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ORIGINAL RESEARCH

# Non-invasive diagnosis of pulmonary hypertension from lung Doppler signal: a proof of concept study

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**Abstract** Transthoracic Parametric Doppler (TPD) is a novel ultrasound technique recently developed for the investigation of pulmonary blood vessels. Lung Doppler Signals (LDS) recorded from TPD provide information regarding the functional mechanical characteristics of pulmonary blood vessels. We aimed to define the specific profile of LDS generated from TPD imaging in patients with pulmonary hypertension (PH), and to evaluate the diagnostic performance of LDS to detect PH using right heart catheterization (RHC) as gold standard reference. Seventy nine PH patients and 79 healthy controls matched for age, gender and BMI were recruited in a prospective case–control multicenter study. LDS recordings were performed by TPD consisting of a pulsed Doppler with a 2 MHz single element transducer. LDS were recorded within 24 h of RHC. Following LDS extraction, classification and performance evaluation were performed offline using a support vector machine (k-fold cross validation method). The best LDS parameters for PH detection were (1) peak velocity of the systolic (S) and diastolic (D) signals, (2) the rise slope of the S and D signals, and (3) time to peak of the S signal. Overall, the sensitivity and specificity of TPD for detection of PH were 82.7 % (95 % CI 81.3–84.1) and 87.4 % (95 % CI 86.3–88.5), respectively, with an area under the receiver operating curve of 0.95 (95 % CI 0.94–0.96). Detection rate of PH increased progressively with the level of mean pulmonary artery pressure. LDS recorded by TPD display a specific profile in PH and appears to be a promising and reliable tool for PH diagnosis. Further studies are required to confirm the clinical usefulness of LDS.

**Keywords** Pulmonary hypertension · Non-invasive diagnosis · Lung doppler signal · Screening · Detection

**Abbreviations**

| | |
|---|---|
| CV | Cross validation |
| ICS | Intercostal space |
| IVC | Inferior vena cava |
| LDS | Lung Doppler signal |
| mPAP | Pulmonary artery mean pressure |
| PH | Pulmonary hypertension |
| RHC | Right heart catheterization |
| sPAP | Pulmonary artery systolic pressure |
| SVM | Support vector machine |
| TPD | Transthoracic parametric Doppler |

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TRJ Tricuspid regurgitation jet
TTE Transthoracic echocardiography
WU Wood units

## 1 Introduction

Pulmonary hypertension (PH) is a condition characterized by an increase in pulmonary artery mean pressure (mPAP) ≥25 mmHg determined by right heart catheterization (RHC) [1, 2]. Although severe complications of RHC are rare [3], it remains an invasive method and novel tool for the non-invasive detection of PH are needed. Transthoracic echocardiography (TTE) is currently the most widely used non-invasive modality for the assessment of pulmonary artery pressures in clinical practice. However, the poor accuracy of TTE is associated with significant rates of false positive or false negative results when used as a screening test for PH [4].

Transthoracic Parametric Doppler (TPD) is a novel ultrasound technique recently developed for the investigation of pulmonary blood vessels and their functional mechanical characteristics [5]. A recent study has demonstrated that TPD is able to distinguish between different atrial rhythmic disorders [6]. Using this technology, clear Doppler signals that are in synchrony with the cardiac cycle can be recorded from the lungs [5]. TPD generates Lung Doppler Signals (LDS), which are ultrasound Doppler spectra containing three main components: S, D and A, corresponding in time with systole, diastole and the atrial contraction period, respectively (Fig. 1). The origin of the LDS is attributed to the movements of the interface between alveolar air and blood vessel walls [5]. These movements are generated by the pulse pressure wave and their extent is determined by the distensibility of the blood vessel walls. The air–tissue junctions are very strong ultrasound reflectors and therefore generate signals that are sufficiently powerful to be recorded on the chest surface, in spite of the high attenuation and scattering of the ultrasound energy by the air contained in the lungs [7].

As lung blood vessel wall motion alteration might be a pathophysiologic correlate of elevation in pulmonary artery pressure [8] [9], we hypothesized that LDS obtained by TPD might represent a novel and potentially useful non-invasive modality for the detection of PH. The aims of this study were to determine the specific profile of the LDS spectrum in PH, and secondly, to determine the diagnostic performance of TPD for the detection of PH according to this profile, using gold standard RHC as reference.

