A New Echo-Doppler Method of Assessing Pulmonary Arterial Wave Reflection: In Vivo Validation

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Abstract

Background: Pulmonary arterial (PA) wave reflection provides additional information for assessing right ventricular afterload, but its applications is hampered by the need for invasive pressure and flow measurements. We tested the hypothesis that PA pressure and flow waveforms estimated by Doppler echocardiography could be used to quantify PA wave reflection.

Methods: Doppler echocardiographic images of tricuspid regurgitation and right ventricular outflow tract flow used to estimate PA pressure and flow waveforms were acquired simultaneously with direct measurements with a dual sensor-tipped catheter under various hemodynamic conditions in a canine model of pulmonary hypertension (n=8). Wave separation analysis was performed on echo-Doppler derived as well as catheter derived waveforms to separate PA pressure into forward (Pf) and backward (Pb) pressures and derive wave reflection coefficient (RC) defined as Pb divided by Pf.

Results: RC by echo-Doppler agreed well with RC indices by catheter (RC: bias = 0.13, 95% limits of agreement = -0.25 to 0.26). RC correlated negatively with pulmonary arterial compliance and right ventricular systolic function.

Conclusions: This echo-Doppler method yields accurate measurement of reflected wave in the pulmonary circulation, paving the way to a more integrative assessment of pulmonary hemodynamics in the clinical setting.

Introduction

Pulmonary hypertension (PH) is a serious disease characterized by increased pulmonary artery pressure (PAP) associated with pulmonary vascular remodeling. It causes right-sided heart failure due to increased afterload on the right ventricle and has been shown to carry poor prognosis ¹. Mean PAP and pulmonary vascular resistance (PVR) are the most common hemodynamic measures used to diagnose PH and monitor treatment effects. However, mean PAP used in isolation cannot characterize the severity of disease or define the pathological process, since it changes depending on various hemodynamic factors such as cardiac output ², and as the disease progresses, an increase in PAP usually lag behind pathological changes in the pulmonary arterial tree, leading to a diagnostic delay ³. Mean PAP and PVR have been shown to correlate, but not closely, with the degree of right ventricular dysfunction and adverse clinical outcomes ^{4,5}. These inherent limitations may be because they do not represent all components of load faced by the right ventricle.

Pulmonary blood flows are pulsatile in nature. A complete description of right ventricular afterload, therefore, should also include the load to pulsatile component. In the pulmonary circulation, it accounts for approximately 25% of the total workload of right ventricle ⁶; the proportion is much higher than that of the systemic circulation, because of lower vascular resistance in the pulmonary circulation. Once pathological changes develop in the pulmonary vasculature, they cause premature wave reflection from

distal sites of pulmonary arterial trees, leading to an additional increase in pulsatile load ⁷. Wave reflection has been studied in the systemic circulation, where altered wave reflection has been shown to be associated with the development of left ventricular hypertrophy and adverse clinical outcomes in left-sided heart failure ^{7,8}. Analysis of pulmonary arterial wave reflection could also provide additional information above and beyond that obtained from mean PAP and PVR, thereby helping better identify or treat patients with PH.

One promising method of estimating the magnitude of wave reflection is to separate pressure into its forward and backward components by wave intensity analysis ⁹. This analysis requires measurements of both pressure (P) and flow velocity (U) waveforms. Previous animal and clinical studies measured these two waveforms directly with catheters ^{10,11}. In clinical practice, pulmonary hemodynamics is assessed using Doppler echocardiography, for example, by estimating PAP from tricuspid regurgitation (TR) velocity and evaluate the pattern of flow profile at right ventricular outflow tract (RVOT) ¹². Accordingly, we tested the hypothesis that pulmonary arterial wave reflection can be assessed noninvasively using Doppler echocardiography.

