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Haemodynamic and structural correlates of the first and second heart sounds in pulmonary arterial hypertension: an acoustic cardiography cohort study

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ABSTRACT

Objective: To examine the relationship between acoustic characteristics of the first and second heart sounds (S1 and S2) and underlying cardiac structure and haemodynamics in patients with isolated pulmonary arterial hypertension (PAH) and controls.

Design: Prospective multicentre cohort study.

Setting: Tertiary referral and community hospitals.

Participants: We prospectively evaluated 40 PAH patients undergoing right-heart catheterisation with contemporaneous digital acoustic cardiography (intensity and complexity) and two-dimensional transthoracic echocardiography. To normalise for differences in body habitus, acoustic variables were also expressed as a ratio (S2/S1). 130 participants (55 also had haemodynamic and/or echocardiographic assessment) without clinical or haemodynamic evidence of PAH or congestive heart failure acted as controls.

Results: Patients with PAH had higher mean pulmonary artery pressure (mPA; 40 ± 13 vs 16 ± 4 mm Hg, $p < 0.0001$) and pulmonary vascular resistance (9 ± 6 vs 1 ± 1 Wood Units, $p < 0.0001$) compared with controls, but cardiac index and mean pulmonary capillary wedge pressure were similar. More PAH patients had evidence of right ventricular (RV) dilation (50% vs 19%) and RV systolic dysfunction (41% vs 9%) in the moderate–severe range (all $p < 0.05$). Compared with controls, the acoustic profiles of PAH patients were characterised by increased S2 complexity, S2/S1 complexity and S2/S1 intensity (all $p < 0.05$). In the PAH cohort, S2 complexity was inversely related to S1 complexity. mPA was the only independent multivariate predictor of S2 complexity. The severity of RV enlargement and systolic impairment had reciprocal effects on the complexity of S2 (increased) and S1 (decreased). Decreased S1 complexity was also related to evidence of a small left ventricular cavity.

Conclusions: Acoustic characteristics of both S1 and S2 are related to the severity of PAH and are associated with RV enlargement and systolic dysfunction. The reciprocal relationship between S2 and S1 complexity may also reflect the underlying ventricular interaction associated with PAH.

ARTICLE SUMMARY

Article focus

- To examine the relationship between acoustic characteristics of the first and second heart sounds (S1 and S2) and underlying cardiac structure and haemodynamics in patients with isolated pulmonary arterial hypertension (PAH) and controls.
- The changes in cardiac structure and haemodynamics with PAH can be detected by quantitative acoustic cardiography.

Key messages

- The normal acoustic profile observed in controls is altered in patients with PAH.
- Acoustic properties of S2 were directly related to invasively derived mean pulmonary artery pressure and pulmonary vascular resistance.
- The reciprocal relationship between S1 and S2 among patients with PAH may reflect the phenomenon of ventricular interaction that develops as the right ventricle remodels during the course of PAH.

Strengths and limitations of this study

- Prospective multicentre study with detailed acoustic recording and correlation with echocardiographic and haemodynamic parameters.
- Relatively small sample size of the control and PAH cohorts.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterised by increased pulmonary vascular resistance (PVR) and consequent right ventricular (RV) failure due to pressure overload.^{1 2} Once considered a rare disease, PAH is recognised as a complication of a spectrum of clinical conditions.³ Recent advances in treatment have intensified the interest in identifying afflicted patients.⁴

The physical examination is the clinician's first opportunity for the objective assessment

of a patient's haemodynamic state. Traditional pedagogy states that abnormal intensity, quality and splitting of the second heart sound (S2) are auscultatory signs of pulmonary hypertension (PH).⁵ However, physical signs of PH were often evaluated in the context of confounding cardiac abnormalities such as left-to-right shunting or left ventricular (LV) systolic dysfunction. Moreover, quantitative relationships between auscultatory findings and derangement of the RV-pulmonary arterial circulatory unit have not been well characterised.⁶ Digital acoustic cardiography permits quantitative analysis of precordial heart sounds.⁷ Our aim was to quantitatively examine the precordial acoustic profile as it relates to cardiac haemodynamic and structural alterations in patients with isolated PAH and controls.

METHODS

Study participants

This was a prospective, multicentre, observational cohort study. The PAH cohort was recruited from the PH clinic of the University Health Network. All patients routinely undergo transthoracic two-dimensional echocardiogram (2D-TTE) and Doppler examination, measurements of B-type natriuretic peptide and 6 min walk tests. Patients with suspected or established PAH are referred for haemodynamic assessment. Consecutive patients referred for right-heart catheterisation (RHC) between November 2010 and July 2011 were invited to participate. Exclusion criteria included the echocardiographic determination of LV systolic dysfunction or valvular heart disease (suspected WHO group II PH) given possible acoustic abnormalities related to left heart disease. Patients with chronic lung diseases (suspected WHO group III PH) were also excluded, as abnormalities of pulmonary function may confound the transmission of acoustic signals. Patients were also excluded if a non-sinus rhythm was identified or if complete right or left bundle branch block was observed (QRS duration >120 m).

The control group consisted of individuals in sinus rhythm without clinical or haemodynamic evidence of PH or congestive heart failure. Healthy volunteers without a history of cardiac or pulmonary diseases were recruited from the community and underwent acoustic cardiography alone (n=75). A second group of controls without PH were derived from patients who underwent acoustic cardiography and 2D-TTE and/or RHC (n=55) for the evaluation of chest pain syndromes.

The study protocols for the PAH cohort were approved by the Mount Sinai Hospital Research Ethics Board (approval number 10-0142-E) and by local US institutional review boards for the control cohorts (University of Utah, approval number was 26801; University of California, San Francisco approval number H8831-22924; and Western Institutional Review Board, Washington, approval number 1037785). All participants provided written informed consent.