## 2 Methods

### 2.1 Study design and study population

This prospective, case–control, multi-center study included two population groups: patients with PH proven by RHC and healthy controls. It was conducted in accordance with the amended Declaration of Helsinki. Local institutional review boards approved the protocol (see supplemental material for detailed IRB). All patients gave written informed consent. Between October 2011 and June 2014, 104 patients undergoing RHC for diagnosis or follow-up of PH were invited to participate. Fifteen patients had no PH at RHC, and ten patients were excluded for technical reasons (see supplemental material). Thus, a total of 79 PH patients were included in the final analysis. Age, gender and BMI matched controls were recruited from Israeli centers. Inclusion criteria for the healthy control group included: no risk factor for PH (HIV, cirrhosis, connective tissue disease, familial history of PH, congenital cardiomyopathy, history of appetite suppressant intake), no history of lung or cardiac disease and no uncontrolled systemic arterial hypertension. Exclusion criteria for both

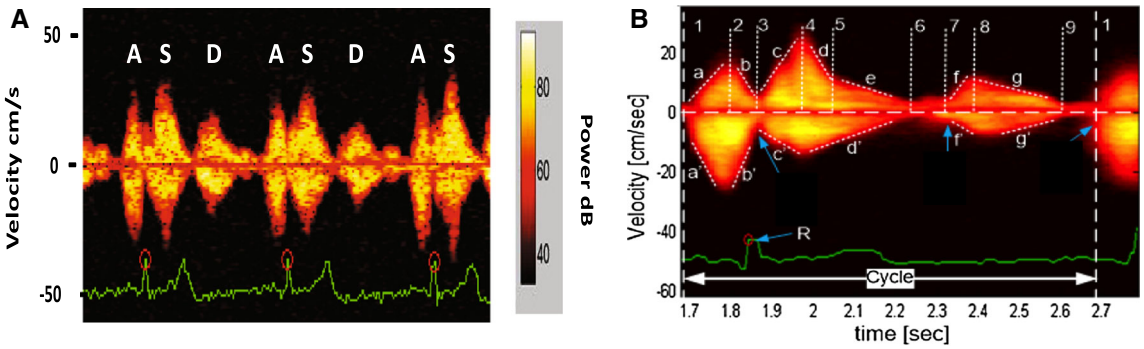


**Fig. 1** LDS recorded by TPD in healthy subject. **a** Typical LDS in healthy subjects with ECG synchronization. Signal amplitude indicates velocity and *color* the power of the reflected ultrasound. **b** Segmentation of a LDS during one cardiac cycle with separation of the *A*, *S* and *D* signal. Slopes of the positive signal: *a* to *g*. Slopes of the negative signal: *a*' to *g*'. Peak velocities: *2*, *4* and *8*. Lowest velocities: *1*, *3*, *5*, *6*, *7* and *9*

groups were: age under 18 years, unwilling or unable to sign the informed consent form, hemodynamically unstable condition requiring inotropic or vasoactive drugs, NYHA functional class IV, myocardial infarction during the past 6 months, acute cardiac decompensation, severe atrio-ventricular conduction disturbance, severe aortic stenosis, severe chest wall deformity, pregnant or lactating women, active neoplasia. All TPD examinations were performed within 24 h of RHC. The study is reported according to the Standards for the Reporting of Diagnostic accuracy studies (STARD) criteria [10].

### 2.2 Right heart catheterization

Hemodynamic evaluation was performed in the supine position. RHC was performed using the modified Seldinger technique with an 8F sheath inserted in the jugular, basilic or cephalic vein. The Swan-Ganz catheter was a 7F, two-lumen, fluid filled and pressure-measuring tipped catheter (Corodyn TD; Braun Medical, Bethlehem, PA, USA). The zero-level reference was determined at mid-thoracic line.

### 2.3 Study device

LDS recordings were performed by TPD (EchoSense, Haifa, Israel) consisting of an FDA-approved pulsed Doppler with a 2 MHz single element transducer (diameter 16 mm, focal length of 5 cm) (Viasys Healthcare, Madison, WI, USA) coupled with an ECG system (Norav, Delray Beach, FL, USA) and signal analysis and classification software (EchoSense, Haifa, Israel). Pulse repetition frequency was 3 kHz and sample volume 3 mm. Maximal transmitted power was 74 mW/cm$^2$, i.e. only about 10 % of the intensity allowed by the FDA. In all the subjects, LDS recordings were performed without any side effects.

