ORIGINAL RESEARCH

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

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***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 participants, 11 patients with PAH, and 10 patients with CTEPH were studied. Wave speed and wave power were significantly greater in PH patients compared with 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 in PH patients (PAH: ≈25%; CTEPH: ≈30%) was significantly greater compared with controls (≈4%), indicating downstream vascular impedance mismatch. Although wave speed was significantly correlated to disease severity, wave reflection indexes of patients with mildly and severely elevated pulmonary pressures were similar.

***Conclusions*—**Wave reflection in the pulmonary artery increased in PH 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 with CTEPH indicates differences in the intrinsic and/or extrinsic ventricular load between the 2 diseases. **(*J Am Heart Assoc*. 2017;6:e006679. DOI: 10.1161/JAHA.117.006679.)**

Key Words: pulmonary artery • pulmonary hypertension • pulse wave velocity • wave intensity

Pulmonary hypertension (PH), defined as an elevated mean pulmonary arterial pressure (PAPm ≥25 mm Hg) 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 are commonly used hemodynamic measures to evaluate disease severity. However, they describe only 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]; 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, in which the results are presented in the frequency domain, WIA is a time domain technique, in which the results are presented as a function of time, allowing

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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 pulmonary arterial hypertension patients than in chronic thromboembolic PH patients, suggesting differences in the intrinsic and/or extrinsic ventricular loads between the 2 diseases.

What Are the Clinical Implications?

- Wave reflection may be an early marker of disease in the pulmonary vasculature.
- Characterizing the pathophysiological differences between pulmonary arterial hypertension and chronic thromboembolic PH may contribute to our understanding of disease progression and treatment response in pulmonary hypertension.

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 humans.[14,15]

The objective of this study was to use WIA in the pulmonary artery to characterize wave propagation in persons without pulmonary vascular disease and in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH). Furthermore, we explored 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 participants were selected from patients undergoing cardiac catheterization for clinical reasons at Hammersmith Hospital, Imperial College Healthcare, and at 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 participants were recruited among patients without significant cardiovascular or lung disease who 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 among patients with confirmed or suspected PAH and CTEPH who were undergoing right heart catheterization as part of a diagnostic investigation or routine follow-up. Patients with normal PAPm and previous history of thromboembolism and patients with elevated pulmonary arterial wedge pressure (>15 mm Hg) with or without elevated PAPm were excluded because they may not have normal pulmonary hemodynamics to be considered as controls and they did not fall into the categories of PAH and CTEPH. The study was approved by the London-Fulham Research Ethics Committee and the Central Denmark Region Committees on Health Research Ethics, respectively (references 13/LO/1305 and M-2013-278-13, respectively), and all participants 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 the right femoral, brachial, or internal jugular vein. A combined dual-tipped pressure and Doppler flow sensor wire (Combowire; Philips Volcano) was then advanced ≈1 cm beyond the end of the catheter.[8] 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 to 60 seconds, together with ECG monitoring in a free breathing state in the main pulmonary artery and subsequently in either the left or right pulmonary artery, hereafter referred to as the *branch pulmonary artery*. In CTEPH patients, data were acquired from both the left and right pulmonary arteries. All participants were in sinus rhythm at the 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. In PH patients, indexed pulmonary vascular resistance was calculated as the transpulmonary pressure gradient (defined as the difference between PAPm and pulmonary arterial wedge pressure) divided by cardiac index.

RV 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 of cross-sectional area of the artery, were derived from the conventionally used formula for calculating steady flow RV stroke work (RVSW Equation 1)[16]:

$$\mathrm{RVSW} = (\mathrm{PAPm} - \mathrm{RAP}) \cdot \mathrm{RVSV} \tag{1}$$

where RAP is the right atrial pressure and RVSV is the RV stroke volume. RAP was measured in all PH patients but not in the control participants and was arbitrarily set to 6 mmHg in controls.

Normalizing RV stroke work to the cross-sectional area (CSA) of the main pulmonary artery yields RV energy density (Equation 2):

$$\begin{aligned}\text{RV energy density} &= \frac{\mathrm{RVSW}}{\mathrm{CSA}} = \frac{(\mathrm{PAPm} - \mathrm{RAP}) \cdot \mathrm{RVSV}}{\mathrm{RVSV} \cdot \mathrm{HR}/\mathrm{U_{mean}}} \\ &= \frac{(\mathrm{PAPm} - \mathrm{RAP})}{\mathrm{HR}/\mathrm{U_{mean}}}\end{aligned} \tag{2}$$

where U_{mean} is the mean flow velocity and HR is the heart rate. Hence,

$$\text{RV energy density} = (\mathrm{PAPm} - \mathrm{RAP}) \cdot \mathrm{U_{mean}} \cdot \mathrm{CCD} \tag{3}$$

where CCD is the duration of the cardiac cycle, and,

$$\text{RV power density} = (\mathrm{PAPm} - \mathrm{RAP}) \cdot \mathrm{U_{mean}}. \tag{4}$$

Wave Intensity Analysis

Pressure and velocity data (shown as a P and U, respectively, in Equation 5) were processed offline using customized Matlab software (MathWorks).[17] Signals were ensemble-averaged with timing gated to the R wave of ECG and smoothed using a Savitzky–Golay differentiating filter (second 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 averaged 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 (shown as c) was calculated using the sum of squares method (Equation 5)[18]:

$$c = \frac{1}{\rho} \cdot \sqrt{\frac{\sum dP^2}{\sum dU^2}}, \tag{5}$$

where ρ is the blood density, assumed to be 1040 kg/m^3, and the sum is taken over 1 cardiac period.