Cardiac catheterisation procedures and haemodynamic data

RHC was performed with standard balloon floatation pulmonary artery catheter in the fasting state, without sedation. Haemodynamic measurements were recorded at end-expiration and included heart rate, systolic/diastolic/mean arterial pressure (SAP/DAP/MAP), right atrial pressure, pulmonary artery systolic/diastolic/mean pressures (PASP/PADP/mPA) and pulmonary capillary wedge pressure (PCWP). Cardiac output was measured using both the Fick method and in triplicate by thermol-dilution. PVR and systemic vascular resistances were calculated using standard formulas.

Transthoracic echocardiography

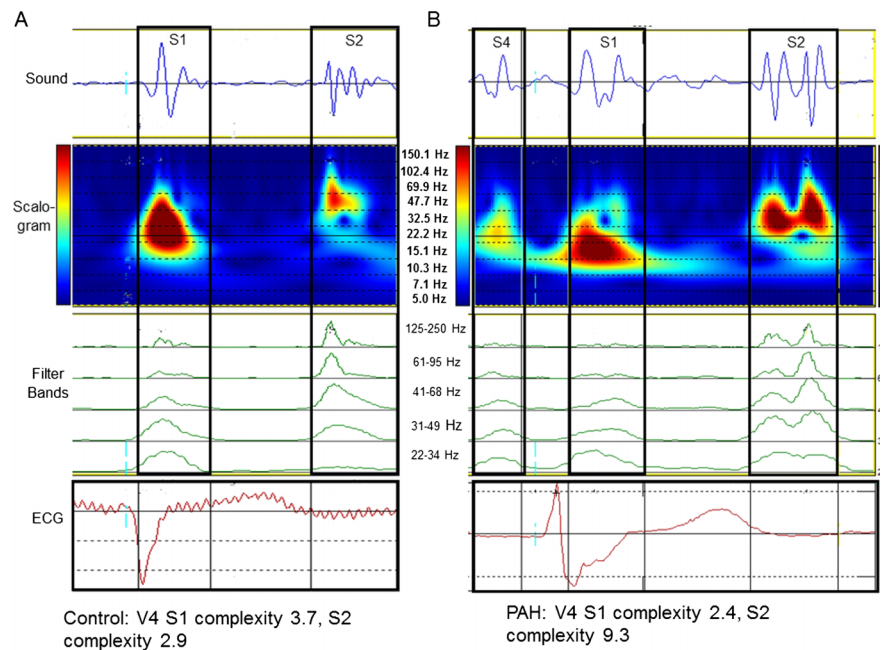
The 2D-TTE assessment was performed within a week of the RHC. LV ejection fraction, end-diastolic and end-systolic volumes were calculated using the biplane method of disc summation and indexed to BSA.⁸ Semiquantitative and qualitative assessment of RV structure and function was performed following review of standard 2D acoustic windows that included RV inflow and outflow tracts, parasternal short-axis views and apical views. Parameters of RV size (at end-diastole from an RV-focused apical four-chamber view) and RV systolic function (at least one of the fractional area change and tricuspid annular plane systolic excursion) were used in the semiquantitative analysis of RV structure and function.

Digital acoustic cardiography and ECG analysis

Acoustic cardiography was performed on the same day as the RHC with the Audicor device (Inovise Medical, Inc, Beaverton, Oregon, USA), either prior to or following RHC with the patient supine with head incline of 30° during tidal respiration. Standard 12-lead placement was performed with two dual-function (audioelectrocardiographic) sensors in the precordial V3 and V4 positions capable of simultaneously capturing cardiac electrical and acoustic signals. Five 10 s artefact-free recordings were obtained and analysed utilising proprietary software. This algorithm utilises wavelet-based signal processing techniques for acoustic analysis. Time-frequency analysis is performed, permitting separation of heart sounds from murmurs and artefacts. The Audicor algorithm reduces the confounders caused by external noise, speech, movement and permits analysis in individuals with high body mass index.⁷

Two acoustic cardiographic characteristics of S1 and S2 were analysed: intensity and complexity. A value for heart sound intensity is generated based on the peak-to-peak amplitude of the sound and expressed in mV units. Heart sound complexity is a correlate of the auditory perception of valve sound crispness and is determined using time-frequency measures of width, intensity and frequency content of the signal, which is influenced by valve splitting or closure abnormalities. Based on spectral analysis, complexity is expressed as a dimensionless index. Figure 1 demonstrates the

Figure 1 Acoustic cardiographic output for a control patient (A) and a patient with pulmonary arterial hypertension (PAH) (B) showing real-time sound trace, scalogram time-frequency representation, filter bands and real-time ECG trace. The scalogram time-frequency representation shows frequency on the vertical axis on a logarithmic scale from 5 to 220 Hz and time on the horizontal axis. The squared magnitude of the wavelet transform energy at each frequency is represented by colours ranging from dark blue (bottom 2%) to deep red (top 2%).



representative acoustic recordings and spectral displays from a control and a PAH participant.

Heart sound intensity, and possibly the complexity, is known to be influenced by factors such as BSA, characteristics of the thoracic cage and cardiac axis.⁵ Therefore, complexity and intensity are expressed in absolute values as well as normalised and expressed as a ratio between S2 and S1 to account for variations in anthropomorphic characteristics.

Statistical analysis

Categorical data are presented as numbers and percentages. Continuous data are presented as mean±SD. Continuous variables were compared with either paired or unpaired Student *t* test, while categorical variables were compared between groups with Pearson χ^2 test or a Fisher exact test where appropriate.