### 2.4 LDS recordings and signal processing

Subjects were placed in a sitting or semi-reclining position. LDS recordings were made over five locations on the right chest wall at the second to sixth intercostal spaces (ICS). Recording duration at each point was sixty seconds. The transducer was positioned at an angle close to 90° with respect to the chest surface, a few centimeters right of the mid-sternal line. ECG was concomitantly recorded. Recordings were made by three trained technicians blinded to the clinical status of patients.

All recorded LDS were processed at a single facility (EchoSense, Haifa, Israel) by a dedicated signal processing software package (Echosense, Haifa, Israel). All the subsequent analyses were carried automatically by the computer software that was blinded to the patient diagnosis. The spectrograms of both velocities and reflected ultrasound power sonograms were averaged over 20 cardiac cycles for each ICS location. Initially, the S, D and A segments of the sonograms were determined. For each segment (Fig. 1b), the features of timing, velocities, slopes and reflected ultrasound power were determined and analyzed. This process was carried separately for the signals of positive polarity (movement towards the ultrasound transmitter) and negative polarity (movement away from the beam source).

### 2.5 Cluster analysis and statistical analysis

The features of the spectra were automatically extracted by the software package and served for cluster analysis and classification using a support vector machine (SVM), which utilized machine-learning methodology for separation of PH from healthy controls [11]. The k-fold cross validation (CV) method was used to evaluate the SVM classification performance. In this cluster analysis method, patients and healthy controls are divided into k sub-groups of equal numbers. The classifier is trained on all except one subgroup and the results are validated on the excluded subgroup. This process is iterated k times and repeated n times.

Results are expressed as mean ± SD or as otherwise stated. The comparisons between the two groups were performed using an unpaired t test or Mann–Whitney test as required. A $p$ value $<0.05$ was considered significant. Receiver operating characteristic (ROC) analyses were performed to evaluate the diagnostic performance of the measured variables of the LDS spectrum. Statistical analyses were performed using Matlab (version 7.13.0.564, MathWorks, Natick, MA, USA).

## 3 Results

### 3.1 Subjects

The study flowchart is given in the Fig. 2. A total of 158 subjects were included in final data analysis (PH, n = 79 and healthy controls, n = 79). Demographic characteristics, hemodynamic and PH etiology are reported in the Tables 1 and 2, respectively. The PH group consists of moderate to severe disease (mPAP 45 ± 4 mmHg and PVR 7.0 ± 4.1 WU). Group 1 pulmonary arterial hypertension (PAH) represented 39 % of PH subjects recruited, and group 4 chronic thromboembolic pulmonary hypertension (CTEPH) represented 30 %, with 44 % of patients being naive to specific PH therapies.

