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
Acoustic cardiography in pulmonary hypertension

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 pul-
monary hypertension (PH). 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 circula-
tory unit have not been well characterised. Digital
acoustic cardiography permits quantitative analysis of
precordial heart sounds. 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 (sus-
pected WHO group II PH) given possible acoustic abnor-
malities 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 flotation
pulmonary artery catheter in the fasting state, without
sedation. Haemodynamic measurements were recorded
at end-expiration and included heart rate, systolic/dia-
stolic/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 thermo-
dilution. PVR and systemic vascular resistances were cal-
culated 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
disc summation and indexed to BSA. 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, para-
stenal 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 follow-
RHC with the patient supine with head incline of
30° during tidal respiration. Standard 12-lead placement
was performed with two dual-function (audioelectrocar-
diographic) sensors in the precordial V3 and V4 posi-
tions capable of simultaneously capturing cardiac
electrical and acoustic signals. Five 10 s artefact-free
recordings were obtained and analysed using proprietary
software. This algorithm utilises wavelet-based
signal processing techniques for acoustic analysis.
Time-frequency analysis is performed, permitting separ-
ation 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.

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
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. 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 $\chi^2$ 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>
<thead>
<tr>
<th>Classification of PAH (n)</th>
<th>PAH (40)</th>
</tr>
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<tbody>
<tr>
<td>Group 1</td>
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<tr>
<td>Idiopathic</td>
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<td>Connective tissue disease</td>
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<tr>
<td>Portal hypertension</td>
<td>2</td>
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<tr>
<td>Other</td>
<td>3</td>
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<tr>
<td>Group 4 (chronic thromboembolic)</td>
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<td>NYHA class</td>
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<td>6 min walk test (total distance) (m)</td>
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<td>B-type natriuretic peptide (pmol/l)</td>
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</tr>
<tr>
<td>Medications (%)</td>
<td></td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td>41</td>
</tr>
<tr>
<td>Calcium channel antagonists</td>
<td>28</td>
</tr>
<tr>
<td>Phosphodiesterase V inhibitor</td>
<td>40</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; 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 significantly increased compared with S1. In contrast, among the PAH group, the complexity of S2 was significantly different from S1. The S2/S1 complexity ratio was also 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.

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 dysfunction.
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 (mPA≥25 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...
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). 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.

In our study, the wavelet-based signal processing analysis of continuous digital acoustic data yielded a measure of complex energy and frequency characteristics, termed complexity. Previous studies have validated the detection of the S3 and S4 sounds by this methodology against echocardiographic and catheterisation-based haemodynamic evidence of LV systolic dysfunction and elevated filling pressures.

### Table 4 Univariate haemodynamic predictors of S1 and S2 complexity

<table>
<thead>
<tr>
<th></th>
<th>B (unstd)</th>
<th>CI</th>
<th>p Value</th>
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<tr>
<td><strong>V3 S2 complexity</strong></td>
<td></td>
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<tr>
<td>Mean pulmonary artery pressure</td>
<td>0.07</td>
<td>0.05 to 0.10</td>
<td>&lt;0.0001</td>
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<tr>
<td>Heart rate</td>
<td>-0.01</td>
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<td>Pulmonary capillary wedge pressure</td>
<td>-0.11</td>
<td>-0.25 to 0.03</td>
<td>0.13</td>
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<tr>
<td>Cardiac output (Fick)</td>
<td>-0.27</td>
<td>-0.71 to 0.18</td>
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<tr>
<td>Right atrial pressure</td>
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<td></td>
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<tr>
<td>Mean systemic artery pressure</td>
<td>0.02</td>
<td>-0.04 to 0.07</td>
<td>0.58</td>
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<tr>
<td><strong>V4 S2 complexity</strong></td>
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<td></td>
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<td>0.08 to 0.19</td>
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<td>Heart rate</td>
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<tr>
<td><strong>V3 S1 complexity</strong></td>
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<td>-0.04 to 0.02</td>
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<td>Right atrial pressure</td>
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<td><strong>V4 S1 complexity</strong></td>
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<td>Mean pulmonary artery pressure</td>
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<tr>
<td>Mean systemic artery pressure</td>
<td>0.02</td>
<td>-0.04 to 0.07</td>
<td>0.57</td>
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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. 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. 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. 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 and/or the narrower separation of the mitral leaflets at the time of valve closure. The PR interval is a known determinant of S1 loudness 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). This concept of reciprocal ventricular interaction is well described in patients with PH 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...
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

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**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.

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

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