We performed univariate and multivariate linear logistic regression to examine the relationship between haemodynamic variables with S1 and S2 complexity. Binary logistic regression, for example, with $mPA \geq 25$ mm Hg as the dependent variable, was performed to examine its association with audioelectrocardiographic variables. Receiver-operating characteristic (ROC) curves were then plotted using the univariate score for each patient allowing the calculation of sensitivity, specificity and the area-under-the-ROC curve (AUC ROC).

All reported *p* values are two-sided. The $p < 0.05$ was considered statistically significant. Data analyses were performed with SPSS V.16 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Study participants

Forty patients were enrolled in the PAH cohort. The baseline characteristics of these patients are presented

in table 1. The predominant aetiology of PAH was classified as idiopathic, followed by that associated with underlying connective tissue disease. A total of 130 controls with acoustic cardiographic data were enrolled. Of these, 55 had contemporaneous echocardiographic data and 28 had RHC and echocardiographic data. Both groups were similar in age (PAH 58 ± 16 years, controls 59 ± 11 , $p = 0.73$). A higher proportion of the PAH cohort were women (78% vs 55%, $p < 0.01$) and thus the PAH cohort also exhibited smaller BSA (1.7 ± 0.2 vs 1.9 ± 0.3 m², $p < 0.01$).

Acoustic cardiography measurements

Heart rate and PR intervals were similar between patients with PAH and controls. Although patients with complete right-bundle or left-bundle branch blocks were excluded, patients with PAH exhibited a slightly greater

Table 1 Baseline clinical characteristics of PAH patients

Classification of PAH (n)	PAH (40)
Group 1	
Idiopathic	13
Connective tissue disease	21
Portal hypertension	2
Other	3
Group 4 (chronic thromboembolic)	1
NYHA class	2.4±0.6
6 min walk test (total distance) (m)	423±96
B-type natriuretic peptide (pmol/l)	345±612
Medications (%)	
Endothelin receptor antagonists	41
Calcium channel antagonists	28
Phosphodiesterase V inhibitor	40

NYHA, New York Heart Association; PAH, pulmonary arterial hypertension.

Table 2 Acoustic cardiography measurements

(n)	PAH (40)	Controls (130)	p Value
PR interval (ms)	156±45	157±29	0.94
QRS duration (ms)	105±21	95±17	0.04
Heart rate (bpm)	72±14	70±11	0.31
S1 intensity			
V3	1.8±1.2*	2.3±1.9*	0.15
V4	2.4±2.0†	2.7±2.6†	0.50
S1 complexity			
V3	4.5±1.6‡	4.5±2.5‡	0.89
V4	4.6±2.0§	5.1±3.0§	0.32
S2 intensity			
V3	1.2±0.9*	1.2±1.1*	0.998
V4	1.7±1.7†	1.4±1.3†	0.16
S2 complexity			
V3	3.7±2.0‡	1.5±1.1‡	<0.0001
V4	4.6±4.7§	1.3±1.1§	<0.0001
S2/S1 intensity			
V3	0.73±0.28	0.54±0.35	0.02
V4	0.74±0.28	0.54±0.30	0.01
S2/S1 complexity			
V3	1.0±0.7	0.5±0.5	<0.0001
V4	1.3±1.7	0.3±0.3	<0.0001

The italicized p value refers to the between group comparisons (between columns or horizontally). The annotated values and legend refer to within group comparisons (within columns or vertically).

*PAH V3 S1 vs S2 intensity, $p=0.01$; control V3 S1 vs S2 intensity, $p<0.0001$.

†PAH V4 S1 vs S2 intensity, $p=0.09$; control V4 S1 vs S2 intensity, $p<0.0001$.

‡PAH V3 S1 vs S2 complexity, $p=0.07$; control V3 S1 vs S2 complexity, $p<0.0001$.

§PAH V4 S1 vs S2 complexity, $p=0.998$; control V4 S1 vs S2 complexity, $p<0.0001$.

PAH, pulmonary arterial hypertension.

QRS duration. Acoustic characteristics of S1 and S2 in the PAH and control groups are presented in [table 2](#).

Among the control group, both the intensity and complexity of S1 were increased compared with S2. In contrast, among the PAH group, the complexity of S2 was increased compared with S1. In the PAH group, the complexity of S2 in both precordial lead positions was also significantly increased compared with the control group. Thus, the S2/S1 complexity ratio was also highly significantly different between the PAH and control groups. Although S2 intensity was not different between PAH and control groups, the S2/S1 intensity ratio was significantly increased among patients with PAH compared with controls.

Haemodynamic measurements: relationship between acoustic cardiographic variables and pulmonary vascular haemodynamics

Haemodynamic and acoustic data were available from the 40 PAH cohort and 28 control participants and are shown in [table 3](#). As expected, patients with PAH demonstrated significantly increased mPA and PVR. Importantly, there were no significant differences in PCWP or cardiac index.

Table 3 Haemodynamic measurements

(n)	PAH (40)	Controls (28)	p Value
Mean right atrial pressure (mm Hg)	5±4	3±4	0.13
Pulmonary artery systolic pressure (mm Hg)	68±23	25±6	<0.0001
Pulmonary artery diastolic pressure (mm Hg)	22±8	11±16	0.001
Mean pulmonary artery pressure (mm Hg)	40±13	16±4	<0.0001
Mean pulmonary capillary wedge pressure (mm Hg)	8±4	9±3	0.37
Cardiac index (Fick) (l/min/m ²)	2.4±0.7	2.5±1.0	0.54
Pulmonary vascular resistance (wood unit)	9±6	1±1	<0.0001

PAH, pulmonary arterial hypertension.

