DOI: 10.1002/pul2.12345

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Pulmonary artery wave intensity analysis in pulmonary hypertension associated with heart failure and reduced left ventricular ejection fraction

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Funding information
Heart Research UK, Grant/Award Number: (NET31/19); Intermediate Clinical Research Fellowship from the British Heart Foundation, Grant/Award Number: FS/15/49/31612

Abstract

Wave intensity analysis (WIA) uses simultaneous changes in pressure and flow velocity to determine wave energy, type, and timing of traveling waves in the circulation. In this study, we characterized wave propagation in the pulmonary artery in patients with pulmonary hypertension associated with left-sided heart disease (PHLHD) and the effects of dobutamine. During right heart catheterization, pressure and velocity data were acquired using a dual-tipped pressure and Doppler flow sensor wire (Combowire; Phillips Volcano), and processed offline using customized Matlab software (MathWorks). Patients with low cardiac output underwent dobutamine challenge. Twenty patients with PHLHD (all heart failure with reduced left ventricular ejection fraction) were studied. Right ventricular systole produced a forward compression wave (FCW), followed by a forward decompression wave (FDW) during diastole. Wave reflection manifesting as backward compression wave (BCW) following the FCW was observed in 14 patients. Compared to patients without BCW, patients with BCW had higher mean pulmonary artery pressure (28.7 ± 6.12 vs. 38.6 ± 6.5 mmHg, $p = 0.005$), and lower pulmonary arterial capacitance (PAC: 2.88 ± 1.75 vs. 1.73 ± 1.16, $p = 0.002$). Pulmonary vascular resistance was comparable. Mean pulmonary artery pressure of 34.5 mmHg (area under the curve [AUC]: 0.881) and PAC of 2.29 mL/mmHg (AUC: 0.833) predicted BCW. The magnitude of the FCW increased with dobutamine ($n = 11$) and correlated with pulmonary artery wedge pressure. Wave reflection in PHLHD is more likely at higher pulmonary artery pressures and lower PAC and the magnitude

Abbreviations: CPC-PH, combined pre and postcapillary pulmonary hypertension; DPAP, diastolic pulmonary artery pressure; IPC-PH, isolated postcapillary pulmonary hypertension; MPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial capacitance; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PHLHD, pulmonary hypertension associated with left-sided heart disease; RAP, right atrial pressure; RHC, right heart catheterization; RVSW, right ventricular stroke work; SPAP, systolic pulmonary artery pressure; SV, stroke volume; TPG, transpulmonary gradient; WIA, wave intensity analysis; WU, Woods units.

of reflected waves correlated with pulmonary artery wedge pressure. Dobutamine increased FCW but did not affect wave reflection.

KEYWORDS
heart failure, pulmonary hypertension, wave intensity analysis

INTRODUCTION

Pulmonary hypertension associated with left-sided heart disease (PHLHD) is subdivided into isolated postcapillary pulmonary hypertension (IPC-PH) and combined pre- and postcapillary pulmonary hypertension (CPC-PH). Previously, a PVR cut-off of 3 Woods units (WU) was used to distinguish CPC-PH from IPC-PH—defined as a mean pulmonary artery pressure (MPAP) of >20 mmHg, pulmonary vascular resistance (PVR) ≤ or >3 WU and pulmonary arterial wedge pressure (PAWP) > 15 mmHg.[1–3] The revised guidelines have lowered the upper limit of normal PVR to 2 WU, on the basis that this is the lowest prognostically relevant threshold.[4] Identifying patients with CPC-PH is relevant for heart transplantation or left ventricular (LV) assist device therapy.[5] We sought to study the physiology of PHLHD in patients with heart failure using wave intensity analysis (WIA).

WIA was first introduced by Parker and Jones in 1990[6] to assess the changes in arterial pressure and velocity simultaneously to ascertain the origin, energy, type, and timing of traveling waves in the circulation. It has a unique advantage over other impedance-based methods in that it analyzes the pressure and velocity waveforms as successive wavefronts and not sinusoidal wavetrains.[7] The analysis is performed in the time domain, allowing clinicians to intuitively relate the arterial waves to events in the cardiac cycle. There have been previous studies which have suggested that wave reflection in the pulmonary circulation is an important factor to be taken into account when assessing pulmonary hemodynamics.[8–10] WIA has been previously applied to the systemic circulation,[11] as a measure of LV performance[12] and also in the coronary circulation.[13] Su et al. have studied WIA in patients with primary pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension.[14–17] There are no studies of WIA in the pulmonary artery in heart failure and PHLHD.

The objective of this study was to characterize wave propagation with WIA in the pulmonary artery in patients with PHLHD. We hypothesized that wave reflection is related to pulmonary arterial pressures, PVR, and pulmonary arterial capacitance (PAC).

MATERIALS AND METHODS

Study population

Study participants were recruited from patients with advanced heart failure who were undergoing right heart catheterization (RHC) as part of their assessment for heart transplantation at the Queen Elizabeth Hospital Birmingham, UK. Patients over the age of 18 years, with left-sided heart disease and high probability of pulmonary hypertension on transthoracic echocardiogram, were eligible. Although not specifically by design, this study included patients with heart failure with reduced left ventricular ejection fraction (LVEF). Exclusion criteria were pulmonary hypertension due to other causes (i.e., non-PHLHD), atrial fibrillation, pregnancy, mechanical ventilation, temporary mechanical circulatory support, and cardiogenic shock. The same investigator (I. H. W. Y.) was present during all cases to ensure hemodynamic data quality. This study was approved by the Health Research Authority and Health Care Research Wales ethics committee (reference 20/WM/0022), with written consent from all participants.