Results

Pulmonary arterial hemodynamics and wave reflection

The changes in pulmonary hemodynamics and right ventricular function induced by pulmonary arterial microembolization and hemodynamic manipulations are summarized in Table 1. The injection of dextran microsphere significantly increased mean PAP from 14 ± 3 to 34 ± 7 mmHg ($p = 0.002$) and PVR from 2.9 ± 1.0 to 13.7 ± 4.9 Woods unit ($p < 0.001$). Cardiac output decreased ($p = 0.006$). Right ventricular systolic function was also reduced, as demonstrated by a significant decrease in TAPSE ($p = 0.01$). There were alterations in RVOT flow profile such as relatively shortened acceleration time ($p = 0.12$) and the presence of mid-systolic notching ($p = 0.04$); TR flow profile exhibited high and late peaking pattern as shown by higher TR velocity ($p < 0.001$) and longer time to peak velocity ($p = 0.001$).

Fluid loading did not change PVR (at baseline, $p = 0.75$; at PH state, $p = 0.53$); it increased cardiac output only marginally at baseline ($p = 0.048$) or not at all at PH state ($p = 0.26$). It also did not affect right ventricular systolic function (at baseline, $p = 0.19$; at PH state, $p = 0.42$). Inotropic stimulation did not change PVR (at baseline, $p = 0.39$; at PH state, $p = 0.76$), although it significantly increased cardiac output (at baseline, $p < 0.001$; at PH state, $p = 0.03$). It enhanced right ventricular systolic function as demonstrated by a significant increase in TAPSE at baseline ($p = 0.01$), but not at PH state ($p = 0.26$).

Correlations of wave reflection indices by Doppler with those by catheter

Figure 1 compares sample separated waveforms obtained from direct P and U measurements and those obtained from echo-Doppler derived P and U measurements. At baseline, no wave reflection was observed. After the induction of PH, pulse pressure by Doppler dramatically increased from 7.7 to 29.2

mmHg with late-peaking pattern; Pb by Doppler started to rise 52 msec later than the onset of ejection and peaked at 12.1 mmHg. This comparison demonstrated that the new echo-Doppler method produced comparable Pb and Pf waveforms with those derived from direct measurements.

When the data for all load-state conditions were pooled, Pb, Pf and RC by Doppler correlated linearly with the corresponding indices by catheter with acceptable variabilities (Figure 2). WS by Doppler also significantly correlated with that by catheter; the regression line in the scatterplot was deviated slightly upward from the identical line, suggesting that the echo-Doppler method overestimated WS. When looking at individual change in wave reflection indices for each dog, the induction of PH increased the indices by Doppler similarly as did those by catheter (Figure 3). This indicated that the echo-Doppler method was able to track the alterations in pulmonary arterial wave reflection associated with the development of PH, with reasonable accuracy.

Wave reflection indices and effects of hemodynamic alterations

Overall, Pb by Doppler was minimal (1.4 ± 1.3 mmHg) at baseline and increased 7.5 times, up to 10.4 ± 3.9 mmHg, associated with the development of PH, even though mean PAP increased only 2.4 times, up to 34 ± 7 mmHg; its increase was substantially larger, compared to 1.9 times increase in Pf by Doppler (from 8.6 ± 2.5 to 16.1 ± 5.1 mmHg), resulting in a significant rise in RC by Doppler (from 0.16 ± 0.10 to 0.65 ± 0.13). WS by Doppler also significantly increased from 1.2 ± 0.3 to 3.3 ± 1.0 m/s.

Table 2 summarizes the changes in wave reflection indices by Doppler induced by preload loading and inotropic stimulation. An increase in preload by fluid loading, which caused a significant, but small increase in cardiac output (Table 1), did not alter the wave reflection indices (Pb, $p = 0.30$; Pf, $p = 0.15$; RC, $p = 0.86$; WS, $p = 0.06$). Inotropic stimulation produced a larger increase in cardiac output than fluid loading (Table 1); it increased Pb ($p = 0.01$) as well as Pf ($p = 0.04$), but did not alter RC ($p = 0.65$), suggesting that both Pb and Pf were flow-dependent and the effect of flow status on Pb can be cancelled out by taking a ratio of it to Pf. Inotropic stimulation also did not alter WS. These trends were also confirmed for catheter-derived wave reflection indices (Supplemental table 1); fluid loading did not change the indices; inotropic stimulation increased Pb ($p = 0.01$) and Pf ($p = 0.03$), but did not change RC ($p = 0.64$).