As the complexity of S2 was significantly increased in the PAH group, we examined the relationship between S2 complexity and pulmonary vascular haemodynamics in the entire cohort. As shown in [figure 2](#), both V3 and V4 S2 complexity correlated significantly with mPA and PVR. We examined the relationship between S2 complexity and other haemodynamic variables including heart rate, cardiac output, right atrial pressure, PCWP, mean systemic arterial pressure and mPA ([table 4](#)). Mean PA pressure was the only independent multivariate predictor for S2 complexity in both precordial lead positions.

In contrast to S2 complexity, we observed that mPA was inversely correlated with V4 S1 complexity. Cardiac output was a univariate predictor of S1 complexity in the both the V3 and V4 positions. The relationship between cardiac output and V3 S1 complexity remained significant after multivariable analysis of other haemodynamic variables.

Echocardiographic measurements: relationship between acoustic cardiographic variables and RV enlargement and systolic dysfunction

Echocardiographic data were available for all the PAH group and the 28 controls who also had haemodynamic data. As expected, compared with the control group, the RVSP was significantly elevated and a larger portion of the PAH group had evidence of RV dilation (50% vs 19%, $p=0.02$) and RV systolic dysfunction (41% vs 9%, $p=0.01$) in the moderate-to-severe range on echocardiography.

We examined the relationship between S2 and S1 complexity based on the abnormalities of RV structure and function within PAH and control groups and in the entire cohort ([table 5](#) and [figure 3](#)). S2 complexity was increased in the PAH group in patients with moderate-to-severe RV enlargement and systolic

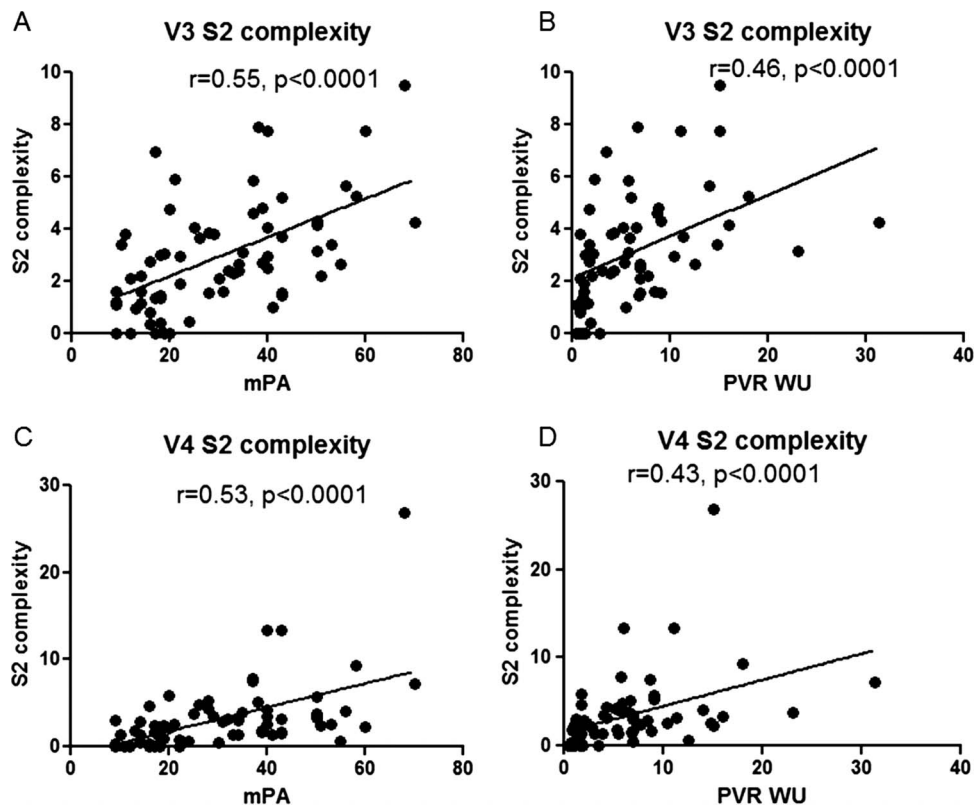


Figure 2 Relationship between S2 complexity and pulmonary vascular haemodynamics. mPA, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; WU, Wood Units.

dysfunction compared with those with only normal or mild abnormalities. In particular, V3 S2 complexity was increased significantly in the PAH group among those with moderate–severe RV systolic dysfunction. In both V3 and V4 positions, in the entire cohort, S2 complexity remained clearly increased among those with moderate–severe RV enlargement and moderate–severe RV systolic dysfunction.

In contrast, S1 complexity showed an inverse relationship with increasing severity of RV enlargement and RV systolic dysfunction (table 5 and figure 3). In patients with PAH and moderate to severe RV enlargement and systolic dysfunction, V4 S1 complexity was reduced significantly compared with those with normal or mild RV enlargement and systolic dysfunction. This observation remained significant when the entire cohort was analysed. No such relationship between RV structure and function with S1 and S2 complexity was noted in controls.

Evidence of ventricular interaction in PAH by acoustic cardiography

We observed a direct relationship between increased mPA/PVR and S2 complexity (figure 2). S1 complexity was inversely correlated with increasing severity of RV enlargement and RV systolic dysfunction (table 5 and figure 3). We hypothesised that these observations and the value of the S2/S1 complexity ratio may represent an acoustic corollary of the ventricular interaction in the

PAH group. Indeed, there was a direct relationship between S1 complexity in both precordial leads and LV end-diastolic diameter (figure 4A). We also observed a significant inverse correlation between V3 S1 complexity and V4 S2 complexity in the PAH cohort, $R=-0.32$, $p=0.049$ (figure 4B).