The sum of squares method was used to calculate wave speed rather than the PU-loop (pressure and velocity 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.[19] The PU-loop method is valid only under the assumption that there is no wave reflection in early systole, namely, that there is an early linear segment on the PU curve. In many of our participants, the PU loop did not display a perfectly linear initial segment, and because wave propagation in the pulmonary artery is not well understood, we could not rule out early wave reflection, especially in PH 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-traveling waves and negative for backward-traveling waves. WIA was performed essentially as described previously,[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 (shown as WI_+) and backward (shown as WI_-) components (Equation 6):

$$WI_{\pm} = \pm\left(\frac{dP \cdot CCD}{dt} \pm \rho c \cdot \frac{dU \cdot CCD}{dt}\right)^2 / (4\rho c) \tag{6}$$

Separated waves were quantified by the peak intensity of the individual waves (W/m^2) and by the cumulative area under each wave corresponding to the wave energy density (J/m^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 Analyses

Data were analyzed for normality using the Q-Q plot. Results are expressed as mean±SD when normally distributed or as median (25–75% quartile) when nonnormally distributed. Proportions are expressed as percentages. Differences among the 3 study groups were compared using 1-way ANOVA followed by a Bonferroni test. A Kruskal–Wallis test followed by a Dunn test was used for nonnormally distributed data and for normally distributed data with unequal variances, as tested by the Bartlett test. The Fisher exact test was used for categorical variables. Differences between data from the main and branch artery within each group were compared using a paired *t* test or the Wilcoxon signed-rank test. Spearman correlation analysis was performed to examine simple relationships between variables. Area under the receiver operating characteristic curve 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).

Results

Patient Characteristics

A total of 36 participants were recruited (Figure 1). Eleven subjects had no significant cardiovascular disease or lung disease and served as control participants, and technically satisfactory data were obtained from 10 of them (aged 59±14 years, 8 male). Eleven patients (aged 56±21 years, 2 male) had confirmed PAH: 6 with idiopathic PAH, 4 with PAH associated with connective tissue disease, and 1 with pulmonary veno-occlusive disease. Of the remaining 14 patients, 10 were diagnosed with CTEPH (aged 66±9 years, 2 male). Satisfactory velocity data from the left pulmonary artery could not be obtained from several 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 PAH patients and 9 CTEPH patients, whereas satisfactory data from the branch pulmonary artery were obtained from all PAH patients and 9 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 with controls. The cardiac index was highest in the control group, although the difference was not statistically significant compared with the PH groups. There were no significant differences in the conventionally used hemodynamic parameters between the PAH and CTEPH groups.

Wave Intensity Parameters

A representative original recording trace for a PAH patient is shown in Figure 2. A midsystolic 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 participant in each group are shown in Figure 3, and wave intensity parameters are summarized in Table 2. Wave speed (Figure 4) in the main

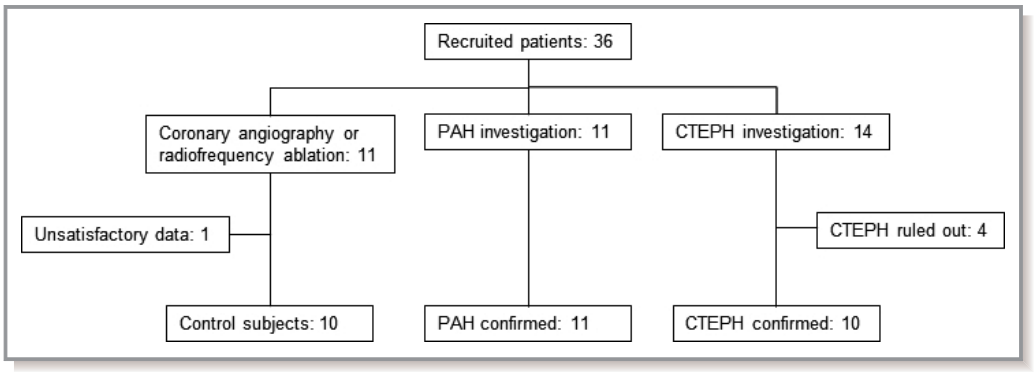

Figure 1. Flow chart for patient recruitment. Of the included patients, all control participants and pulmonary arterial hypertension (PAH) patients were recruited from Hammersmith Hospital, London, whereas 6 of the chronic thromboembolic pulmonary hypertension patients (CTEPH) were recruited from Aarhus University Hospital.

Table 1. Patient Characteristics and Hemodynamic Values

	Control (n=10)	PAH (n=11)	CTEPH (n=10)	*P* Value
Demographics				
Age, y	59±14*	56±21*	66±9	0.36
Male, n (%)	8 (80)*	2 (18)*	2 (20)	0.009†
BMI, kg/m^2	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
ACEI/angiotensin II antagonist	2 (20)	0 (0)	3 (30)	0.16
Diuretic	1 (0)	6 (55)	7 (70)	0.022†
PDE-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, mm Hg	129±19	116±14	125±20	0.19
DBP, mm Hg	73±19	71±10	86±16	0.080
Right atrial pressure, mm Hg	…	8±2	9±5	0.36
PAPs, mm Hg	26±3*	76±16*	72±17	<0.001†
PAPd, mm Hg	12±3*	33±9*	27±5	<0.001†
PAPm, mm Hg	17±3*	47±11*	42±8	<0.0.001†
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 per m^2	2.57±0.46	2.33±1.08	2.35±0.77	0.77
Indexed TPR, WU/m^2	6.96±1.97	24.6±12.8	19.6±7.8	<0.001†
Cp, mL/mm Hg	5.34±1.62	1.33±0.83	1.38±0.68	<0.001†
Indexed RV stroke work, mm Hg·mL/m^2	388±75	1062±326	990±503	0.003†
RV stroke power density, W/m^2	403±143	1016±221	887±441	<0.001†
RV stroke energy density, J/m^2	331±114	757±180	665±318	0.001†

Data are presented as mean±SD or n (%). Cardiac index was calculated using thermodilution (n=4), direct Fick method (n=22), or indirect Fick method (n=4). ACEI indicates angiotensin-converting enzyme inhibitor; BMI, body mass index; Cp, global pulmonary compliance; CTEPH, chronic thromboembolic pulmonary hypertension; DBP, diastolic blood pressure; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAPd, diastolic pulmonary arterial pressure; PAPm, mean pulmonary arterial pressure; PAPs, systolic pulmonary arterial pressure; PDE-5, phosphodiesterase type 5; RV, right ventricle; SBP, systolic blood pressure; TPR, total pulmonary resistance; WU, wood unit.

*Previously published data.[20]

†Control significantly different from PAH and CTEPH.