Study protocol

RHC was performed via the right internal jugular vein with a 7.5 Fr balloon flotation pulmonary artery catheter. Cardiac output studies were performed using the thermodilution method. Following the standard RHC study, a combined dual-tipped pressure and Doppler flow sensor wire (Combowire; Philips Volcano) was inserted and advanced 1–1.5 cm beyond the tip of the catheter and the position confirmed on fluoroscopy. The PA catheter with the wire was then manipulated in the main pulmonary artery to obtain clear Doppler velocity signals. Once the signals were stable, velocity and pressure data were recorded simultaneously at a sampling rate of 200 Hz. Initially, data were recorded in both the right pulmonary artery and main pulmonary artery, but we found that the velocity signals were much more stable in the main PA. Therefore, all data used for analysis were taken from the main pulmonary artery. Routine

transthoracic echocardiogram and blood tests were also performed within 48 h of the RHC.

Selected patients with low baseline cardiac output (cardiac index <2.4 L/min/m^2) underwent dobutamine challenge. Following acquisition of baseline velocity and pressure data, dobutamine was started at 5 mcg/kg/min and uptitrated by 5 mcg/kg/min at 2-min intervals up to 20 mcg/kg/min. Velocity and pressure data acquisition continued throughout this period and for at least 5 min at 20 mcg/kg/min.

WIA

Pressure and velocity data were processed offline using customized Matlab software (Mathworks) as previously described.[18] The signals were ensemble-averaged with timing gated to the R wave of ECGs and smoothed using a Savitzky–Golay differentiating filter (second-order polynomial fit, windows size 11). The Matlab program eliminates outlying velocity waveforms from the ensemble by calculating and ranking the cross-correlation of each beat with the global ensemble average. The beats with the lowest correlation coefficient were removed until the integral of the standard error of the ensemble average velocity waveform over the cardiac period was minimized. The ensemble-averaged pressure waveform is then calculated for the same beats. Hardware-related delay between pressure and velocity signals is corrected by shifting the velocity data until the beginning of the upslope of the velocity and pressure waveforms are aligned. This procedure has been published previously.[16]

Wave speed was determined from the measured pressure and velocity data using the P-U loop method. Once the wave speed has been calculated, the measured pressure and velocity and the calculated wave intensity waveforms can be separated into their forward and backward components, this has previously been described.[6] Waves generated are either forward going (net positive wave intensity) or backward going (net negative wave intensity waves). Forward waves originate proximally from the right ventricle and are either compression waves (FCW) which increase the pressure and velocity or decompression waves (forward decompression wave [FDW]) which decrease the pressure and flow. Forward waves can be reflected at distal sites generating backward waves at the measurement site. These reflected waves (net negative wave intensity) can be either backward compression waves (BCW) which increases the pressure but decreases flow or backward decompression waves (BDWs) which decreases the pressure whilst increasing flow.[7] Early BCWs are defined as occurring during right ventricular systole (<300 ms from the index forward compression wave [FCW]) and late reflected waves are backward-going waves observed during diastole (>300 ms).[6]

The wave speed was determined from the measured pressure and velocity data using the P-U loop method. Once the wave speed has been calculated, the measured pressure and velocity and the calculated wave intensity waveforms can be separated into their forward and backward components, this has previously been described.[6] After wave separation, the net wave intensity (W/m^2) which is the peak of the forward or backward waves can be measured and also the magnitude of wave reflection can be calculated as the wave reflection index. This is the percentage of the peak backward wave relative to the peak forward wave.

PAC was calculated by dividing stroke volume by the pulmonary arterial pulse pressure. Indexed right ventricular stroke work (RVSW) is calculated by the following formula: $(\text{MPAP} - \text{RAP}) \times \text{SV Index} \times 0.0136$; where MPAP: mean pulmonary artery pressure, RAP: right atrial pressure, and SV: stroke volume. The wave reflection index was calculated as the ratio of the maximal BCW in relation to the peak FCW.

Statistical analysis

Data were analyzed for normality using histograms and the Shapiro–Wilk test. Normally distributed data are displayed as means ± standard deviation (SD), nonparametric data are expressed as medians and interquartile ranges (IQRs) and proportions are expressed as percentages. All normally distributed data were compared using the independent Student's *t* test using the two-tailed *p* value and level of significance set at 0.05. Non-normal data were compared using the Mann–Whitney *U* test. The effects of dobutamine were assessed using the paired Student's *t* test for normally distributed data, the Wilcoxon signed-rank test was used for nonparametric data, and the McNemar test was applied to nominal data. Correlation analyses were performed using the Pearson correlation coefficient. All analyses were performed on SPSS software (SPSS for Macintosh, Version 29; IBM Corp.).

RESULTS

Patient characteristics

A total of 20 patients with left-sided heart disease were studied and data acquisition was complete in all patients. The most common diagnosis was ischemic cardiomyopathy

TABLE 1 Patient characteristics.