Hemodynamic determinants of wave reflection indices

The results of linear regression analyses identifying the determinants of echo-Doppler derived wave reflection indices are shown in Table 3. RC was correlated strongly with PAC and systolic PAP, moderately with PVR and mean PAP, and weakly with cardiac output. WS was also correlated strongly with PAC and PVR, moderately with cardiac output, systolic and mean PAP. The magnitude of the associations with both RC and WS was the highest for PAC (RC by Doppler, $r = -0.85$; WS by Doppler, $r = -0.71$). PAC was also identified as the strongest hemodynamic determinant for catheter-derived RC and WS (RC, $r = -0.70$; WS, $r = -0.79$, Supplemental table 2).

Right ventricular - pulmonary arterial coupling by wave reflection indices

Figure 4 relates right ventricular systolic function measured by TAPSE with echo-Doppler derived wave reflection indices. Overall, TAPSE was negatively correlated with both RC ($r = -0.40$, $p = 0.005$) and WS ($r = -0.49$, $p = 0.001$). When analyzed separately for loading conditions, the relationships of TAPSE with RC and WS did not change by fluid loading (RC, $p = 0.48$; WS, $p = 0.28$). However, the relationships were shifted upward by inotropic stimulation (RC, $p = 0.06$; WS, $p = 0.008$). When catheter-derived RC and WS were used instead for the above analysis, similar upward shifts by inotropic stimulation were observed (Supplemental figure 1).

Discussion

The present study demonstrated that pulmonary arterial wave reflection can be assessed noninvasively using Doppler echocardiography. This was feasible by performing wave intensity analysis to separate pulmonary arterial pressure waveform estimated from TR velocity profile into its forward and backward components. The present study validated this method in vivo against invasive wave separation analysis, and showed that reflection coefficient and wave speed stayed unchanged by alterations in cardiac output and correlated with PAC and right ventricular systolic function, suggesting that the both wave reflection indices can serve as a flow-independent measure of pulsatile load on right ventricle.

Noninvasive assessment of pulmonary arterial wave reflection

To infer a diagnosis of PH, the effects of PH on the right heart are imaged with echocardiography in clinical practice. Some of such echocardiographic signs are related to the presence of pulmonary arterial wave reflection. For example, a late-peaking pattern on TR velocity profile is caused by PAP augmentation by early arrival of reflected wave¹³. A mid-systolic notching on RVOT flow profile represents an abrupt reduction in right ventricular ejection flow secondary to wave reflection¹⁴. Although these signs are reasonably specific, the diagnostic sensitivity is generally low and these signs are absent in some patients¹⁵. The signs are also not sensitive enough to be used for monitoring the treatment course of patients.

To provide a more accurate assessment of wave reflection, wave separation analysis is performed on pulmonary arterial pressure and flow waveforms into their forward and backward components. This analysis is classically undertaken in the frequency domain, but it is fairly complicated and needs sophisticated software¹⁶. An alternative method, called wave intensity analysis, has been particularly attracting attention, because it is a time-domain based approach and therefore can be more easily applied to study the timing and magnitude of wave reflection.¹⁰ The results are easier to interpret in physiological terms.

Most previous studies of pulmonary arterial wave intensity analysis measured pressure and flow waveforms directly with catheters, which hinders its use in the clinical setting⁹. A recent study has

attempted to obtain these waveforms noninvasively, using magnetic resonance imaging, where It measured the temporal changes in cross-sectional area of pulmonary artery for a surrogate for PAP¹⁷. The noninvasive method we introduce herein uses Doppler echocardiography to obtain pulmonary arterial pressure and flow waveforms from TR and RVOT flow profiles. These measurements are routinely performed for diagnosing PH or monitoring the treatment course, so this echo-Doppler method can be easily applied in the clinical setting.