‡PAH significantly different from control and CTEPH.

§Branch PA significantly different from main PA.

pulmonary artery was ≈3 m/s in control participants 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 with controls but not PAH patients.

During systole, 2 distinct forward traveling waves were consistently identified in all 3 groups. An FCW, the incident wave, was observed in early systole, which is generally attributed to RV ejection, and a forward decompression wave was observed in late systole just before the dicrotic notch on the pressure waveform. The forward decompression wave decreased the pressure and flow and is assumed to correspond to ventricular relaxation before the closure of the pulmonary valve. The magnitude of the FCW (both peak wave

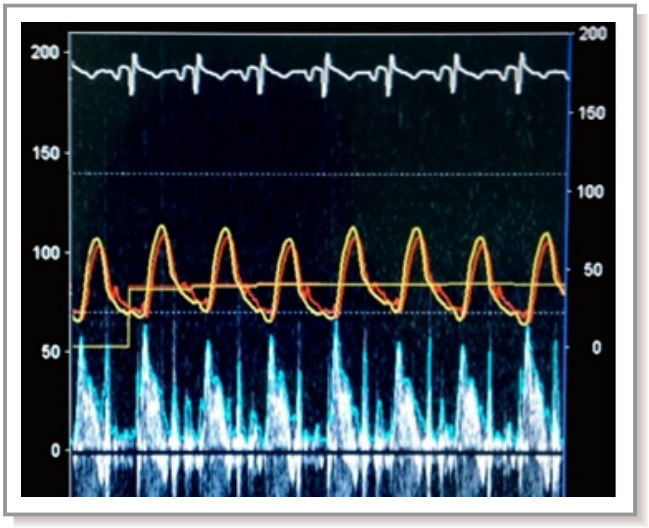

Figure 2. Representative original trace from a patient with pulmonary arterial hypertension. (Top) ECG trace. (Middle) Simultaneous pressure traces from a fluid-filled catheter (red line) and high-fidelity solid state catheter (Combowire; yellow line). (Bottom) Doppler flow signal with velocity tracking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

intensity and wave energy) in the main pulmonary artery was significantly greater in PH patients compared with controls indicating increased RV work, whereas there was no significant difference between the PAH and CTEPH patients (Table 2).

Backward waves were observed in mid-systole. In control participants, an identifiable BCW was present in mid-systole in 7 cases, whereas a 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 with controls. The arrival time of the BCW was not significantly different between PAH (63 ms [range: 55–85 ms]) and CTEPH (70 ms [range: 60–100 ms]) patients.

Similar findings were observed in the branch pulmonary arteries (Table 2). The observed differences in wave propagation among the 3 study groups persisted when nonnormalized 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 by cross-sectional area of the artery. They were significantly higher in PH patients compared with controls, whereas there were no significant differences between PAH and CTEPH patients (Table 2).

FCW to RV power and energy density ratios were significantly lower in the PAH group than both the control and CTEPH groups, whereas there were no significant differences between the 2 latter groups (Figure 5A and 5B). Moreover, FCW to RV power and energy density ratios showed significant discriminatory capacity between CTEPH and PAH patients (Figure 5C and 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 BNP (B-type natriuretic peptide) was investigated. Because the data from the controls and from PH patients were very different, the control data 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 pulmonary arterial pulse pressure ($\rho=0.78$, $P<0.01$)—and with the steady flow parameters PAPm ($\rho=0.62$, $P<0.01$) and pulmonary vascular resistance ($\rho=0.46$, $P=0.05$) and a significant association with the tricuspid annular plane systolic excursion ($\rho=-0.58$, $P<0.01$). In addition, there was a significant correlation between the magnitude of FCW—both peak wave intensity and wave energy—and pulmonary arterial pulse pressure.

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 with 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 participants with and without PH. We observed similar wave intensity patterns in the main and branch pulmonary arteries within each group.