Variables	All patients ($N = 20$)	No BCW ($N = 6$)	BCW present ($N = 14$)	p
Male, %	75%	83.30%	71.40%	0.025*
Age, years	50.5± 11.4	49.3± 11.4	50.9± 11.8	0.792
BSA, m^2	1.96± 0.26	1.93± 0.16	1.97± 0.30	0.685
BMI, kg/m^2	28.1± 4.55	25.5± 2.46	29.3± 4.83	0.087
Hb, g/L	134± 14.4	147± 8.29	128± 12.4	0.002*
Cl, mmol/L	96.8± 3.29	99.1± 2.29	95.9± 3.22	0.038*
Na, mmol/L	137± 3.73	139± 2.79	137± 4	0.223
Creatinine, μmol/L	107 (55.3)	102 (309)	110 (61.8)	0.779
Albumin, g/L	37.7± 5.55	40± 4.64	36.6± 5.75	0.224
Billirubin, μmol/L	17.5 (30)	24.5 (43)	17.5 (27.3)	1
NTproBNP, pg/mL	6764± 4113	7387± 5182	6497± 3760	0.67
LVEF, %	20.5 (14.3)	22 (18.5)	17.5 (17.8)	0.312
RV diameter (cm)	3.6 (0.4)	3.5 (0.5)	3.6 (0.4)	0.819
TAPSE, mm	14 (4)	14 (4)	14 (5)	0.239
TAPSE/PASP	0.30 (0.13)	0.39 (0.18)	0.25 (0.07)	0.020
RV FAC (%)	26.0 (11.7)	28.3 (15.1)	24.6 (9.9)	0.601
MR	Severe = 1	Severe = 0	Severe = 1	0.560
	Moderate = 6	Moderate = 1	Moderate = 5	
	Mild = 10	Mild = 5	Mild = 5	
	None = 3	None = 0	None = 3	
TR	Severe = 3	Severe = 2	Severe = 1	0.423
	Moderate = 6	Moderate = 1	Moderate = 5	
	Mild = 7	Mild = 3	Mild = 4	
	None = 4	None = 0	None = 4	

Note: Patients separated into two groups those with a backward compression wave (BCW) and those without.

Abbreviations: BMI, body mass index; BSA, body surface area; Cl, chloride; Hb, hemoglobin; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; Na, sodium; NTproBNP, B-type natriuretic peptide; RV FAC, right ventricular fractional area change; TAPSE, tricuspid annular place systolic excursion; TR, tricuspid regurgitation.

*Statistically significant results.

followed by idiopathic dilated cardiomyopathy (Table 1). The mean age was 50.5± 11.4 years, 15 of the 20 patients were males and the median LVEF was 20.5% (IQR: 10.8–25).

Characterization of wave propagation in heart failure

All patients displayed a dominant FCW related to right ventricular contraction. Immediately following the FCW, 14 patients displayed an early BCW suggesting wave reflection immediately following the FCW. All patients displayed an FDW during diastole and 11 patients had a BDW in diastole related to the dicrotic notch. Figure 1a,b shows representative examples of a patient with and without BCW, respectively.

Analysis of the hemodynamic data was performed with the patients separated into two groups, based on the presence or absence of BCW. Patients with BCW had significantly lower hemoglobin and chloride levels (Table 1), indicative of more severe heart failure. Patients with BCW also had significantly higher systolic, diastolic, and mean PA pressures (Table 2), and significantly lower ratio of tricuspid annular plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP ratio) and PAC. Pulmonary vascular resistance, indexed PVR and wave speed were not significantly different between the two groups. Pulmonary artery wedge pressure was higher in patients with BCW, but this difference was not statistically significant.

The magnitude of the FCW, BCW, and wave reflection index (the ratio of the maximal BCW in relation to the peak FCW) and their association with the hemodynamic parameters were investigated. The magnitude of the FCW correlated with MPAP ($\rho = 0.485$, $p = 0.030$) and RVSWi ($\rho = 0.512$, $p = 0.021$) (Figure 2) but not PVR, indexed PVR or PAC. The magnitude of the BCW correlated with the TAPSE/PASP ratio ($r = -0.389$, $p = 0.040$). The wave reflection index however, was related to PVR ($\rho = 0.576$, $p = 0.031$) and PAC ($\rho = -0.733$, $p = 0.003$). In the cases with early BCW, the timing of the arrival of the reflected waves ranged from 140 to 260 ms (190 ms).

An MPAP of 34.5 mmHg or greater (sensitivity = 71.4%, specificity = 16.7%, receiver operator characteristics AUC 0.881) and a PAC of 2.29 mL/mmHg or lower (sensitivity = 71.4% and specificity = 16.7%, receiver operator characteristics AUC 0.833) were determined to be the optimal cut-offs for early BCW (Figure 3).