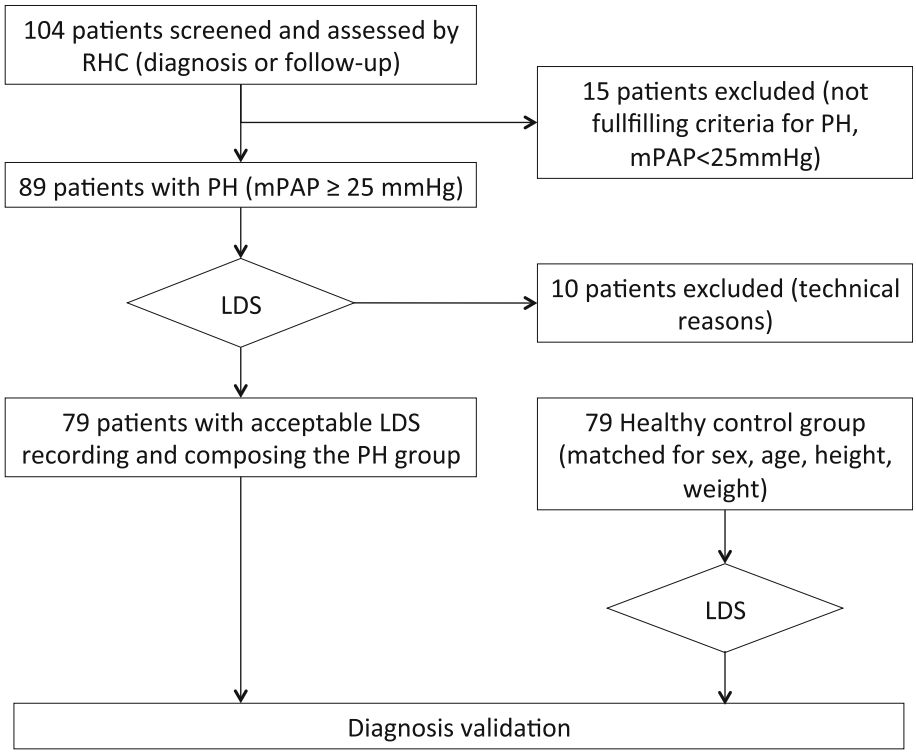


**Fig. 2** Flowchart of the study. 104 patients were screened for RHC. 15 patients were excluded of the final analysis (mPAP < 25 mmHg). 89 patients with mPAP ≥ 25 mmHg were assessed by LDS. 10 patients were excluded due to technical reasons. 79 patients were included in the recording group and matched with 79 healthy control subjects

**Table 1** Demographic and hemodynamic variables of the PH and healthy groups

| | PH group (n = 79) | Healthy controls (n = 79) |
|---|---|---|
| Age, (years) | 56.3 (±15.6) | 59.7 (±10.7) |
| Female gender (%) | 56 | 63 |
| Body mass index (kg/m$^2$) | 28.5 (±5.2) | 26.0 (±3.2) |
| Smoking history (%) | 27 | 39 |

Results are expressed as mean (±SD) until otherwise stated

### 3.2 Feature analysis of LDS spectrum

The values of the velocities, time of occurrence, slopes and power of the reflected ultrasound waves were measured with an automatic extraction algorithm for the positive and negative segments of S, D and A. The time values were normalized to heart rate by dividing them by the R–R interval time. The five LDS parameters that contained the highest level of discriminating power of PH *vs* controls, as determined by the SVM classifier, were: peak velocity of the negative phase of the S and of the positive phase of D signals, rise slope of the S and D signals and time to peak (fraction of R–R interval) of S signal (Table 3).

### 3.3 LDS diagnostic accuracy

The sensitivity and specificity of LDS for discriminating PH patients from healthy controls were 82.7 % (95 % CI 81.3–84.1) and 87.4 % (95 % CI 86.3–88.5) respectively (Table 4). The ROC curve AUC was 0.95 (95 % CI 0.94–0.96) for performance of LDS in PH detection (Fig. 3). PH detecting performance was subsequently analyzed according to the range of mPAP. The lowest performance in detecting PH was for mild PH (mPAP between 25 and 35 mmHg) with a detection rate of 76.0 %. Ability of LDS to detect PH increased progressively with the value of mPAP (Table 5). PH detecting performance was subsequently analyzed according to the classification of PH, with the lowest detection performance for group 1 with a detection rate of 74.2 % (Table 6).

## 4 Discussion

In this proof-of-concept study, we have shown that acquisition of LDS using TPD is feasible in patients with PH, differences in LDS spectral profile are present in PH *vs* controls, and LDS represents a potentially useful non-

**Table 2** Specific variables of the PH group

| | PH group (n = 79) |
|---|---|
| RHC required for clinical follow-up/PH first evaluation (%) | 54/46 % |
| mPAP (mmHg) | 45 (±14) |
| PCWP (mmHg) | 11 (±5.5) |
| CO (L/min) | 5.6 (±1.7) |
| CI (L/min/m2) | 3.1 (±0.8) |
| PVR (mmHg/L/min) | 7 (±4.1) |
| Classification of PH (%) | |
| Group 1 (PAH) | 39 |
| Group 2 (Left heart disease) | 15 |
| Group 3 (Lung disease) | 5 |
| Group 4 (CTEPH) | 30 |
| Group 5 (miscellaneous causes) | 11 |
| Specific PAH therapies (%) | 56 |
| Monotherapy | 20 |
| Double therapy | 24 |
| Triple therapy | 12 |