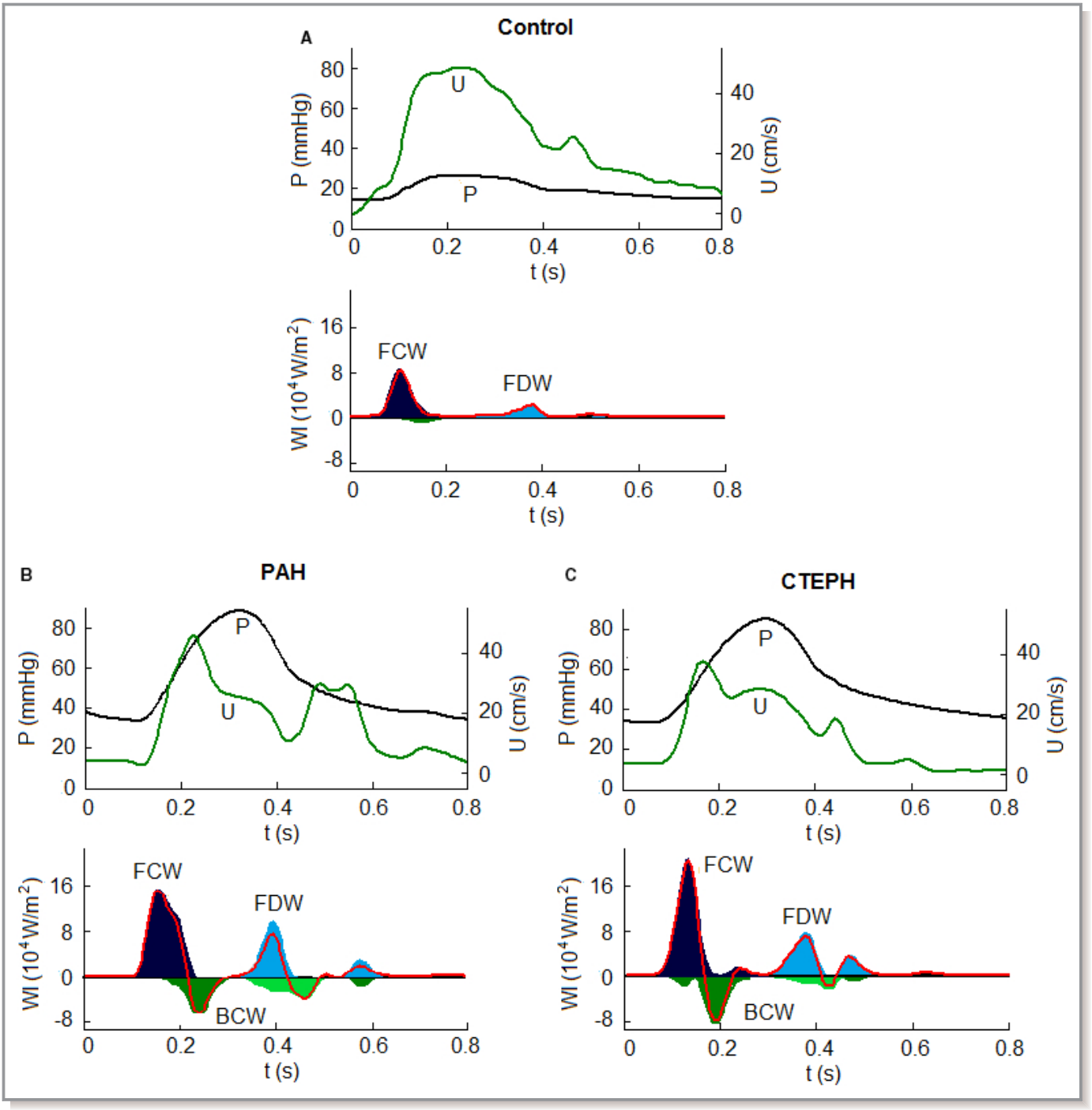

Figure 3. Pressure and flow velocity profile (upper panel) and wave intensity pattern (lower panel) for a control participant (A), a pulmonary arterial hypertension (PAH) patient (B), and a chronic thromboembolic pulmonary hypertension (CTEPH) patient (C). There is minimal backward wave intensity in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

Consistent with a previous short report,[14] we observed that wave speed, magnitude of waves, and WRI were significantly greater in PH patients compared with control participants, 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 with CTEPH patients and controls. Finally, we observed that there was no strong association between WRI and the conventionally used hemodynamic measurements, echocardiographic parameters, BNP,

Table 2. Magnitude of the Separated Waves in the Main and Branch Pulmonary Arteries

	Control	PAH	CTEPH	*P* Value
Main pulmonary artery				
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 (0.82–1.80)	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 waves in 3 of the control participants and as backward compression waves in the rest of the control participants and in all pulmonary hypertension patients. BW indicates backward wave; CTEPH, chronic thromboembolic pulmonary hypertension; FCW, forward compression wave; FDW, forward decompression wave; PAH, pulmonary arterial hypertension.

*Control significant different from PAH and CTEPH.

†CTEPH significantly different from control.

‡PAH significant different from control.

§Previously published data.[20]

‖Branch significantly different from main pulmonary artery.

¶PAH significantly different from control and CTEPH.

or PH severity. Consequently, this study revealed distinct differences in arterial wave propagation between persons with and without PH.

RV Hydraulic Power

PH is a progressive disease of the pulmonary vasculature that often leads to right heart failure[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 the wave speed were low in the control participants. 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.[22,23] Wave speed, ie, local arterial stiffness, increased 4- to 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 ≈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.[15]

The conventional calculation of RV work accounts for the steady-flow fraction of RV stroke work.[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 and energy exceed the total steady hydraulic power and energy; however, this is the result of the definition of normalized wave intensity, in which the number of samples is squared. We have demonstrated that the fraction of wave power and energy relative to the mean hydraulic power and energy, as expressed by FCW to RV power and energy density ratios, reduced in PAH patients. The oscillatory power fraction of total RV power has been shown to be reduced in PH in previous studies[24,25] and this has been interpreted as an efficient RV adaption to increased afterload, as the oscillatory power is considered an unavoidable "waste."[26] This may explain the reduced wave power fraction in PAH. Although not directly related to RV oscillatory power,

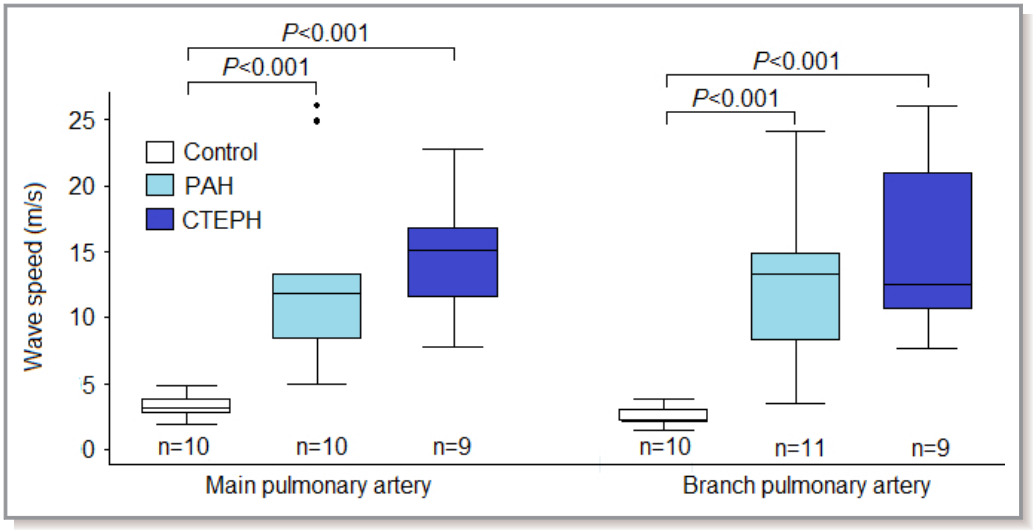

Figure 4. Wave speed was significantly higher in patients with pulmonary hypertension compared with controls. There was no significant difference between patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) or between main and branch pulmonary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

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[27] or increased[28] ratio of oscillatory power to mean hydraulic power in PAH. It is unclear why these studies differ, but differences may relate to methodological differences.