Value of quantitative acoustic variables for the detection of PAH

We investigated the value of S2 complexity and S2/S1 complexity ratio for the detection of PAH ($\text{mPA} \geq 25 \text{ mm Hg}$) by constructing ROC curves to assess the predictive performance in the 40 PAH cases and 28 controls with haemodynamic data. As shown in figure 5, the AUC ROC curve for V3 and V4 S2 complexity was 0.80 and 0.85, respectively. The optimal S2 complexity cut-offs for the discrimination of PAH was 1.44 (sensitivity 81%, specificity 70%, likelihood ratio 2.70) and 2.06 (sensitivity 70%, specificity 87%, likelihood ratio 5.27) for V3 and V4 S2 complexity, respectively. When we examined the S2/S1 complexity ratio, the AUC ROC was 0.89; however, this was not statistically superior to the AUC ROC for V4 S2 complexity ($p=0.53$).

DISCUSSION

In this prospective cohort study, we investigated the quantitative relationship between acoustic characteristics of S2 and S1 and the haemodynamic severity of PAH as

Table 4 Univariate haemodynamic predictors of S1 and S2 complexity

	B (unstd)	CI	p Value
V3 S2 complexity			
Mean pulmonary artery pressure	0.07	0.05 to 0.10	<0.0001
Heart rate	-0.01	-0.06 to 0.05	0.85
Pulmonary capillary wedge pressure	-0.11	-0.25 to 0.03	0.13
Cardiac output (Fick)	-0.27	-0.71 to 0.18	0.23
Right atrial pressure			
Mean systemic artery pressure	0.02	-0.04 to 0.07	0.58
V4 S2 complexity			
Mean pulmonary artery pressure	0.14	0.08 to 0.19	<0.0001
Heart rate	0.03	-0.09 to 0.15	0.63
Pulmonary capillary wedge pressure	-0.09	-0.36 to 0.19	0.52
Cardiac output (Fick)	-0.46	-1.53 to 0.62	0.40
Right atrial pressure	0.04	-0.20 to 0.28	0.74
Mean systemic artery pressure	0.02	-0.12 to 0.15	0.81
V3 S1 complexity			
Mean pulmonary artery pressure	-0.01	-0.04 to 0.02	0.46
Heart rate	-0.01	-0.06 to 0.03	0.51
Pulmonary capillary wedge pressure	-0.09	-0.21 to 0.03	0.15
Cardiac output (Fick)	0.37	0.02–0.72	0.04
Right atrial pressure	-0.13	-0.24 to -0.02	0.02
Mean systemic artery pressure	0.04	-0.01 to 0.08	0.11
V4 S1 complexity			
Mean pulmonary artery pressure	-0.04	-0.07 to -0.004	0.03
Heart rate	-0.03	-0.08 to 0.02	0.24
Pulmonary capillary wedge pressure	0.09	-0.06 to 0.23	0.23
Cardiac output (Fick)	0.49	0.04 to 0.93	0.03
Right atrial pressure	-0.10	-0.22 to 0.03	0.12
Mean systemic artery pressure	0.02	-0.04 to 0.07	0.57

well as the presence of RV dilation and systolic dysfunction. We demonstrated that the normal acoustic profile observed in controls, of increased S1 intensity/complexity compared to that of S2, was altered in the PAH group. S2 complexity was increased in the PAH group, and was directly related to mPA and PVR. Importantly, among PAH patients, the reciprocal relationship between S1 and S2 complexity likely represents the acoustic corollary of ventricular interaction that develops as the RV remodels during the course of PAH. These findings extend our mechanistic understanding of the relationship between pulmonary vascular and ventricular haemodynamics and the precordial acoustic profile.

Landmark investigations from the 1960s examined analogue phonocardiographic recordings and emphasised the relative amplitude of the aortic and pulmonic component of S2 (A2 and P2).^{5–9} The pulmonic component was said to be accentuated, reflecting the forceful closure of the pulmonary valve with the associated left-parasternal heave indicating RV pressure overload. An audible right-sided S3 and S4 was thought to indicate RV volume and pressure overload, respectively.¹⁰ Sutton *et al*⁸ studied 116 patients. Twelve were classified as primary PH by cardiac catheterisation though only 50% of this cohort exhibited a P2 of higher amplitude than A2 by phonocardiography. Studies from this era acknowledged the challenges of discriminating A2 and

P2 by auscultation, and qualitative assessment of the summated S2 was also advocated. Thus, the detection of P2 in the mitral area⁹ or the relative loudness of S2 in the left versus the right parasternal second intercostal spaces⁵ was also shown to be common in PH. These studies described the auscultatory or phonocardiographic findings prior to the systematic classification of PAH.^{5–9–11} Thus, classic lessons describing clinical auscultation findings of PH might have been confounded by the presence of the associated cardiac abnormalities such as left-to-right shunting or LV systolic dysfunction.

In the National Institutes of Health-sponsored Primary Pulmonary Hypertension Registry, abnormal auscultatory findings were highly prevalent. An increase in P2 of S2 was reported in 93% of 187 PAH patients.¹⁰ Cardiac auscultation is a highly cognitive process influenced by patient factors as well as the heuristic bias of the practitioner, contributing to poor interobserver agreement.¹² In our study, the wavelet-based signal processing analysis of continuous digital acoustic data yielded a measurement not only of amplitude or intensity but also of time, energy and frequency characteristics,⁷ termed complexity. Previous studies have validated the detection of the S3 and S4 sounds by this methodology against echocardiographic¹³ and catheterisation-based haemodynamic evidence of LV systolic dysfunction and elevated filling pressures.^{14–18}

Table 5 S2 and S1 complexity according to right ventricular size and systolic function