This echo-Doppler method involves a couple of assumptions. Firstly, right atrial pressure is assumed to be constant during systole. This method therefore may not be applicable to patients with severe TR which causes a significant rise in right atrial pressure in late systole. Secondly, RR interval on electrocardiogram is assumed to be constant throughout image acquisitions. In this method, pressure and flow waveforms are obtained from echo-Doppler images acquired at different cardiac cycle and the both waveforms are aligned in time with reference to the R wave on electrocardiogram. Therefore, this method cannot be applied to patients with large heart rate variability such as atrial fibrillation. Despite the above assumptions, the present study demonstrated that the echo-Doppler method can quantify pulmonary arterial wave reflection with reasonable accuracy and it is sensitive for detecting the changes in pulmonary arterial wave reflection associated with the development of PH.

Potential for clinical applications

Pulmonary arterial hypertension remains a fatal disease with a 1-year mortality of approximately 20%, despite advances in disease-specific therapies¹. This may be because the disease is often far established at diagnosis as demonstrated by contemporary disease registries reporting that mean PVR at diagnosis ranged between 8 and 10 Wood units¹⁸. Early initiation of the therapies may be effective, as suggested by a previous randomized control study including patients with mildly symptomatic pulmonary arterial hypertension¹⁹. At the early stage of disease, PAC falls considerably while PVR increases only slightly. Thus, the assessment of pulsatile load may allow an early diagnosis even when PVR stays within normal limits. In the present study, wave reflection, an important component of the pulsatile load, rose substantially despite a slight increase in mean PAP induced by pulmonary arterial microembolization. This finding is consistent with another study of wave intensity analysis, evidencing that a significant wave reflection was present even in PH patients with mildly elevated PAP¹¹. Therefore, this echo-Doppler assessment of wave reflection may be able to offer an early diagnosis of PH.

PH-specific treatments do not always produce desirable clinical outcomes. For example, some patients with chronic thromboembolic pulmonary hypertension exhibit exercise intolerance even after pulmonary endarterectomy, often despite normalization of pulmonary arterial hemodynamics. This may partly be attributable to persistent pulmonary arterial wave reflection after the surgery. A previous study demonstrated using wave intensity analysis that there remained a large reflected pressure wave 3 months after the surgery, even in patients without residual PH²⁰. Pulmonary arterial wave reflection could be an attractive target for the treatment of PH. However, it remained to be tested whether a reduction in pulmonary arterial wave reflection will lead to a significant improvement in clinical outcomes.

Limitations

To validate the echo-Doppler method, the present study created an animal model of PH which mimicked pulmonary arterial hypertension by embolizing peripheral pulmonary arterial with microsphere. The magnitude and timing of wave reflection vary depending on the site of narrowing in pulmonary vasculature; this was evidenced by previous studies of wave intensity analysis observing a larger reflected wave that arrived earlier during systole in chronic thromboembolic pulmonary hypertension than that in pulmonary arterial hypertension²¹. It needs to be investigated whether or not the echo-Doppler method can detect the alterations in the magnitude and timing of pulmonary arterial wave reflection by changes in the site of narrowing.

Some studies questioned the accuracy of echocardiographic estimates of pulmonary arterial systolic pressure in the clinical setting, because TR velocity is sometimes difficult to measure or to obtain clear spectral Doppler envelopes²². Therefore, this echo-Doppler method should also be tested for feasibility and accuracy in patients before clinical application.

Conclusions

The new echo-Doppler method yields an accurate measurement of pulmonary arterial wave reflection and can sensitively detect the alterations associated with the development of PH. The results of the present study provide the basis for integrating this assessment of pulmonary arterial wave reflection for more detailed description of right ventricular afterload, thereby, diagnosis of PH and treatment monitoring in the clinical setting.