In contrast to PAH, we observed that the fraction of wave power and energy in CTEPH patients was not significantly different compared with controls. The lower FCW to RV power and energy ratios in PAH compared with 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 mechanisms differ. CTEPH is characterized by elevated pressure after an episode (or multiple episodes) of pulmonary embolism in the proximal pulmonary arterial segments,[29] whereas PAH is caused by gradual changes in the distal pulmonary vasculature.[30] Although not statistically significant, the wave speed (ie, 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 and energy may thus reveal subtle dissimilarities in the altered RV afterload between the 2 diseases. Albeit less likely, another possibility is that it reflects differences in RV adaptation. RV remodeling in response to pressure overload is complex,[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.[32] Whether the mechanism of RV remodeling in CTEPH differs from that in 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, that is, altered cross-sectional area or arterial stiffening, causing impedance mismatch between the proximal and distal vasculature.[2] In the control participants, 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 while minimizing wave reflection and thereby minimizing the ventricular workload.[33] In contrast to previous studies in open-chested canine models[34,35] and a recent magnetic resonance imaging–based study in humans,[15] we did not consistently observe a BDW in mid-systole that accelerated pulmonary flow in control participants. One participant aged 46 years and another aged 55 years showed an evident BDW (WRI >5%). It has been shown that the pulmonary artery stiffens with age[36]; therefore, it is conceivable that a more prominent BDW may be present in younger healthy persons.

In PH patients, a large BCW (ie, a reflection wave) was present in mid-systole, indicating a mismatch in pulmonary vascular impedance. Previous studies in animal models[34,37] and humans[14,15] have used the local wave speed and half the traveling time between the peak of FCW to BCW to give an

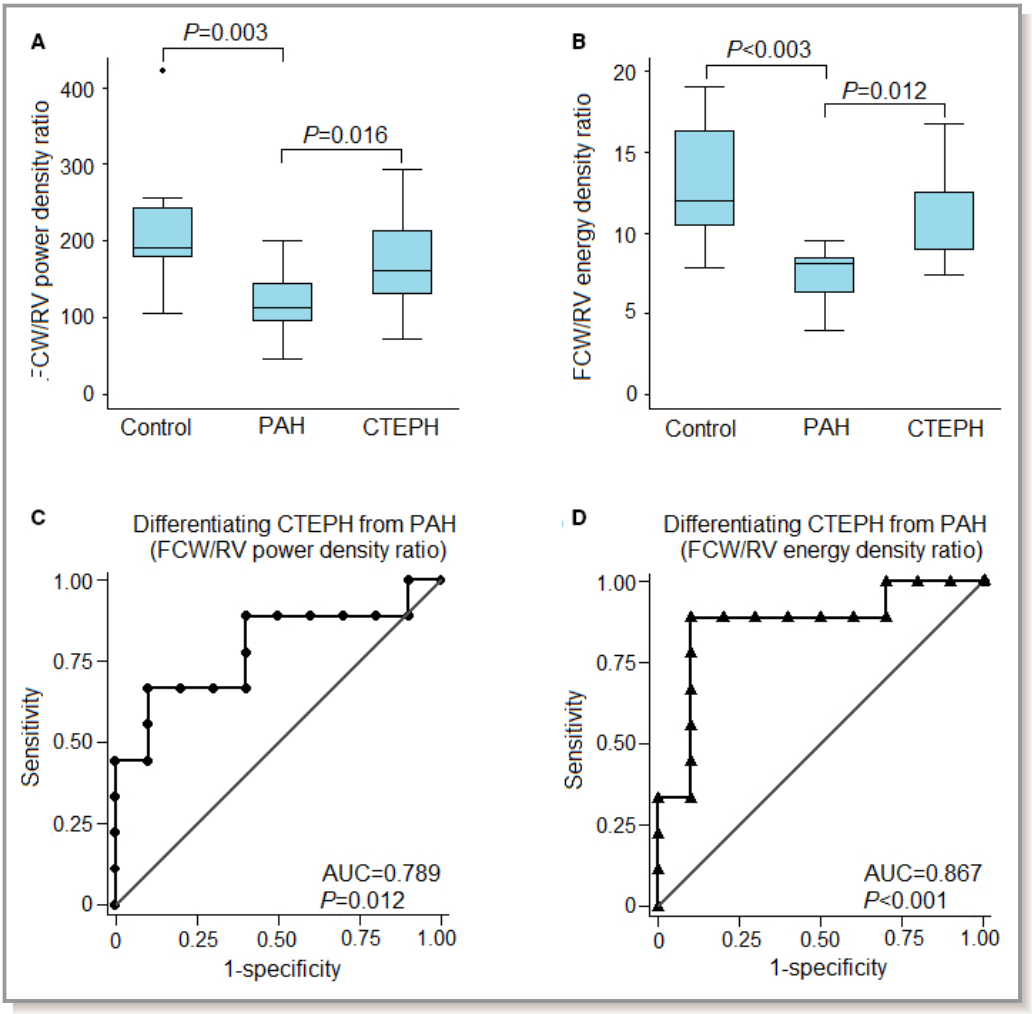

Figure 5. Wave to RV power and energy density ratios. Forward compression wave (FCW) to right ventricular (RV) power (A) and energy (B) density ratios in the 3 groups and receiver operating characteristics analysis (C and D) for distinguishing chronic thromboembolic pulmonary hypertension (CTEPH) from pulmonary arterial hypertension (PAH) are shown. AUC indicates area under the curve.

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. Applying the calculation in the PAH group and CTEPH group in this study, for instance, would give a reflection site of ≈40 and ≈56 cm, respectively, downstream of the main pulmonary artery, 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 2 nonoperable CTEPH patients. As discussed, PAH is considered a disease of the distal pulmonary artery, whereas 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,[38,39] is present in CTEPH patients and may be used as an additional marker to differentiate between the 2 diseases; however, the use of this method to evaluate wave reflection in the systemic circulation has been questioned.[40] A recent study suggests that the energy of BCW is increased in CTEPH patients with proximal clots compared with PAH patients[15]; however, we did not observe any significant differences in reflection time, magnitude of the reflective wave, or WRI between the 2 groups, suggesting that the main apparent reflection site is similar in the 2 types of PH. 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,[29] which may explain the similarity in the wave reflection pattern between the 2 groups of patients.