Results are expressed as mean (±SD) unless otherwise stated. *RHC* right heart catheterization, *6MWD* six-minutes walk distance, *BNP* b-type natriuretic peptide, *mPAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *CO* cardiac output, *CI* cardiac index, *TPR* total pulmonary resistance, *PVR* pulmonary vascular resistance, *PH* pulmonary hypertension

**Table 3** Average feature values that contain the highest classification power

| Cycle features | PH (n = 79) | Healthy controls (n = 79) |
|---|---|---|
| Peak velocities (cm/s) | | |
| S | −10.5 (±4.6) | −16.0 (±5.7) |
| D | 6.8 (±3.3) | 9.4 (±3.4) |
| Slope (cm/s$^2$) | | |
| S | 120 (±80) | 251 (±140) |
| A | 77 (±58.8) | 127 (±51) |
| Time to peak (fraction of R–R) (%) | | |
| S | 15 (±6) | 10 (±4) |

Values are presented as mean (±SD)

**Table 4** Detection performance in PH versus healthy controls with the k-fold CV method

| | PH versus healthy controls |
|---|---|
| True positive | 82.3 (81.3–84.1) |
| True negative | 87.3 (86.3–88.5) |
| False positive | 12.6 (11.5–13.7) |
| False negative | 17.7 (15.9–18.7) |
| Accuracy | 85.0 (83.8–86.2) |
| Sensitivity | 82.7 (81.3–84.1) |
| Specificity | 87.4 (86.3–88.5) |

Results are expressed as percent (95 % CI)

invasive marker for the presence of PH. Further validation studies are required to determine the performance of TPD as a novel diagnostic tool for PH.

PH patients appear to have a distinct LDS signature as reflected by differences in various features of the LDS spectrum compared to controls (Fig. 4). Alterations of the LDS spectrum in PH patients were evident in both the velocity and the power of the reflected ultrasound waves representing different phases of the cardiac cycle (systolic, diastolic and atrial contraction) [5].

The velocity changes are likely to reflect variations of the rate of motion of the vessel walls, representing changes in pulse pressure and vessel compliance. On the other hand, the reflected power is thought to be a function of the number of open and, pulsating vessels in the field investigated by the probe. Additional parameters of diagnostic value that can be derived from the three basic LDS components are slopes of velocities and area under the power curve. Combined together, these features extracted from the LDS spectrum could reflect the mechanical properties of the distal pulmonary blood vessels.

Regardless of the underlying PH etiology, elevation of the vessel distending transmural pressure may lead to changes in the mechanical properties of the pulmonary vessels resulting in a loss of distensibility [12] [13], which could be a marker of early pulmonary vascular disease [14]. Such changes in vascular compliance could have

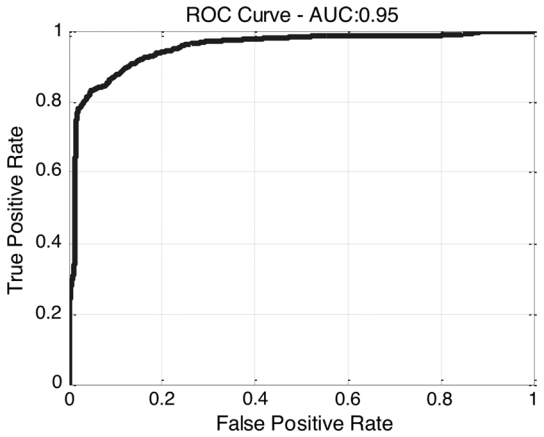


**Fig. 3** ROC curve of the detection rate of PH subjects in comparisons with healthy controls for the complete LDS with an AUC of 0.95 (95 % CI 0.94–0.96)

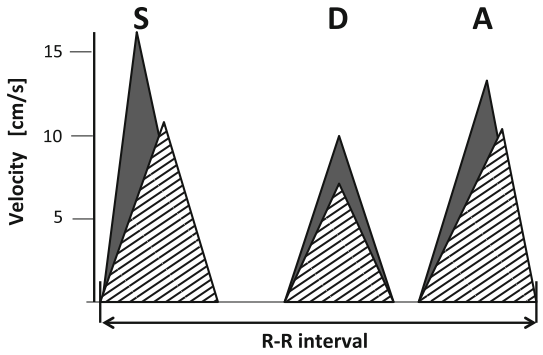


**Fig. 4** Schematic presentation of typical LDS of PH subjects (*striped triangles*) and of healthy controls (*black triangles*). *Y*-axis: velocity in absolute values. *X*-axis: R–R interval. LDS in PH display a decrease in the peak velocities of the *S*, *D* and *A* signal, a lowering of the slopes in *S* and *A* signals and a nightshift of the peak velocities in *S* and *A* signals