	RV dilation		RV systolic dysfunction	
	Normal/mild	Moderate/severe	Normal/mild	Moderate/severe
<i>S2 complexity</i>				
All (PAH and Controls) (n)	37	23	43	17
V3	2.71±1.99	3.89±2.14*	2.55±1.68	4.85±2.20***
V4	2.63±2.40	4.89±5.88*	2.49±2.57	5.74±6.33**
PAH (n)	20	20	23	16
V3	3.33±1.66	4.12±2.18	2.95±1.21	4.97±2.21**
V4	3.64±2.54	5.53±6.05	3.50±2.89	6.10±6.36
Controls (n)	17	3	20	1
V3	1.98±2.15	2.39±1.02	2.08±2.04	2.96±0.00
V4	1.45±1.57	0.59±1.02	1.32±1.52	0.00±0.00
<i>S1 complexity</i>				
All (PAH and Controls) (n)	37	23	42	17
V3	4.55±2.06	3.97±1.32	4.60±2.00	3.67±1.14
V4	4.95±2.23	3.81±1.34*	4.93±2.13	3.69±1.35*
PAH, (n)	20	20	23	16
V3	4.78±1.78	4.11±1.30	4.97±1.77	3.80±1.05*
V4	5.48±2.32	3.68±1.21**	5.29±2.20	3.68±1.40*
Controls, (n)	17	3	20	1
V3	4.29±2.38	3.08±1.24	4.19±2.20	1.68±0.00
V4	4.33±2.02	4.68±2.08	4.52±2.04	3.83±0.00

*p<0.05.

**p<0.01.

***p<0.0001.

Comparison of heart sound complexity is performed between PAH and controls as a cohort, and within the PAH and control groups based on RV size and systolic dysfunction.

PAH, pulmonary arterial hypertension; RV, right ventricular.

In the current study, we examined the haemodynamic and structural correlates of digitally recorded precordial acoustic characteristics in PAH. S2 intensity was actually similar between the PAH and control groups. It is well understood that the intensity of precordial heart sounds is influenced by anatomic factors such as BSA, characteristics of the thoracic cage and cardiac axis.⁵ Beyond intensity, we observed that the complexity of S2 was significantly increased in PAH patients, consistent with the observation that S2 is frequently perceived to be abnormal in this condition.⁹ We also demonstrated that the perceived audible characteristics of S2 may in fact relate to the acoustic characteristics of S1. The ratio of S2/S1 complexity was shown to be strikingly increased in the PAH group, interestingly with the leads in the precordial V3 and V4 position. This observation may be consistent with the older concept that P2 is frequently detectable in the mitral area in PH. Moreover, we observed a reciprocal relationship between S2 and S1 complexity that may have been related to ventricular interaction in PAH patients. Thus, the perception of an abnormally accentuated S2 may also relate to the abnormally diminished complexity or the audibility of S1.

We observed that mPA was an independent multivariate haemodynamic predictor of S2 complexity, consistent with other studies examining S2 acoustic qualities and TTE or RHC-derived pulmonary artery pressure.^{19 20} These findings provide support for the traditional construct that elevated PVR causes forceful closure of the

pulmonic valve. We made several observations regarding the complexity of S1. In contrast to S2 complexity, mPA pressure was correlated with decreased S1 complexity. Worsening RV enlargement and systolic dysfunction were related to not only increased S2 complexity but also decreased S1 complexity. Diminished S1 complexity appeared related to decreased LV filling as measured by left ventricular end-diastolic diameter which may account for the observation that cardiac output was also independently associated with S1 complexity. LV underfilling may decrease the complexity of S1 as a result of either decreased LV force generation^{21 22} and/or the narrower separation of the mitral leaflets at the time of valve closure.^{23 24} The PR interval is a known determinant of S1 loudness,^{23 24} but was not statistically different between PAH and control groups. These observations suggest that the S2/S1 complexity ratio likely represents both the effect of PVR on pulmonic valve closure (increased S2 complexity) and reciprocal RV enlargement-LV underfilling (decreased S1 complexity).^{21 22} This concept of reciprocal ventricular interaction is well described in patients with PH,^{25–27} for whom we have now described the precordial acoustic corollary.

LIMITATIONS

Several limitations merit consideration. The sample size of the control cohort with both haemodynamics and echocardiography was relatively small, and we did not