Methods

Principles of echo-Doppler method of assessing pulmonary arterial wave reflection

Pulmonary arterial wave reflection can be assessed based on the concept of wave intensity analysis. This analysis determines the origin, type and timing of traveling waves in a circulation from combined P and U measurements and allows wave separation into forward-traveling and backward-traveling components. Theoretical background and practical applications have been described elsewhere⁹. Briefly, wave speed (WS), which represents the elastic properties of the local artery, can be determined by P-U loop method²³; it takes advantage of the water hammer equation relating P and U on the condition that there is no wave reflection.

$$c = (dP / dU) / \rho \quad (1)$$

, where dP and dU are the changes in P and U, ρ is the density of blood (1050 kg/m³) and c is WS. Pulse pressure can be separated into those attributed to forward-traveling (Pf) and backward-traveling (Pb) waves using equations 2 and 3.

$$dP_f = (dP + \rho c dU)/2 \quad (2)$$

$$dP_b = (dP - \rho c dU)/2 \quad (3)$$

, where dP_f and dP_b are the changes in P_f and P_b . P_f and P_b can then be found by summing these differences.

$$P_f = \sum dP_f \quad (4)$$

$$P_b = \sum dP_b \quad (5)$$

The new noninvasive method we propose herein uses echo-Doppler derived P and U waveforms, instead of the direct measurements. A pulsed-wave Doppler tracing of RVOT flow is used as a surrogate for U waveform. On the other hand, P waveform is estimated by applying the simplified Bernoulli equation to a continuous-wave Doppler tracing of TR flow and adding a term of right atrial pressure as below.

$$P(t) = 4 \times TRV(t)^2 + RAP \quad (6)$$

, where t is time, TRV is TR velocity and RAP is right atrial pressure which we assume is constant throughout the cardiac cycle. End-diastolic P is determined as P value at the beginning of ejection (shown as t_0) identified from the U waveform.

$$\text{End-diastolic } P = 4 \times TRV(t_0)^2 + RAP \quad (7)$$

Subtracting end-diastolic P from P waveform yields pulse pressure waveform; this subtraction eliminates the term of right atrial pressure.

$$\text{Pulse pressure}(t) = 4 \times TRV(t)^2 - 4 \times TRV(t_0)^2 \quad (8)$$

Wave separation analysis is performed on the pulse pressure and flow velocity waveforms. The pulse pressure waveform will then be separated into P_f and P_b . This analysis yields 4 wave reflection indices: WS , peak P_b , peak P_f and reflection coefficient (RC) calculated as the ratio of peak P_b to peak P_f .

Animal preparation

The present study was approved by the Animal Experimental Committee of Tokyo University of Agriculture and Technology (approval number: 30-146). All process of the study was carried out in compliance with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines and the regulations on animal experiments and the guide for the care and use of laboratory animals of Tokyo University of Agriculture and Technology¹. Eight healthy Beagle dogs (Kitayama Labes, Nagano, Japan) were used in the present study (all females, aged 4–5 years old, weighted 10–13 kg). All dogs were sedated with butorphanol (0.2 mg/kg), midazolam hydrochloride (0.2 mg/kg) and meloxicam (0.2 mg/kg) and initially anesthetized with propofol (4 mg/kg) before intubated and mechanically ventilated. Complete anesthesia was maintained by inhalation of isoflurane (end-tidal concentration $1.5 \pm 0.1\%$). The

dog was then placed in right lateral recumbency. Heparin sodium (100 IU/kg) was administered for preventing thrombosis.

A 4-Fr catheter (Atom nutrition catheter, Atom Medical, Tokyo, Japan) was inserted into the right femoral artery to monitor systemic arterial pressure. A 4.2-Fr multipurpose angiographic catheter (Goodtec angiographic catheter, GOODMAN, Aichi, Japan) was advanced retrograde into the left atrium through the left carotid artery to monitor left atrial pressure. Another 4.2-Fr multipurpose angiographic catheter was placed in the right atrium through the left jugular vein to monitor right atrial pressure. These fluid-filled catheters were connected to pressure transducers (Life kit DX-360, Nihon Kohden, Tokyo, Japan) and pressure waveforms were displayed using a multi-channel monitor (Life Scope BSM-5192; Nihon Kohden, Tokyo, Japan). These two catheters were also used to sample blood from the left and right atriums to calculate cardiac output.

