ± 18.3| 32.4 ± 9.8  | 0.002†|
| Cardiac index, L/min/m² | 2.57 ± 0.46    | 2.33 ± 1.08 | 2.35 ± 0.77   | 0.77  |
| Indexed TPR, WU/m²     | 6.96 ± 1.97     | 24.6 ± 12.8 | 19.6 ± 7.8    | <0.001†|
| Cp (ml/mmHg)           | 5.34 ± 1.62     | 1.33 ± 0.83  | 1.38 ± 0.68   | <0.001†|
Indexed RV stroke work (mmHg·ml/m²) & 388 ± 75 & 1062 ± 326 & 990 ± 503 & 0.003† \\
RV stroke power density, W/m² & 403 ± 143 & 1016 ± 221 & 887 ± 441 & <0.001† \\
RV stroke energy density, J/m² & 331 ± 114 & 757 ± 180 & 665 ± 318 & 0.001† \\

Data are presented as mean ± SD or n (%). Cardiac index was calculated using thremodilution (n = 4), direct Fick’s method (n = 22) or indirect Fick’s method (n = 4).

ACE, angiotensin converting enzyme; CTEPH, chronic thromboembolic pulmonary hypertension; DBP, diastolic blood pressure; Cp, global pulmonary compliance; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAPd: diastolic pulmonary arterial pressure; PAPm, mean pulmonary arterial pressure; PAPs, systolic pulmonary arterial pressure; SBP, systolic blood pressure; TPR, total pulmonary resistance; RV: right ventricle.

*Previously published data²⁰.
†Control significantly different from PAH and CTEPH.
‡PAH significantly different from control and CTEPH.
§Branch PA significantly different from main PA.
Table 2. Magnitude of the Separated Waves in the Main and Branch Pulmonary Arteries

| Main pulmonary artery | Control | PAH     | CTEPH   | p        |
|-----------------------|---------|---------|---------|----------|
| FCW intensity, \(10^4\) W/m\(^2\) | 8.70 (5.95 – 10.9) | 11.2 (8.5 – 15.0) | 13.3 (11.6 – 16.0) | 0.027† |
| FCW energy density, \(10^3\) J/m\(^2\) | 3.95 (3.51 – 4.66) | 5.83 (3.95 – 6.82) | 6.20 (5.07 – 8.51) | 0.041† |
| FDW intensity, \(10^4\) W/m\(^2\) | 2.33 (1.29 – 3.06) | 4.11 (2.77 – 5.92) | 4.21 (2.56 – 5.65) | 0.044† |
| FDW energy density, \(10^3\) J/m\(^2\) | 1.55 (1.04 – 1.94) | 1.88 (1.51 – 3.02) | 2.96 (2.00 – 3.77) | 0.18  |
| BW intensity, \(10^4\) W/m\(^2\) | 0.48 (0.35 – 0.54) | 3.18 (2.46 – 4.70) | 2.45 (1.68 – 5.92) | <0.001† |
| BW energy density, \(10^3\) J/m\(^2\) | 0.16 (0.14 – 0.21) | 1.51 (0.82 – 0.80) | 1.08 (0.73 – 2.72) | <0.001† |
| Wave reflection index, % | 3.93 (3.38 – 6.78) | 25.1 (19.3 – 29.6) | 30.2 (11.8 – 35.5) | <0.001† |

| Branch pulmonary artery |         |         |         |         |
|-------------------------|---------|---------|---------|---------|
| FCW intensity, \(10^4\) W/m\(^2\) | 8.01 (4.40 – 15.1) | 14.1 (10.1 – 21.2) | 9.66 (9.21 – 14.4) | 0.12§ |
| FCW energy density, \(10^3\) J/m\(^2\) | *4.48 (1.75 – 5.49) | *6.43 (4.17 – 9.34) | 4.11 (3.94 – 7.25) | 0.10† |
| FDW intensity, \(10^4\) W/m\(^2\) | 1.68 (1.05 – 3.38) | 3.90 (2.46 – 7.72) | 2.74 (1.64 – 2.24) | 0.018† |
| FDW energy density, \(10^3\) J/m\(^2\) | *1.26 (0.73 – 1.88) | *2.41 (1.35 – 3.71) | 1.33 (0.58 – 1.55)# | 0.098||
| BW intensity, \(10^4\) W/m\(^2\) | 0.35 (0.19 – 0.89) | 3.07 (2.26 – 5.90) | 2.80 (1.78 – 4.10) | <0.001† |
| BW energy density, \(10^3\) J/m\(^2\) | *0.16 (0.13 – 0.31) | *1.70 (1.06 – 2.02) | 1.31 (1.01 – 1.87) | <0.001† |
| Wave reflection index, % | *6.36 (3.20 – 9.09) | *24.7 (18.9 – 32.6) | 31.8 (25.8 – 36.6) | <0.001† |

Data are presented as median (25 % - 75 % quartile). Backward waves appear as backward decompression wave in three of the control subjects and backward compression wave in the rest of the control subjects as well as all the pulmonary hypertension patients.

BW, backward wave; CTEPH, chronic thromboembolic pulmonary hypertension; FCW, forward compression wave; FDW, forward decompression wave; PAH, pulmonary arterial hypertension.