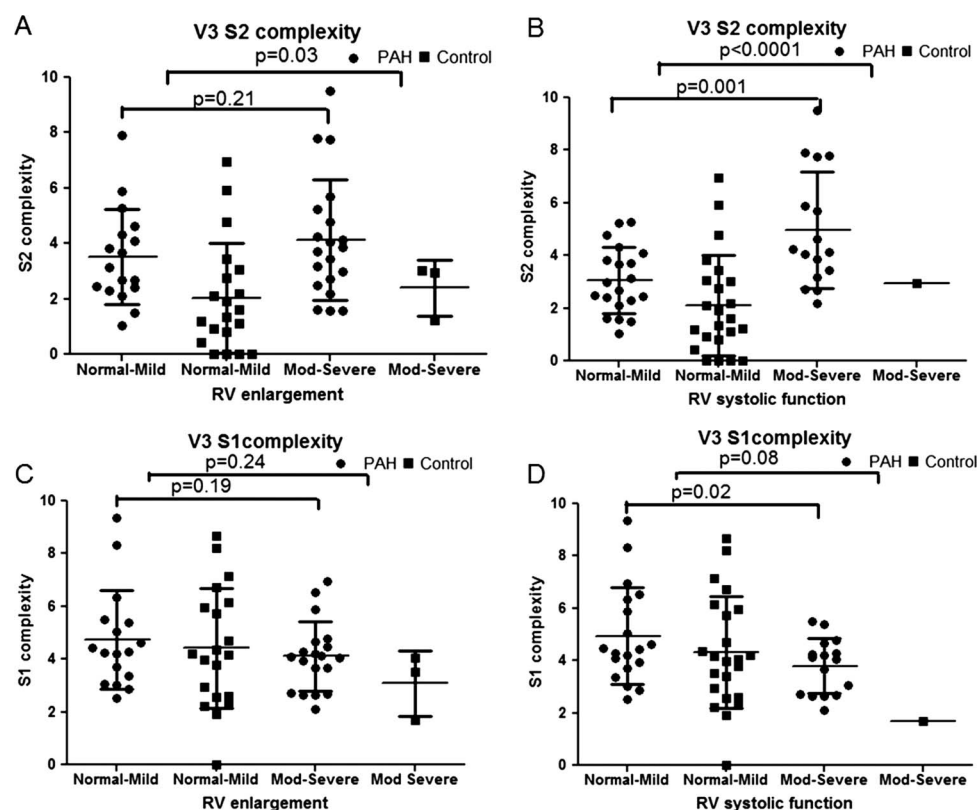


Figure 3 V3 S2 and S1 complexity according to right ventricular size and systolic function. V3 S2 complexity stratified according to severity of RV enlargement (A) and RV systolic dysfunction (B). V3 S1 complexity stratified according to severity of RV enlargement (C) and RV systolic dysfunction (D). Comparison of heart sound complexity is performed within the PAH group and also between PAH and controls as a cohort based on RV size and systolic dysfunction. PAH, pulmonary arterial hypertension; RV, right ventricular.

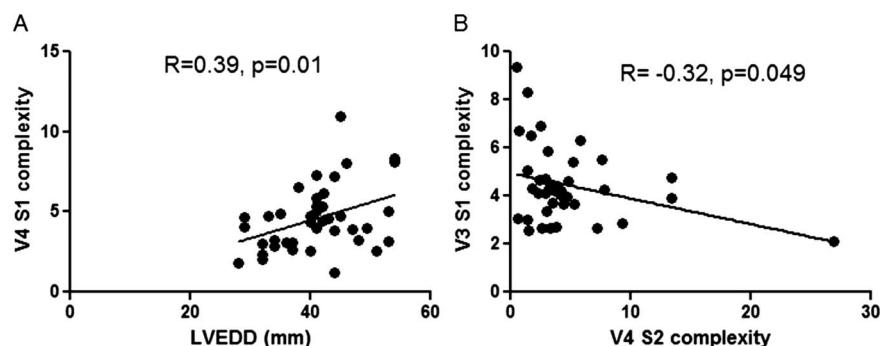
match the PAH group against age and sex match. However, we adjusted for possible intersubject anthropomorphic differences by calculating the S2/S1 intensity and complexity ratios. Whether haemodynamic intervention and alteration of ventricular interaction influenced acoustic variables was not examined. Although S2 complexity and S2/S1 complexity ratio displayed potential predictive utility for the discrimination of PAH, the study cohort was preselected to elucidate the physiological underpinnings of transmitted heart sounds, and thus patients with conditions that could be confused with PAH were excluded. Finally, the implication of our findings for clinical practice is unclear at present

because the assessment and management of patients with PAH is guided more by functional class and RV remodelling.

CONCLUSION

The acoustic characteristics of S2 and S1 correlated significantly with the severity of PAH and evidence of RV dilation and systolic dysfunction. The reciprocal S2 and S1 complexity relationship among patients with PAH likely reflects ventricular interaction due to progressive RV remodelling. Our findings demonstrate that the perception of an abnormally accentuated S2 in PAH may be

Figure 4 Relationship between S1 complexity and left ventricular filling and S2 complexity. Significant correlation between V4 S1 complexity and left ventricular end-diastolic diameter (LVEDD) as a measure of left ventricular filling (A). Inverse correlation between S1 and S2 complexity measures suggests the presence of ventricular interaction in the PAH cohort (B).