To obtain P and U waveforms as a reference for validating the new echo-Doppler method, a dual sensor-tipped pressure and flow wire (Combwire, Royal Philips, Amsterdam, Netherlands) was advanced to approximately 1 cm beyond the pulmonary valve through another 4.2-Fr multipurpose angiographic catheter inserted from the left jugular vein. Careful catheter and wire manipulation ensured that signals were steadily obtained.

List Of Abbreviations

AcT, acceleration time; LAP, left atrial pressure; P, pressure; PA, pulmonary arterial; PAC, pulmonary artery compliance; PAP, pulmonary artery pressure; Pb, backward-traveling; Pf, forward-traveling; PH, pulmonary hypertension; Pt, pulse pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RC, reflection coefficient; RV, right ventricle; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid valve regurgitation; U, velocity; WS, wave speed

Declarations

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T. Yoshida and T.U. designed the study and wrote the initial draft of the manuscript. S.K. and K.M., Z.Y. acquired and analyzed data. A.U. and H.H., Z.Y. interpreted results and critically reviewed. T. Yamashita and R.T. edited manuscript and approved final version of manuscript.

Competing interests

The authors declare no competing interests.

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Tables

Table 1. The changes in hemodynamic and echocardiographic variables.

	Baseline			Pulmonary hypertension		
	Before challenge	Fluid challenge	DOB challenge	Before challenge	Fluid challenge	DOB challenge
Hemodynamic variables						
SAP, mmHg						
Systolic	110±9	108±17	111±16	97±16†	96±14	106±15
Diastolic	89±16	83±23	81±26	76±18†	73±19	84±18
Mean	93±17	88±17	95±20	83±18	83±19	95±17
LAP, mmHg	6±1	8±2*	8±2*	7±2	8±3*	7±3
PAP, mmHg						
Systolic	21±4	25±6	28±12*	47±7†	49±14	63±22*
Diastolic	11±3	13±5	15±10	28±8†	28±16	31±14
Mean	14±3	17±5	19±11	34±7†	35±15	42±16
RAP, mmHg	4±2	6±2*	4±3	5±2	7±2*	5±3
HR, /min	126±7	130±21	126±22	124±12	131±17*	137±12*
CO, L/min	2.7±0.1	2.9±0.3*	3.2±0.1*	2.1±0.5†	2.2±0.4*	2.4±0.5*
SV, ml	22±1	23±5	26±4	17±4†	17±4*	18±4
PVR, Wood units	2.9±1.0	3.2±2.1	3.5±2.1	13.7±4.9†	12.1±5.2*	14.6±5.4*
PAC, ml/mmHg	2.1±0.5	2.0±0.6	2.0±0.3	1.1±0.6†	0.9±0.4*	0.6±0.2*
Echocardiographic variables						
LVEF, %	66.0±6.5	77.8±7.7*	81.7±5.9*	74.5±9.8	80.4±8.6	79.8±19.9
TAPSE, mm	11.2±2.1	12.1±2.3	13.0±1.0*	9.3±2.1†	9.6±1.5	10.1±1.3
RVOT flow						
AcT, ms	93±23	99±20	88±18	71±14	71±14	73±11
Mid-systolic notching, %	0	0	0	50†	63	63
TR jet						
Peak velocity, m/s	2.08±0.22	2.21±0.37	2.43±0.38	3.13±0.38†	3.38±0.47	3.90±0.62
Time to peak, ms	135±32	132±33	125±41	185±35†	182±51	185±56

Abbreviations: SAP, systemic arterial pressure; LAP, left atrial pressure; PAP, pulmonary arterial pressure; RAP, right atrial pressure; HR, heart rate; CO, cardiac output; SV, stroke volume; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; RVOT, right ventricular outflow tract; AcT, acceleration time; TR, tricuspid regurgitation; * denotes p value < 0.05 vs before challenge and † denotes p value < 0.05 vs baseline.