**Table 5** Detection rate of PH in subgroups according to the value of mPAP

| mPAP range (mmHg) | Detection rate |
|---|---|
| 25-35 (n = 16) | 76 % (74.1–77.9) |
| 36-45 (n = 27) | 82 % (80.4–83.6) |
| 46-55 (n = 22) | 86 % (84.5–87.5) |
| ≥56 (n = 14) | 93 % (90.8–95.2) |

Results are expressed in % (95 % confidence interval)

**Table 6** Detection rate of PH in subgroup of PH according to the updated classification of PH

| | PH detection rate |
|---|---|
| Group 1 (PAH) (n = 31) | 74.2 % |
| Group 2 (left heart disease) (n = 12) | 75.0 % |
| Group 3 (Pulmonary disease) (n = 5) | NA |
| Group 4 (CTEPH) (n = 23) | 91.6 % |
| Group 5 (multifactorial) (n = 6) | NA |

Results are expressed in % (95 % confidence interval). The detection rate for group 3 and 5 was not calculated due to insufficient data

direct impact on the pulse wave and on the motion of vessels during cardiac cycle with subsequent variation in the movement of the interface between the alveolar air and blood vessel walls, all of which may profoundly transform the LDS spectrum.

The specific LDS characteristics that corresponded best with the presence of PH were a decrease in the peak velocity of the systolic signal (S) and a delay in time reaching this peak. This is effectively translated into a decrease in the slope of the rising phase of the velocity signal of the S segment. The changes in the velocity of the diastolic signal D showed a similar pattern. Overall, the changes in features observed in this study are consistent with a decreased compliance of the pulmonary vessels.

Using RHC as the reference gold standard, we found that TPD has overall high sensitivity (83 %) and specificity (87 %) for the detection of PH. Although detection rate for PH did increase with increasing mPAP, TPD achieved a detection rate of 76 % for patients with only mild elevation in mPAP (25–35 mmHg). It has been shown that loss of distensibility could be an early marker of pulmonary vascular diseases [9]. The fact that LDS achieved reasonable accuracy for detection of mild PH is consistent with the hypothesis that LDS signal represents a measure of small vessel distensibility. These elements suggest a potential capability of LDS to serve as a complementary screening tool for early PH in at-risk populations.

Although TTE is currently the most widely used imaging modality for screening of PH, important limitations exist. Detection of PH using TTE is based predominantly on measurement of the tricuspid regurgitation jet (TRJ) velocity, which can be absent in patients with mild or early disease. In addition, precise determination of TRJ velocity can be difficult in cases of incomplete envelope or when Doppler alignment is imperfect. Furthermore, the estimation of right atrial pressure by variations of the diameters of the IVC is inaccurate. All these pitfalls result in under or overestimation of PAP by TTE [15, 16], an examination that is also highly operator dependent. Thus, novel bedside screening tools are required to complement currently available techniques in the evaluation of patients with suspected PH. From our experience, TPD has a relatively short learning curve and few skills are required to obtain high quality LDS.

Meaningful differences exist between the information harvested by TTE and TPD. TTE provides right ventricle function assessment as well as pulmonary vascular pressure evaluation, while TPD provides direct evaluation of pulmonary vascular characteristics, thus enabling PH detection by the vascular structural changes associated with the disease. Indeed, TPD provides diagnostic and pathophysiological information, such as information about distal vessel compliance, that is complementary to that provided by TTE. Furthermore, pulmonary vascular distensibility assessment can only be assessed indirectly by TTE during exercise and by calculating a complex $\alpha$ coefficient [14]. Moreover, while the evaluation of PH by TTE requires highly trained operator and the interpretation by an expert physician, the TPD can be operated by far less trained personal as the both diagnosis of PH and evaluation of the pulmonary vascular characteristics are based on computer signal analysis programs that provide parametric results that can be readily evaluated. Furthermore, patient testing by the TPD is of short duration, about 5 min and is operator independent. Thus, TTE and TPD provide complementary information concerning the pulmonary circulation and, as the TPD is basically a software package, it can be readily integrated within the modern echocardiographic devices currently in use. An additional advantage of the TPD use in PH is its ability to detect with high reliability both atrial fibrillation and atrial flutter [6] which have prognostic value in PH [17].