Dobutamine challenge

Eleven patients underwent dobutamine challenge following baseline hemodynamic assessment. On 20 mcg/kg/min of dobutamine, stroke volume, cardiac output, cardiac index, indexed right ventricular stroke work and

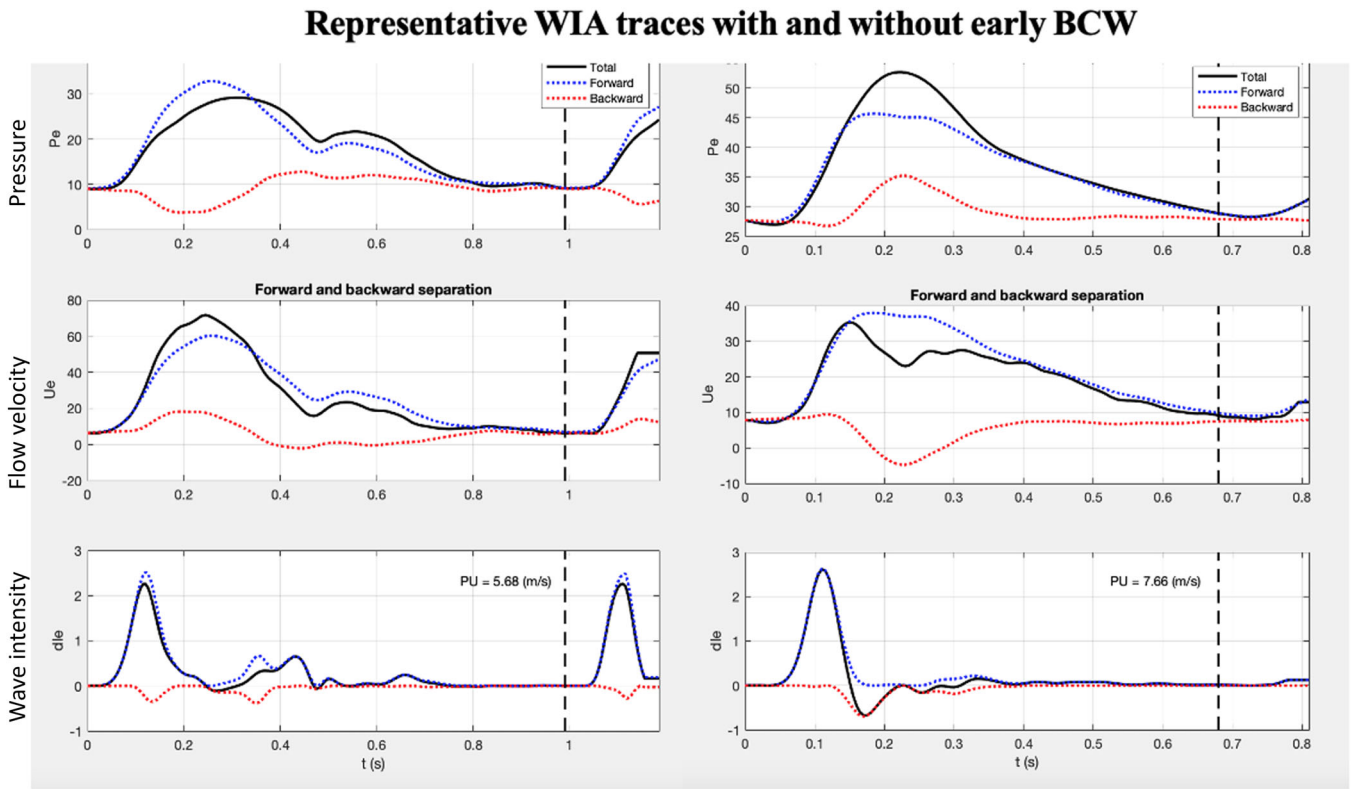

FIGURE 1 (a) and (b) Displays representative traces of patients with and without a backward compression wave (BCW). The top panels display ensemble averaged pressure data (P, mmHg), the middle panel displays ensembled average velocity data (U, cm/s), and the bottom panel displays wave intensity (dI, 104 W/m^2). Black line represents the net P, U, and dI; blue line denotes the forward component; and red line represents the backward component. It is the net P, U, and wave intensity that is used for data analysis. (a) A forward compression wave (FCW) in early systole followed by a forward decompression wave in diastole related to the dicrotic notch. Whereas in (b), there is the addition of a backward compression wave in early systole immediately following the FCW. WIA, wave intensity analysis.

FCW intensity significantly increased (Table 3). The box plots in Figure 4 display the changes following dobutamine challenge. There were no significant changes in BCW intensity, wave reflection index, or wave speed. Of the 11 patients who received dobutamine, eight patients had a BCW at baseline and seven out of the eight patients continued to display a BCW following dobutamine (BCW was no longer present following dobutamine in one patient). The three patients who did not display a BCW at baseline did not develop a BCW after dobutamine.

We examined the relationship between PAWP and BCW, as PAWP is a determinant of PAC and right ventricular afterload. Combining the data at baseline and on dobutamine challenge, the magnitude of BCW correlated with PAWP ($R^2 = 0.214$, $p = 0.01$).

DISCUSSION

This is the first study to characterize wave propagation in the pulmonary artery in patients with PHLHD. The main findings are: (i) the pattern of wave propagation in the pulmonary circulation in heart failure is comparable to that of the systemic circulation[19]; with a dominant FCW during systole followed by an FDW in diastole; (ii) wave reflection is associated with higher PAWP and lower PAC; (iii) TAPSE/PASP ratio was lower in patients with BCW; (iv) forward compression wave intensity correlated with right ventricular stroke work; and (v) dobutamine administration FCW intensity but did not affect backward wave intensity, wave reflection index or wave speed.