Table 2. Effects of hemodynamic manipulations

Fluid challenge						
	Whole		Baseline		Pulmonary hypertension	
	Before	After	Before	After	Before	After
Pb, mmHg	5.9±5.4	5.8±5.3	1.4±1.3	1.8±0.7	10.4±3.9	9.8±4.7
Pf, mmHg	12.4±5.5	13.1±4.6	8.6±2.5	9.8±2.5	16.1±5.1	16.3±3.9
RC	0.41±0.27	0.38±0.23	0.16±0.10	0.18±0.05	0.65±0.13	0.58±0.14
WS, m/s	2.2±1.3	2.4±1.3	1.2±0.3	1.5±0.6	3.3±1.0	3.4±1.1
Dobutamine challenge						
	Whole		Baseline		Pulmonary hypertension	
	Before	After	Before	Before	After	Before
Pb, mmHg	5.9±5.4	7.8±5.2*	1.4±1.3	3.0±1.3	10.4±3.9	11.9±3.0
Pf, mmHg	12.4±5.5	16.7±7.5*	8.6±2.5	10.1±1.6	16.1±5.1	22.5±5.3*
RC	0.40±0.27	0.42±0.18	0.16±0.10	0.29±0.11	0.65±0.13	0.55±0.14
WS, m/s	2.2±1.3	2.6±1.3	1.2±0.3	1.5±0.4	3.3±1.0	3.6±1.0

Abbreviations: Pb, backward pressure; Pf, forward pressure; RC, reflection coefficient; WS, wave speed; * denotes p value < 0.05 vs before challenge

Table 3. Hemodynamic determinants of wave reflection indices

	RC		WS	
	R	P value	R	P value
PVR	0.58	<0.001	0.62	<0.001
PAC	-0.85	<0.001	-0.71	<0.001
CO	-0.34	0.02	-0.59	<0.001
HR	0.26	0.08	0.06	0.68
sPAP	0.74	<0.001	0.58	<0.001
mPAP	0.55	<0.001	0.48	0.001
mLAP	-0.17	0.250	-0.09	0.53

Abbreviations: RC, reflection coefficient; WS, wave speed; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance; CO, cardiac output; SV, stroke volume; HR, heart rate; sPAP, systolic pulmonary arterial pressure; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; mLAP, mean left atrial pressure.

Figures

Figure 1

Comparison between catheter derived and echo-Doppler derived separated pressure waveforms
Separated pressure waveforms obtained using direct pressure and flow measurements acquired from one sample dog (left side) and those obtained using echo-Doppler images of RVOT and TR flows from the

same dog (right side). Pt, Pf and Pb denote pulse pressure, forward pressure and backward pressure, respectively.

Figure 2

Linear regression and Bland-Altman analyses Linear regression (top) and Bland-Altman (bottom) plots comparing catheter derived and echo-Doppler derived Pb (A), Pf (B), RC (C) and WS (D).

Figure 3

The changes in wave reflection indices induced by pulmonary hypertension The changes in echo-Doppler derived Pb (A), Pf (B), RC (C) and WS (D) from baseline (black circle) to pulmonary hypertension state (open circle) were compared to those in corresponding catheter derived indices.

Figure 4

Relationship between wave reflection indices and RV systolic function TAPSE was plotted against echo-Doppler derived RC (A) and WS (B), with separate regression lines for data acquired before challenge (solid line), during fluid challenge (dashed line) and during dobutamine challenge (dotted line).

Figure 5

Pt, Pf and Pb denote pulse pressure, forward pressure and backward pressure, respectively.

Supplementary Files

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- [SupplementalFigure1.tif](#)
- [SupplementalTables.docx](#)