There was no strong association between pulmonary WRI and conventionally used hemodynamic, echocardiographic, or biochemical parameters, that is, the degree of vascular

Table 3. Spearman Rank Correlation Between Wave Intensity Indices and Conventionally Used Clinical Values

	Wave Speed		FCW Intensity		FCW Energy		BCW Intensity		BCW Energy		WRI	
	ρ	*P* Value	ρ	*P* Value	ρ	*P* Value	ρ	*P* Value	ρ	*P* Value	ρ	*P* Value
PAPm	0.62*	<0.01*	0.14	0.56	0.14	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 indicates 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 index, indexed right atrium area; RA, right atrium; RV FAC, right ventricular fractional area change; RV/LV, right:left ventricular area ratio; RVSVI, indexed right ventricular stroke volume; TAPSE, tricuspid annular plane systolic excursion; WRI, wave reflection index.
*$P<0.05$.

impedance mismatch (as expressed by WRI) was not related to the dynamic and steady-flow components of the RV workload, nor was it associated with measures of RV function. The lack of correlation among 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 nonperfused vessels.[41] Consequently, increased PAPm (≥25 mm Hg) occurs relatively late in the progression of disease when damage to the vasculature is advanced[42]; therefore, PAPm may not reveal the true severity of pulmonary vascular disease. Early diagnosis of pulmonary vascular disease before an increase in resting PAPm may be advantageous in patients at high risk of PH, for example, patients with systemic sclerosis,[43] patients with persistent symptoms after acute pulmonary embolism,[44] or first-degree family members of patients with heritable PAH.[45] Early detection of pulmonary vascular disease remains a great challenge. Potential clinical techniques for early detection such as stress Doppler echocardiography, magnetic resonance imaging adenosine stress test, and invasive cardiopulmonary exercise test still lack validation.[46–48] The current study showed minimal wave reflection in persons without pulmonary vascular disease, whereas 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 that of 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. Although 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. Conversely, 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 participants was small; 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 the possibility that the uneven distribution in of men and women may have a small influence on the observed differences in wave characteristics among the 3 groups. The aim of this

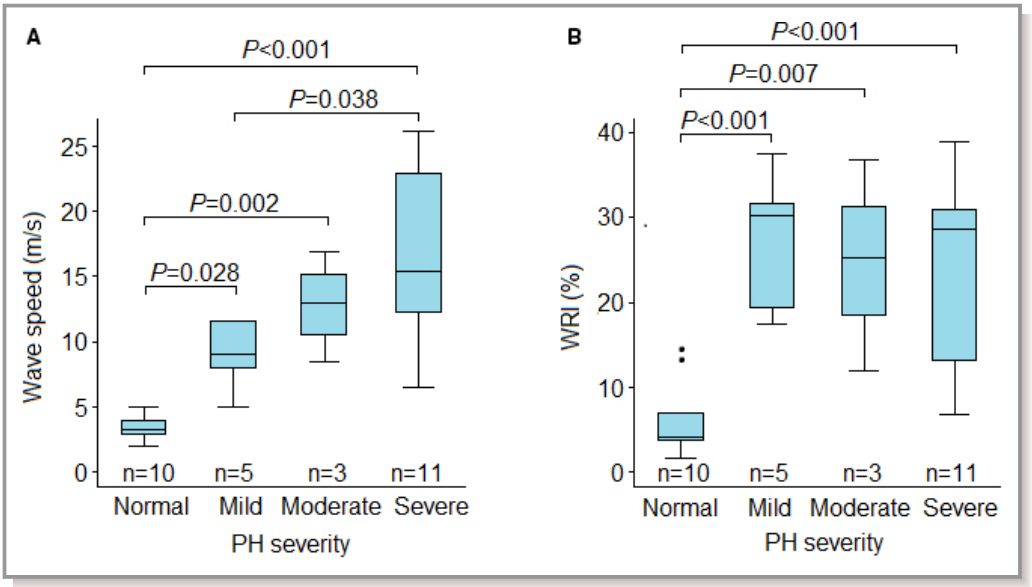

Figure 6. Wave speed and wave reflection in relation to mean pulmonary arterial pressure. Pulmonary hypertension patients were assigned as having mildly elevated mean pulmonary arterial pressure (PAPm=25–34 mm Hg), moderately elevated pressure (PAPm=35–44 mm Hg), or severely elevated pressure (PAPm ≥45 mm Hg). 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.

study, however, was to apply WIA in health and disease, and the wave intensity pattern was consistent for all participants in each group. The numbers of patients recruited from the 2 centers were not equally distributed. Consequently, care was taken to avoid measurement bias, as mentioned. To recruit completely healthy control participants in a catheterization laboratory was not feasible; however, we included only 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, recruiting PH patients without other cardiovascular or respiratory morbidities was challenging.

We do not have simultaneous recordings from the right ventricle; 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, in whom the pulmonary flow may be highly disturbed,[49] which induces signal noises and artefacts on the Doppler flow tracings. Vibration and axial movements of the catheter and 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 participant 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 participants. 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 in several patients, and because all 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

WIA in the pulmonary artery revealed distinct differences in arterial wave propagation between persons with and without PH. Wave reflection was minimal in those without pulmonary vascular disease, whereas large wave reflection was observed in patients with PH, indicating downstream vascular impedance mismatch. In contrast to wave speed, the magnitude of wave reflection was unrelated to disease severity. Consequently, although WRI does not serve as an indicator of the degree of PH or RV dysfunction in established disease, it may be 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 and energy density ratios differ between PAH and CTEPH patients, suggesting

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. Although this is unlikely to change, we demonstrated that FCW to RV power and energy ratios display significant discriminatory capacity to distinguish between CTEPH and PAH. Characterizing the pathophysiological differences between the 2 diseases may contribute to our understanding of disease progression and treatment responses, whether in terms of the pulmonary vasculature or the right ventricle.

The complex nature of data acquisition and processing may limit the use of WIA in clinical settings at present; however, recent advances in multisensor catheters, magnetic resonance imaging technologies, and automated data processing could facilitate future use of pulmonary WIA.