Su et al. studied WIA in the pulmonary circulation in healthy subjects and patients with PAH and chronic thromboembolic pulmonary hypertension.[16] The pattern of wave propagation in this study is consistent with their findings, but we were not able to determine the mechanism(s) for wave reflection in the pulmonary artery. In the systemic circulation in the human ascending aorta, wave reflection during mid-systole has also previously been reported, possibly related to impedance mismatch at bifurcations.[20] We postulate that the BCW in the pulmonary artery, like the systemic circulation may be due, at least in part to

TABLE 2 Hemodynamic parameters shown for the entire cohort, those with a BCW and those without a BCW.

Variables	All patients ($N = 20$)	No BCW ($N = 6$)	BCW present ($N = 14$)	p
RAP, mmHg	14.7± 5.21	15± 4.81	14.5± 5.54	0.85
SPAP, mmHg	50.6± 13.9	38.7± 8.26	55.6± 12.7	0.008*
DPAP, mmHg	25.2± 5.15	20.2± 5.04	27.3± 3.56	0.002*
PPP, mmHg	25.4± 10.6	18.5± 4.59	28.4± 11.2	0.54
MPAP, mmHg	35.7± 7.80	28.7± 6.12	38.6± 6.50	0.005*
PAWP, mmHg	23.9± 5.56	20.3± 5.92	25.4± 4.85	0.062
TPG, mmHg	11.8± 5.34	8.33± 2.94	13.3± 5.51	0.054
DPG, mmHg	0 (2)	0 (1.25)	0.5 (3.25)	0.397
PVR, WU	3.14± 1.45	2.28± 1.08	3.5± 1.46	0.081
Indexed PVR, WU/m^2	5.55± 2.27	4.27± 1.71	6.10± 2.31	0.098
PAC, mL/mmHg	2.28 (1.39)	2.88 (1.75)	1.73 (1.16)	0.02*
PAPI	1.58 (1.46)	1.35 (0.92)	2.04 (1.74)	0.207
Stroke volume, mL	52.5± 20.6	58.8± 20.2	49.8± 20.9	0.384
Heart rate, bpm	78.1± 14.5	68.7± 10.6	82.1± 14.3	0.054
CO, L/min	3.89 (1.42)	3.87 (2.3)	3.88 (1.27)	0.779
CI, L/min/m^2	1.92 (0.78)	2 (0.9)	1.91 (0.72)	0.718
Indexed RVSW, mmHg. mL/m^2	6.77 (4.78)	5.49 (4.67)	8.04 (5.50)	0.274
FCW intensity, 10^4 W/m^2	2.85 (1.79)	2.38 (1.71)	3.11 (3.85)	0.274
Wave speed, cm/s	3.33 (4.67)	3.28 (2.55)	3.33 (5.42)	0.904

Abbreviations: CI, cardiac index; CO, cardiac output; DPAP, diastolic pulmonary arterial pressure; DPG, diastolic pulmonary gradient; FCW, forward compression wave; MPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial compliance; PAPI, pulmonary arterial pulsatility index; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSW, right ventricular stroke work; SPAP, systolic pulmonary arterial pressure; TPG, transpulmonary gradient.

*Statistical significance with $p < 0.05$.

wave reflection due to vascular impedance mismatch probably as a result of changes in the diameter of the pulmonary arteries.[21]

Changes in PAC may also contribute to the development of BCW. Pulmonary artery wedge pressure alters the PVR–PAC relationship, shifting the hyperbolic curve downwards and leftwards, such that the PAC is lower at the same PVR. Lower PAC may increase pulse wave velocity and promote wave reflection.[22] On this basis, we examined the relationship between PAWP and BCW. That PAWP correlated with the magnitude of BCW suggests that the adverse effects of elevated PAWP on the right ventricle may be related to increased pressure loading from reflected waves. It is possible that wave reflection and associated reduced PAC in patients with PHLHD may compound the afterload on the right heart. Our finding that patients with BCW had lower TAPSE/PASP ratio,[23] lower hemoglobin[24] and chloride levels[25] suggest more advanced (right) heart failure. Indeed, PAC had been shown to be a superior prognostic indicator in both primary PAH[26,27] and in advanced heart failure,[28] probably because of the greater adverse effect of pulsatile load on the right heart. Of note, while PVR may not be directly related to the presence of BCW, PVR, like PAC was related to the relative magnitude of wave reflection (i.e., wave reflection index) when BCWs were present. Thus, PVR may have a role in modulating wave reflection.