*Previously published data\(^20\).
†Control significant different from PAH and CTEPH.
‡CTEPH significantly different from control.
§PAH significant different from control.
||PAH significantly different from control and CTEPH.
#Branch significantly different from main pulmonary artery.
Table 3. Spearman’s Rank Correlation between Wave Intensity Indices and Conventionally Used Clinical Values.

|       | Wave speed | FCW intensity | FCW energy | BCW intensity | BCW energy | WRI |
|-------|------------|---------------|------------|---------------|------------|-----|
| PAPm  | 0.62       | <0.01         | 0.14       | 0.56          | 0.58       | 0.26| 0.29| 0.07| 0.79| -0.08| 0.74|
| RA pressure | 0.35 | 0.15 | 0.07 | 0.78 | -0.05 | 0.83 | -0.05 | 0.83 | -0.03 | 0.89 | -0.05 | 0.83 |
| PAPp  | 0.78       | <0.01         | 0.48       | 0.04          | 0.54       | 0.02| 0.14| 0.58| -0.01| 0.96| -0.20| 0.41|
| Cp    | -0.62      | <0.01         | 0.09       | 0.71          | 0.22       | 0.36| 0.07| 0.76| 0.20 | 0.41| 0.26 | 0.27|
| CI    | -0.26      | 0.29          | 0.08       | 0.75          | 0.32       | 0.19| -0.18| 0.45| -0.07| 0.77| -0.07| 0.78|
| RVSVI | -0.31      | 0.20          | 0.20       | 0.41          | 0.38       | 0.11| 0.03| 0.91| 0.11 | 0.66| 0.06 | 0.81|
| PVRI  | 0.46       | 0.05          | -0.02      | 0.93          | -0.19      | 0.45| 0.17| 0.48| 0.02 | 0.95| -0.07| 0.78|
| RA index | -0.10 | 0.69 | 0.18 | 0.45 | 0.13 | 0.60 | 0.06 | 0.79 | 0.19 | 0.43 | 0.05 | 0.84 |
| RV/LV | 0.26       | 0.29          | 0.10       | 0.68          | -0.03      | 0.89| 0.17| 0.48| 0.06 | 0.81| 0.04 | 0.87|
| RV FAC| -0.18      | 0.46          | 0.13       | 0.59          | -0.05      | 0.84| -0.36| 0.13| -0.29| 0.22| -0.25| 0.29|
| TAPSE | -0.58      | 0.01          | -0.07      | 0.79          | -0.14      | 0.58| -0.01| 0.96| 0.07 | 0.79| 0.20 | 0.40|
| BNP   | 0.21       | 0.38          | 0.31       | 0.19          | 0.12       | 0.64| 0.11| 0.65| 0.20 | 0.40| 0.04 | 0.89|

In contrast to wave speed, there was no strong association between pulmonary WRI and conventionally used hemodynamic, echocardiographic or biochemical parameters.

BCW, backward compression wave; BNP, B-type natriuretic peptide; CI, cardiac index; Cp, global pulmonary compliance; FCW, forward compression wave; PAPm, mean pulmonary arterial pressure; PAPp, pulmonary arterial pulse pressure; PVRI, indexed pulmonary vascular resistance; RA, right atrium; RA index, indexed RA area; RV FAC, right ventricular fractional area change; RV/LV, right ventricular area to left ventricular area ratio; RVSVI, indexed right ventricular stroke volume; TAPSE, tricuspid annular plane systolic excursion.

Bold font represents \( p < 0.05 \).
Figure Legends:

Figure 1. Flow chart for patient recruitment. Of the included patients, all of the control subjects and pulmonary arterial hypertension (PAH) patients were recruited from Hammersmith Hospital, London, while six of the chronic thromboembolic pulmonary hypertension patients (CTEPH) were recruited from Aarhus University Hospital.

Figure 2. Representative original trace from a patient with pulmonary arterial hypertension. Top panel shows the electrocardiography (ECG) trace, middle panel shows the simultaneous pressure traces from a fluid filled catheter (red line) and high fidelity solid state catheter (Combowire, yellow line) and the bottom panel shows the Doppler flow signal with velocity tracking (blue line). There is a mid-systolic notch in the Doppler flow signal.

Figure 3. Pressure and flow velocity profile (upper panel) and wave intensity pattern (lower panel) for a control (A), pulmonary arterial hypertension (PAH, B) and chronic thromboembolic pulmonary hypertension (CTEPH, C) patient, respectively. There is minimal backward wave intensity in the control subject. The wave intensities of the forward waves increased in the pulmonary hypertension patients and there is a distinctive backward compression wave present in mid-systole. Red line outlines the net wave intensity profile. BCW (dark green), backward compression wave; FCW (dark blue), forward compression wave; FDW (light blue), forward decompression wave; P, pressure; U, velocity.

Figure 4. Wave speed was significantly higher in patients with pulmonary hypertension compared to controls. There was no significant difference between patients with pulmonary hypertension.
arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), or between main and branch pulmonary artery

**Figure 5.** Wave to RV power/energy density datios. Forward compression wave (FCW) to right ventricular (RV) power (A) and energy (B) density ratios in the three groups and receiver operating characteristics analysis (C & D) for distinguishing chronic thromboembolic pulmonary hypertension (CTEPH) from pulmonary arterial hypertension (PAH) are shown. AUC: area under the curve.

**Figure 6.** Wave speed and wave reflection in relation to mean pulmonary arterial pressure. Pulmonary hypertension patients are assigned to have mildly elevated mean pulmonary arterial pressure (PAPm = 25 – 34 mmHg), moderately elevated pressure (PAPm = 35 – 44 mmHg) and severely elevated pressure (PAPm ≥ 45 mmHg). In contrast to the wave speed (A), the degree of vascular impedance mismatch, as expressed by wave reflection index (WRI, B) was shown to be unrelated to the severity of pulmonary hypertension.
Recruited patients: 36

- Coronary angiography or radiofrequency ablation: 11
  - Unsatisfactory data: 1
    - Control subjects: 10
  - PAH investigation: 11
    - PAH confirmed: 11
  - CTEPH investigation: 14
    - CTEPH ruled out: 4
    - CTEPH confirmed: 10