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Disclosures

None.

References

1. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F, Wilkins MR, Badesch DB. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013;24:D42–D50.
2. Parker KH. An introduction to wave intensity analysis. *Med Biol Eng Comput*. 2009;47:175–188.
3. Kussmaul WG III, Altschuler JA, Herrmann HC, Laskey WK. Effects of pacing tachycardia and balloon valvuloplasty on pulmonary artery impedance and hydraulic power in mitral stenosis. *Circulation*. 1992;86:1770–1779.
4. Laskey WK, Ferrari VA, Palevsky HI, Kussmaul WG. Pulmonary artery hemodynamics in primary pulmonary hypertension. *J Am Coll Cardiol*. 1993;21:406–412.
5. Huez S, Brimioulle S, Naeije R, Vachiery JL. Feasibility of routine pulmonary arterial impedance measurements in pulmonary hypertension. *Chest*. 2004;125:2121–2128.
6. Parker KH, Jones CJ. Forward and backward running waves in the arteries: analysis using the method of characteristics. *J Biomech Eng*. 1990;112:322–326.
7. Ohte N, Narita H, Sugawara M, Niki K, Okada T, Harada A, Hayano J, Kimura G. Clinical usefulness of carotid arterial wave intensity in assessing left ventricular systolic and early diastolic performance. *Heart Vessels*. 2003;18:107–111.
8. Davies JE, Alastruey J, Francis DP, Hadjiloizou N, Whinnett ZI, Manisty CH, Aguado-Sierra J, Willson K, Foale RA, Malik IS, Hughes AD, Parker KH, Mayet J. Attenuation of wave reflection by wave entrapment creates a "horizon effect" in the human aorta. *Hypertension*. 2012;60:778–785.
9. Davies JE, Whinnett ZI, Francis DP, Manisty CH, Aguado-Sierra J, Willson K, Foale RA, Malik IS, Hughes AD, Parker KH, Mayet J. Evidence of a dominant backward-propagating "suction" wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation*. 2006;113:1768–1778.
10. Hadjiloizou N, Davies JE, Malik IS, Aguado-Sierra J, Willson K, Foale RA, Parker KH, Hughes AD, Francis DP, Mayet J. Differences in cardiac microcirculatory wave patterns between the proximal left mainstem and proximal right coronary artery. *Am J Physiol Heart Circ Physiol*. 2008;295:H1198–H1205.
11. Bleasdale RA, Mumford CE, Campbell RI, Fraser AG, Jones CJ, Frenneaux MP. Wave intensity analysis from the common carotid artery: a new noninvasive index of cerebral vasomotor tone. *Heart Vessels*. 2003;18:202–206.
12. Manisty C, Mayet J, Tapp RJ, Parker KH, Sever P, Poulter NR, Thom SA, Hughes AD. Wave reflection predicts cardiovascular events in hypertensive individuals independent of blood pressure and other cardiovascular risk factors: an ASCOT (Anglo-Scandinavian Cardiac Outcome Trial) substudy. *J Am Coll Cardiol*. 2010;56:24–30.
13. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, Tarkin J, Petraco R, Broyd C, Jabbour R, Sethi A, Baker CS, Bellamy M, Al-Bustami M, Hackett D, Khan M, Lefroy D, Parker KH, Hughes AD, Francis DP, Di MC, Mayet J, Davies JE. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol*. 2012;59:1392–1402.
14. Lau EM, Abelson D, Dwyer N, Yu Y, Ng MK, Celermajer DS. Assessment of ventriculo-arterial interaction in pulmonary arterial hypertension using wave intensity analysis. *Eur Respir J*. 2014;43:1804–1807.
15. Quail MA, Knight DS, Steeden JA, Taelman L, Moledina S, Taylor AM, Segers P, Coghlan GJ, Muthurangu V. Noninvasive pulmonary artery wave intensity analysis in pulmonary hypertension. *Am J Physiol Heart Circ Physiol*. 2015;308:H1603–H1611.
16. Chemla D, Castelain V, Zhu K, Papelier Y, Creuze N, Hoette S, Parent F, Simonneau G, Humbert M, Herve P. Estimating right ventricular stroke work and the pulsatile work fraction in pulmonary hypertension. *Chest*. 2013;143:1343–1350.
17. Khir AW, Henein MY, Koh T, Das SK, Parker KH, Gibson DG. Arterial waves in humans during peripheral vascular surgery. *Clin Sci (Lond)*. 2001;101:749–757.
18. Davies JE, Whinnett ZI, Francis DP, Willson K, Foale RA, Malik IS, Hughes AD, Parker KH, Mayet J. Use of simultaneous pressure and velocity measurements to estimate arterial wave speed at a single site in humans. *Am J Physiol Heart Circ Physiol*. 2006;290:H878–H885.
19. Khir AW, O'Brien A, Gibbs JS, Parker KH. Determination of wave speed and wave separation in the arteries. *J Biomech*. 2001;34:1145–1155.
20. Su J, Manisty C, Simonsen U, Howard LS, Parker KH, Hughes AD. Pulmonary artery wave propagation and reservoir function in conscious man: impact of pulmonary vascular disease, respiration and dynamic stress tests. *J Physiol*. 2017;595:20 6463–6476.
21. Chemla D, Castelain V, Herve P, Lecarpentier Y, Brimioulle S. Haemodynamic evaluation of pulmonary hypertension. *Eur Respir J*. 2002;20:1314–1331.
22. Schultz MG, Davies JE, Roberts-Thomson P, Black JA, Hughes AD, Sharman JE. Exercise central (aortic) blood pressure is predominantly driven by forward traveling waves, not wave reflection. *Hypertension*. 2013;62:175–182.
23. Zambanini A, Cunningham SL, Parker KH, Khir AW, McG Thom SA, Hughes AD. Wave-energy patterns in carotid, brachial, and radial arteries: a noninvasive approach using wave-intensity analysis. *Am J Physiol Heart Circ Physiol*. 2005;289:H270–H276.
24. Laskey WK, Ferrari VA, Palevsky HI, Kussmaul WG. Ejection characteristics in primary pulmonary hypertension. *Am J Cardiol*. 1993;71:1111–1114.
25. Milnor WR, Conti CR, Lewis KB, O'Rourke MF. Pulmonary arterial pulse wave velocity and impedance in man. *Circ Res*. 1969;25:637–649.
26. Grignola JC, Gines F, Bia D, Armentano R. Improved right ventricular-vascular coupling during active pulmonary hypertension. *Int J Cardiol*. 2007;115:171–182.
27. Saouti N, Westerhof N, Helderman F, Marcus JT, Stergiopulos N, Westerhof BE, Boonstra A, Postmus PE, Vonk-Noordegraaf A. RC time constant of single lung equals that of both lungs together: a study in chronic thromboembolic pulmonary hypertension. *Am J Physiol Heart Circ Physiol*. 2009;297:H2154–H2160.