The effect of inotropy on wave propagation in the pulmonary artery has not been studied in humans. Jones et al. reported the effects of dobutamine on WIA in the canine ascending aorta.[29] In the canine systemic circulation, dobutamine increased peak FCW but had no effect on the FDW. Our finding that dobutamine significantly increased the FCW intensity is consistent with this animal study. The increase in FCW intensity

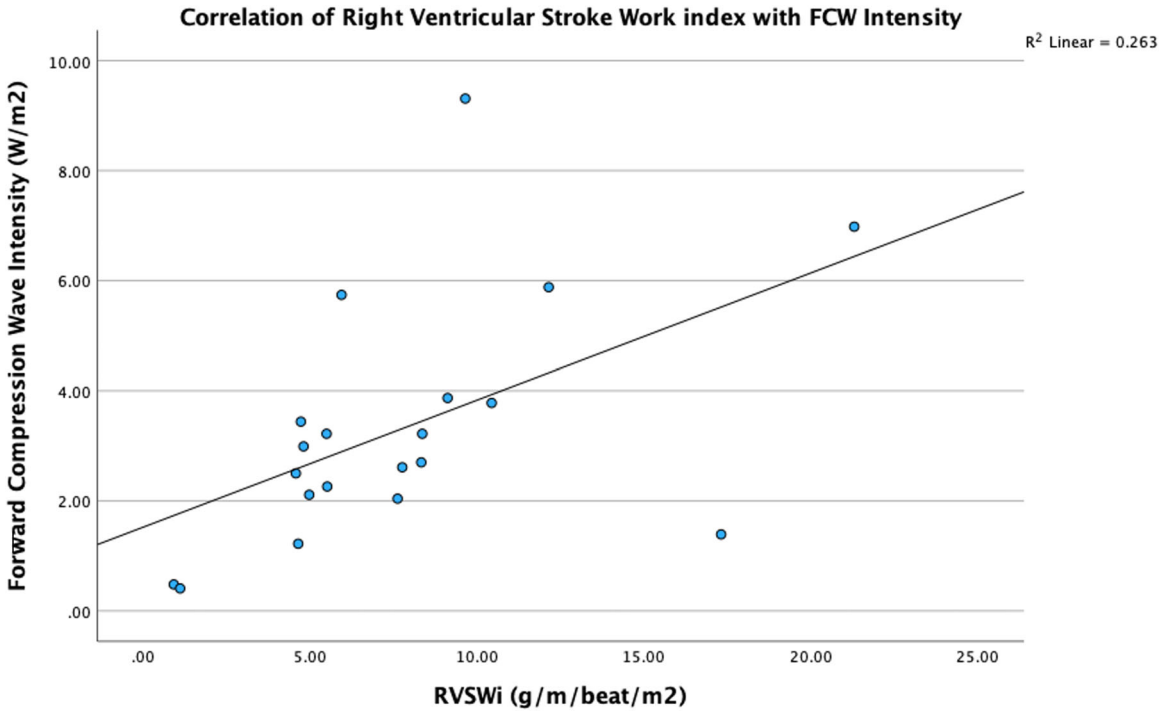

FIGURE 2 The positive correlation between right ventricular stroke work index (RVSWi) and forward compression wave (FCW) intensity $R^2 = 0.263$, $\rho = 0.512$, $p = 0.02$.

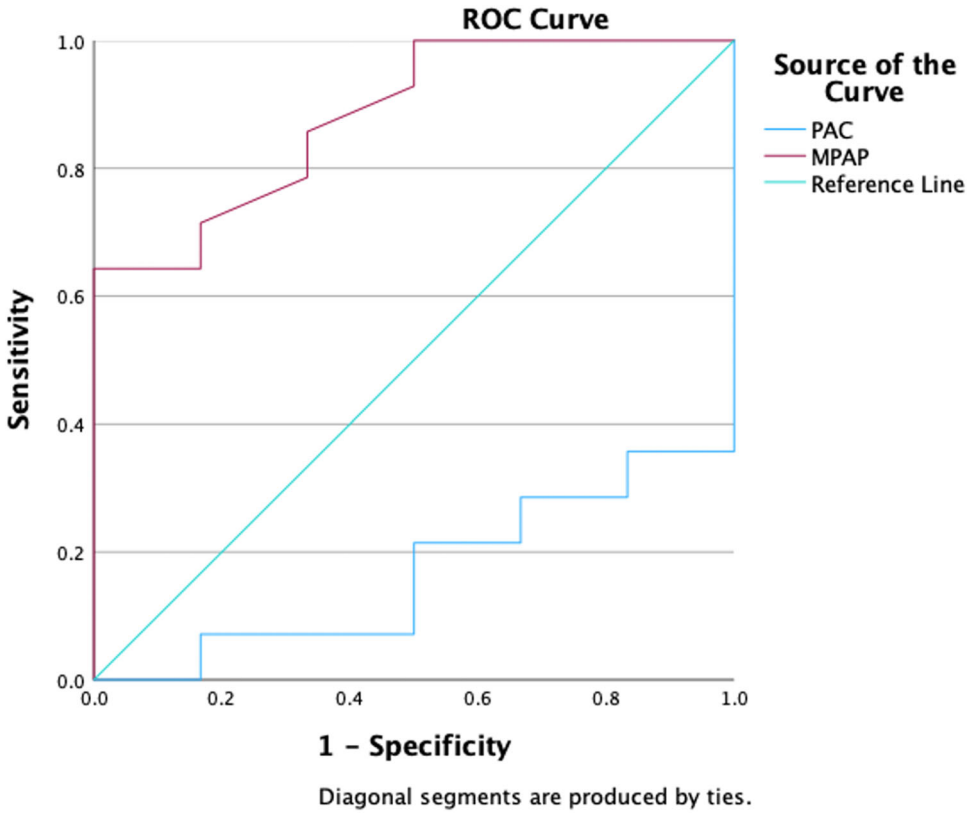

FIGURE 3 ROC for MPAP and PAC. MPAP has an AUC of 0.881 and PAC has an AUC of 0.833. AUC, area under the curve; MPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial capacitance; ROC, receiver operator characteristics.