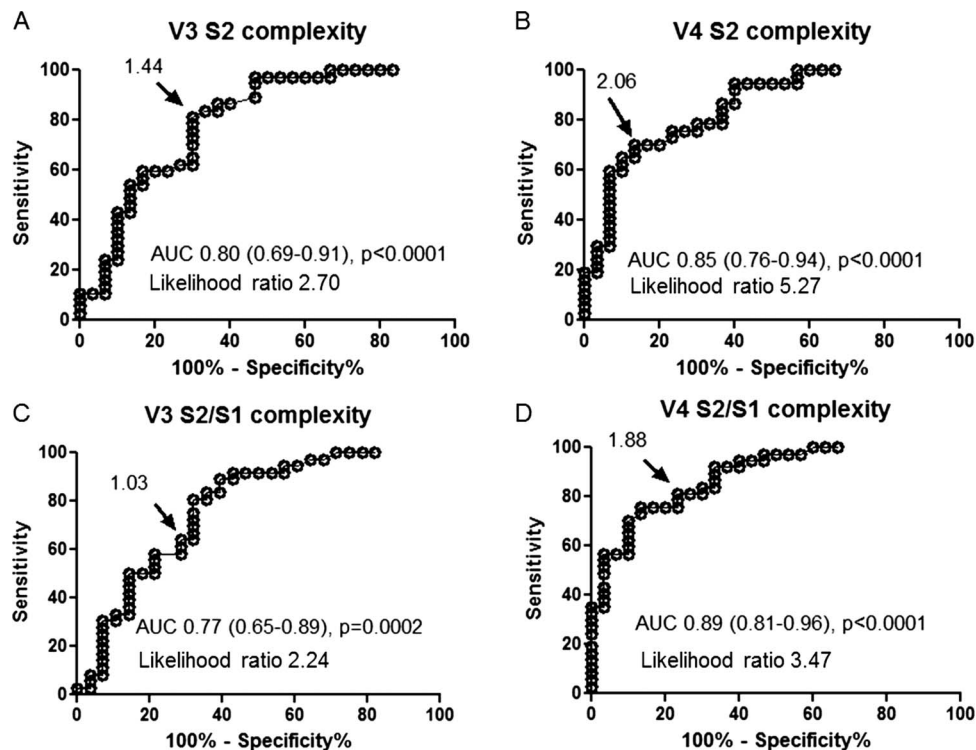


Figure 5 S2 and S2/S1 complexity receiver-operating characteristic curves for the detection of pulmonary arterial hypertension (mean pulmonary artery pressure ≥ 25 mm Hg). Receiver-operating characteristic curves for V3 S2 complexity (A); V4 S2 complexity (B); V3 S2/S1 complexity ratio (C) and V4 S2/S1 complexity ratio (D) for the detection of pulmonary arterial hypertension. AUC, area-under-curve.

derived both from not only increased S2 complexity but also diminished complexity or audibility of S1.

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REFERENCES

1. Runo JR, Loyd JE. Primary pulmonary hypertension. *Lancet* 2003;361:1533–44.
2. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation* 2006;114:1417–31.
3. Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54 (1 Suppl):S43–54.
4. Benza RL, Miller DP, Gomberg-Maitland M, *et al.* Predicting survival in pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). *Circulation* 2010;122:164–72.
5. Perloff JK. Auscultatory and phonocardiographic manifestations of pulmonary hypertension. *Prog Cardiovasc Dis* 1967;9:303–40.
6. McGoon M, Guterman D, Steen V, *et al.* Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126(1 Suppl):14S–34S.
7. Erne P. Beyond auscultation—acoustic cardiography in the diagnosis and assessment of cardiac disease. *Swiss Med Wkly* 2008;138:439–52.
8. Lang RM, Bierig M, Devereux RB, *et al.* Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–63.
9. Sutton G, Harris A, Leatham A. Second heart sound in pulmonary hypertension. *Br Heart J* 1968;30:743–56.
10. Rich S, Dantzker DR, Ayres SM, *et al.* Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;107:216–23.
11. Wood P. Pulmonary hypertension. *Br Med Bull* 1952;8:348–53.
12. Marcus GM, Vessey J, Jordan MV, *et al.* Relationship between accurate auscultation of a clinically useful third heart sound and level of experience. *Arch Intern Med* 2006;166:617–22.
13. Zuber M, Kipfer P, Attenhofer Jost C. Systolic dysfunction: correlation of acoustic cardiography with Doppler echocardiography. *Congest Heart Fail* 2006;12(Suppl 1):14–18.
14. Collins SP, Arand P, Lindsell CJ, *et al.* Prevalence of the third and fourth heart sound in asymptomatic adults. *Congest Heart Fail* 2005;11:242–7.
15. Peacock WF, Harrison A, Maisel AS. The utility of heart sounds and systolic intervals across the care continuum. *Congest Heart Fail* 2006;12(Suppl 1):2–7.

16. Shapiro M, Moyers B, Marcus GM, *et al*. Diagnostic characteristics of combining phonocardiographic third heart sound and systolic time intervals for the prediction of left ventricular dysfunction. *J Card Fail* 2007;13:18–24.
17. Efstratiadis S, Michaels AD. Computerized acoustic cardiographic electromechanical activation time correlates with invasive and echocardiographic parameters of left ventricular contractility. *J Card Fail* 2008;14:577–82.
18. Marcus GM, Gerber IL, McKeown BH, *et al*. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. *JAMA* 2005;293:2238–44.
19. Chen D, Pibarot P, Honos G, *et al*. Estimation of pulmonary artery pressure by spectral analysis of the second heart sound. *Am J Cardiol* 1996;78:785–9.
20. Michaels AD, Karabsheh S, Neuharth RM, *et al*. Non-invasive computerized acoustic cardiographic prediction of pulmonary hypertension. *J Electrocardiogr* 2009;42:617–18.
21. Sakamoto T, Kusukawa R, Maccanon DM, *et al*. Hemodynamic determinants of the amplitude of the first heart sound. *Circ Res* 1965;16:45–57.
22. Genest J Jr., Durand LG. Relationship of the left ventricular and apical first sounds to the left ventricular pressure derivative. *Med Biol Eng Comput* 1985;23:95–8.
23. Leech G, Brooks N, Green-Wilkinson A, *et al*. Mechanism of influence of PR interval on loudness of first heart sound. *Br Heart J* 1980;43:138–42.
24. Stept ME, Heid CE, Shaver JA, *et al*. Effect of altering P-R interval on the amplitude of the first heart sound in the anesthetized dog. *Circ Res* 1969;25:255–63.
25. Dong SJ, Crawley AP, MacGregor JH, *et al*. Regional left ventricular systolic function in relation to the cavity geometry in patients with chronic right ventricular pressure overload. A three-dimensional tagged magnetic resonance imaging study. *Circulation* 1995;91:2359–70.
26. Marcus JT, Vonk Noordegraaf A, Roelvelde RJ, *et al*. Impaired left ventricular filling due to right ventricular pressure overload in primary pulmonary hypertension: noninvasive monitoring using MRI. *Chest* 2001;119:1761–5.
27. Gurudevan SV, Malouf PJ, Auger WR, *et al*. Abnormal left ventricular diastolic filling in chronic thromboembolic pulmonary hypertension: true diastolic dysfunction or left ventricular underfilling? *J Am Coll Cardiol* 2007;49:1334–9.