28. Hadinnapola C, Li Q, Su L, Pepke-Zaba J, Toshner M. The resistance-compliance product of the pulmonary circulation varies in health and pulmonary vascular disease. *Physiol Rep*. 2015;4:e12363.
29. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. *Circulation*. 2006;113:2011–2020.
30. Chan SY, Loscalzo J. Pathogenic mechanisms of pulmonary arterial hypertension. *J Mol Cell Cardiol*. 2008;44:14–30.
31. Ryan JJ, Archer SL. The right ventricle in pulmonary arterial hypertension: disorders of metabolism, angiogenesis and adrenergic signaling in right ventricular failure. *Circ Res*. 2014;115:176–188.
32. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. *Circulation*. 2008;117:1717–1731.
33. Womersley JR. Oscillatory flow in arteries. II. The reflection of the pulse wave at junctions and rigid inserts in the arterial system. *Phys Med Biol*. 1958;2:313–323.
34. Hollander EH, Wang JJ, Dobson GM, Parker KH, Tyberg JV. Negative wave reflections in pulmonary arteries. *Am J Physiol Heart Circ Physiol*. 2001;281:H895–H902.
35. Bouwmeester JC, Belenkie I, Shrive NG, Tyberg JV. Wave reflections in the pulmonary arteries analysed with the reservoir-wave model. *J Physiol*. 2014;592:3053–3062.
36. Gozna ER, Marble AE, Shaw A, Holland JG. Age-related changes in the mechanics of the aorta and pulmonary artery of man. *J Appl Physiol*. 1974;36:407–411.
37. Dwyer N, Yong AC, Kilpatrick D. Variable open-end wave reflection in the pulmonary arteries of anesthetized sheep. *J Physiol Sci*. 2012;62:21–28.
38. Castelain V, Herve P, Lecarpentier Y, Duroux P, Simonneau G, Chemla D. Pulmonary artery pulse pressure and wave reflection in chronic pulmonary thromboembolism and primary pulmonary hypertension. *J Am Coll Cardiol*. 2001;37:1085–1092.
39. Nakayama Y, Nakanishi N, Hayashi T, Nagaya N, Sakamaki F, Satoh N, Ohya H, Kyotani S. Pulmonary artery reflection for differentially diagnosing primary pulmonary hypertension and chronic pulmonary thromboembolism. *J Am Coll Cardiol*. 2001;38:214–218.
40. Hughes AD, Park C, Davies J, Francis D, McG Thom SA, Mayet J, Parker KH. Limitations of augmentation index in the assessment of wave reflection in normotensive healthy individuals. *PLoS One*. 2013;8:e59371.
41. Barnes PJ, Liu SF. Regulation of pulmonary vascular tone. *Pharmacol Rev*. 1995;47:87–131.
42. Lau EM, Manes A, Celermajer DS, Galie N. Early detection of pulmonary vascular disease in pulmonary arterial hypertension: time to move forward. *Eur Heart J*. 2011;32:2489–2498.
43. Pope JE, Lee P, Baron M, Dunne J, Smith D, Docherty PS, Bookman A, Abu-Hakima M. Prevalence of elevated pulmonary arterial pressures measured by echocardiography in a multicenter study of patients with systemic sclerosis. *J Rheumatol*. 2005;32:1273–1278.
44. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barbera JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Hamid AM, Jais X, Simonneau G. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation*. 2011;124:1973–1981.
45. Aldred MA, Vijayakrishnan J, James V, Soubrier F, Gomez-Sanchez MA, Martensson G, Galie N, Manes A, Corris P, Simonneau G, Humbert M, Morrell NW, Trembath RC. BMPR2 gene rearrangements account for a significant proportion of mutations in familial and idiopathic pulmonary arterial hypertension. *Hum Mutat*. 2006;27:212–213.
46. Reichenberger F, Voswinckel R, Schulz R, Mensch O, Ghofrani HA, Olschewski H, Seeger W. Noninvasive detection of early pulmonary vascular dysfunction in scleroderma. *Respir Med*. 2009;103:1713–1718.
47. Grunig E, Weissmann S, Ehlken N, Fijalkowska A, Fischer C, Fourme T, Galie N, Ghofrani A, Harrison RE, Huez S, Humbert M, Janssen B, Kober J, Koehler R, Machado RD, Mereles D, Naeije R, Olschewski H, Provencher S, Reichenberger F, Retailleau K, Rocchi G, Simonneau G, Torbicki A, Trembath R, Seeger W. Stress Doppler echocardiography in relatives of patients with idiopathic and familial pulmonary arterial hypertension: results of a multicenter European analysis of pulmonary artery pressure response to exercise and hypoxia. *Circulation*. 2009;119:1747–1757.
48. Baillie TJ, Sidharta S, Steele PM, Worthley SG, Willoughby S, Teo K, Sanders P, Nicholls SJ, Worthley MI. Noninvasive assessment of cardiopulmonary reserve: toward early detection of pulmonary vascular disease. *Am J Respir Crit Care Med*. 2017;195:398–401.
49. Kondo C, Caputo GR, Masui T, Foster E, O'Sullivan M, Stulbarg MS, Golden J, Catterjee K, Higgins CB. Pulmonary hypertension: pulmonary flow quantification and flow profile analysis with velocity-encoded cine MR imaging. *Radiology*. 1992;183:751–758.