TABLE 3 Hemodynamic parameters pre- and post-dobutamine challenge.

Variables	Pre-dobutamine ($N = 11$)	Post-dobutamine ($N = 11$)	p
RAP, mmHg	15.6± 5.10	17.2± 7.36	1
SPAP, mmHg	46.1± 13.4	53.5± 15.6	0.212
DPAP, mmHg	23.5± 4.99	25.4± 8.17	0.753
MPAP, mmHg	32.9± 7.63	36.1± 10.5	0.515
PAWP, mmHg	23.1± 5.28	22.6± 6.95	0.44
TPG, mmHg	9.82± 4.73	13.5± 5.46	0.5
PVR, WU	2.92± 1.4	2.49± 1.00	0.155
Indexed PVR, WU/m^2	4.94± 2.14	4.7± 1.66	0.375
PAC, mL/mmHg	2.44 (1.92)	2.45 (1.39)	0.878
PAPI	1 (1.40)	1.77 (1.42)	0.11
SV, mL	48.1± 20.1	65± 20.9	0.001*
HR, bpm	76.7± 15.4	83.5± 21.2	0.128
CO, L/min	3.6 (1.55)	5.47 (1.37)	0.004*
CI, L/min/m^2	1.8 (0.63)	2.69 (0.97)	0.004*
Indexed RVSW, mmHg. mL/m^2	4.96 (3.76)	8.93 (8.54)	0.005*
FCW Intensity, 10^4 W/m^2	2.7 (2)	3.73 (2.13)	0.033*
BCW Intensity, 10^4 W/m^2	0.69 (1.81)	1.15 (1.31)	0.612
WRI, %	31.4 (40.6)	29.2 (7.6)	0.866
Wavespeed, cm/s	2.77 (5.11)	4.71 (2.49)	0.477

Abbreviations: BCW, backward compression wave; CI, cardiac index; CO, cardiac output; DPG, diastolic pulmonary gradient; FCW, forward compression wave; HR, heart rate; MPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial compliance; PAPI, pulmonary arterial pulsatility index; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RVSW, right ventricular stroke work; SV, stroke volume; TPG, transpulmonary gradient; WRI, wave reflection index.
*Statistical significance with $p < 0.05$.

was related to an increase in stroke volume from increased inotropy; which explains the increase in indexed RVSW. Indexed RVSW has been shown to be related to adverse outcomes in patients with advanced heart failure[30,31] and right heart failure following LV assist device implantation.[32] RVSW is a surrogate marker for right ventricular workload taking into account RV contractility and the stroke volume generated, which may explain our observed relationship between RVSW and FCW intensity. Su et al. had similarly shown (weak) correlations between the FCW intensity and other right ventricular parameters such as right ventricular stroke volume index, RV fractional area change, and TAPSE.[16] This implies that the FCW intensity generated from WIA may also be a surrogate of RV performance.

Our finding that dobutamine did not alter BCW suggests that dobutamine may not reduce the pulsatile load on the right heart.[33] Indeed, the increase in FCW with dobutamine was accompanied by a comparable increase in BCW (i.e., no change in wave reflection index), suggesting that dobutamine is unlikely to have direct effects on the pulmonary vasculature. There may be several explanations for the lack of change in BCW with dobutamine. Firstly, the acute dobutamine infusion in this study produced a significant increase in stroke volume but did not result in significant reduction in pulmonary artery wedge pressure. The lack of a significant effect on pulmonary artery wedge pressure may be related to the short duration of infusion unlike previous studies,[34] or the limited effect in this specific population of patients with advanced heart failure. As pulmonary artery wedge pressure is correlated with BCW, the relatively unchanged pulmonary artery wedge pressure may explain the lack of a significant effect of dobutamine on BCW in this study. It is possible that a longer period of dobutamine infusion and/or additional vasodilator therapy (e.g., with sodium nitroprusside)[35] may reduce BCWs. Secondly, this study included a small cohort of patients and may be inadequately powered to detect a statistically significant change in BCWs.

Study limitations

The study included only a small number of patients, which may limit the statistical power of the analyses. The pressure and Doppler wire used in this study is no longer in production, which limited our study. Secondly, all the patients in this study had reduced LVEF, and it is not clear if our results can be extrapolated to patients with heart failure and preserved ejection fraction. Thirdly, echocardiographic characterization during dobutamine stress study would have provided relevant data on LV response to dobutamine. However, echocardiographic study during cardiac catheterization was abandoned because of challenging and undiagnostic studies in many cases. Finally, we were not able to determine the mechanisms for our observations and the effects of other interventions, such as vasodilator therapy or LV unloading.