## 5 Limitations

As a proof-of-concept study, the present results should be viewed as preliminary. Although we report encouraging data regarding the sensitivity and specificity of TPD for detection of PH, prospective validation in an independent cohort is required to confirm the current results. Furthermore, our present study enrolled patients encompassing all spectrum of PH severity with different disease etiologies, as our primary hypothesis was that LDS could identify pathologic elevation in PAP whatever the underlying disease mechanism. Thus, we were not able to evaluate whether LDS can differentiate patients with different PH etiologies. We cannot exclude the possibility that modifications of lung parenchyma or abnormal ventilation may affect the detection rate of PH by LDS. However, the diagnostic accuracy of the LDS algorithm appeared quite similar in the different subgroups of PH. Despite these concerns, our results demonstrate, for the first time, that TPD represents a potentially simple and reliable technique to non-invasively determine the presence of PH.

Current algorithms for detection of PH are mainly based on TTE. Our study was not designed to compare LDS with TTE for detection of PH. TTE were not routinely performed at the same time as RHC in our centers, precluding reliable post hoc analysis of these data. TPD was tested only for its dichotomous diagnostic power (PH *vs* no PH), not for estimating the PAP values. It remains to be determined whether parameters of the LDS spectrum can be used to provide a sufficiently accurate estimate of PAP.

Another limitation of this study was the need to exclude 11 % of patients from the final analysis due to signal quality. The excluded subjects were mainly patients with CTEPH (Group 4) and PH due to lung disease (Group 3). Complete vessels occlusion leading to absence of local blood flow in CTEPH could explain the poor quality of signals collected in these subjects. In the case of PH due to lung disease, rarefaction of the vascular bed with enlargement of air spaces in emphysema could explain the poor quality of the signals. Further studies are required to determine the factors that contribute to reliable and interpretable LDS.

Furthermore, pulmonary artery pressures and LDS were not recorded simultaneously. Indeed, the mPAP is sensitive to different aspects of the haemodynamic status such as preload, afterload or contractility. The delay between recordings could potentially conduce to discrepancies between both measurements. However, the patients were assessed during stable conditions (i.e. not undergoing acute intervention such as diuretic dose change, inotropic support or fluid infusion). Moreover, all the subjects where assessed during complete rest in both tests. Resting and stable conditions preclude major and meaningful changes in haemodynamic status. The exact origin and physiologic correlates of LDS remain unresolved. However, several elements support our hypothesis that LDS signals are of vascular origin. The perfect synchronization of LDS with the cardiac cycle implies that the source of signal lies in vascular elements. These vascular elements are most likely distal vessels which consist a uniform vascular bed, consistent with the fact that the signals remain mostly unchanged by local movement of the probe. We can reasonably assume that, irrespective of the interpretation of the source of the LDS, the signal contains a sufficient amount of information to enable PH detection.

## 6 Conclusion

LDS recorded by the TPD display a specific profile in PH and is a promising non-invasive tool that provides reliable sensitivity and specificity for the bedside detection of PH. Further studies are required to confirm the clinical usefulness of LDS in different clinical settings and for different PH etiologies.

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**Authors contribution** Study conception and design: LG, FL, RS, SG, YP, OS. Acquisition of data: LG, FL, SG. Analysis and interpretation of data: LG, FL, RS, MS, YP, EM. Drafting of manuscript: LG, FL, RS, YP, OS, GS. All authors have approved the submitted manuscript. Guarantors of the paper, taking responsibility for the integrity of the work as a whole: LG, FL, YP, OS.

**Compliance with ethical standards**

**Conflict of interests** LG, FL, SG, MS, OS and GS have no conflict of interest. RS and EM are employees of Echosense Ltd. YP is an officer and a shareholder of Echosense Ltd.

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