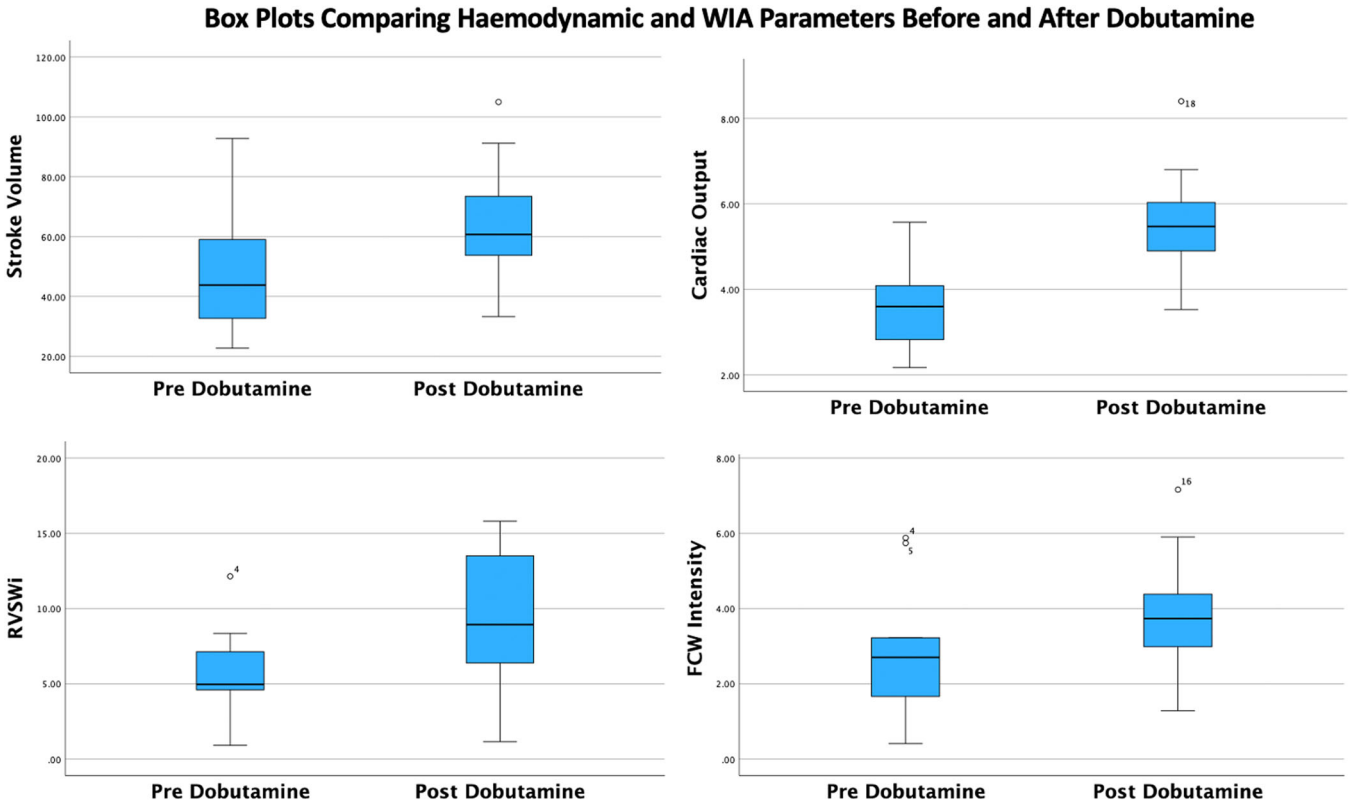

FIGURE 4 Boxplots showing the difference in hemodynamic parameters pre- and post-dobutamine challenge. CardIndex, cardiac index; CO, cardiac output; FCW, forward compression wave intensity; RVSWi, right ventricular stroke work index; SV, stroke volume; WIA, wave intensity analysis.

CONCLUSION

This is the first study to report WIA in patients with advanced heart failure with reduced ejection fraction and PHLHD. Wave reflection was associated with higher pulmonary artery wedge pressures and lower PAC. Patients with wave reflection had features of advanced heart failure (lower hemoglobin and chloride) and lower TAPSE/PASP ratio. Acute dobutamine challenge increased the FCW intensity but did not alter wave reflection, a finding that suggests that dobutamine does not reduce pulsatile load on the right heart.

AUTHOR CONTRIBUTIONS

Ivan H. W. Yim: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; visualization; writing—original draft. **Kim H. Parker**: Conceptualization; methodology; supervision; writing—review and editing. **Nigel E. Drury**: Writing—review and editing. **Hoong Sern Lim**: Conceptualization; methodology; supervision; writing—review and editing.

ACKNOWLEDGMENTS

The authors thank James Hodson, UHB Statistician, for his advice on data analysis. This study was supported by a Novel and Emerging Technologies grant from Heart Research UK (NET31/19). Nigel E. Drury was funded by an Intermediate Clinical Research Fellowship from the British Heart Foundation (FS/15/49/31612).

CONFLICT OF INTEREST STATEMENT

Hoong Sern Lim received honoraria from Abbott and Abiomed unrelated to this work. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

We can confirm that this study has approval from research ethics committee, institutional R&D approval, and informed consent from all study participants.

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How to cite this article: Yim IHW, Parker KH, Drury NE, Lim HS. Pulmonary artery wave intensity analysis in pulmonary hypertension associated with heart failure and reduced left ventricular ejection fraction. Pulm Circ. 2024;14:e12345. https://doi.org/10.1002/pul2.12345