Journal of Clinical Monitoring and Computing (2019) 33:1055–1060
https://doi.org/10.1007/s10877-019-00258-3

ORIGINAL RESEARCH

Pulmonary lung Doppler signals: normative data in a pediatric population compared with adults

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Received: 20 June 2018 / Accepted: 14 January 2019 / Published online: 19 January 2019

Abstract

Lung Doppler signals (LDS) acquired via transthoracic echocardiography is a novel technology previously reported in adults for use in detecting pulmonary hypertension. The aim of this study was to characterize LDS in healthy children to establish normative pediatric LDS data, and compare the pediatric data to the previously published healthy adult LDS. In this prospective, two-center study, LDS were acquired in children without cardiopulmonary disease using a 2 MHz transthoracic pulsed Doppler transducer. The data were processed to obtain Doppler velocity patterns corresponding to phases of the cardiac cycle. Signals were analyzed using a parametric Doppler signal-processing package and performance evaluation of the trained classifiers was performed using cross validation method. Pediatric signals were then compared to a retrospective cohort of healthy adults. Eighty-six healthy pediatric subjects (mean age 9.1 ± 5.1 years) and 79 healthy adult controls (mean age 59.7 ± 10.7 years) were included. The normative LDS velocity profiles were defined for pediatric subjects and then compared to adults; the highest discriminating LDS parameters between healthy children and adults were acceleration of atrial (A) signal contraction (46 ± 18 vs. 90 ± 34; $p < 0.001$), peak systolic (S) signal velocity (10.0 ± 3.5 vs. 11.7 ± 3.5; $p < 0.001$), and ratio of peak diastolic (D)-to-atrial (A) signal velocity (1.4 ± 0.5 vs. 0.4 ± 0.3; $p < 0.001$). The sensitivity and specificity of this LDS based method to discern between healthy children and adult subjects was 98.6% and 97.4%, respectively. Subgroup analyses between younger (2–8 years) and older (9–18 years) pediatric LDS yielded significant differences between atrial (A) acceleration (43.7 ± 33.9 vs. 47.7 ± 42.1; $p = 0.04$) and diastolic (D)-to-atrial (A) signal velocity (1.2 ± 0.5 vs. 1.5 ± 0.5; $p = 0.01$) but not systolic (S) signals (0.14 ± 0.05 vs. 0.14 ± 0.05; $p = 0.97$). In this study, we defined the normal LDS profile for healthy children and have demonstrated differences in LDS between children and adults. Specifically, healthy children had lower atrial contraction power, differences in ventricular compliance and increased chronotropic response. Further studies are warranted to investigate the application of this technology, for example as a tool to aid in the detection of pulmonary hypertension in children.

Keywords Non-invasive diagnosis · Lung doppler signal · Screening · Pediatric

1 Introduction

For children with pulmonary hypertension (PH), non-invasive diagnostic imaging provides a convenient alternative to right heart catheterization for screening and monitoring disease progression. Currently, transthoracic echocardiography is a commonly employed technique for non-invasive evaluation of PH by monitoring upstream changes in right heart function but has significant limitations in accurately estimating pulmonary artery pressure or changes in the distal pulmonary vasculature [1–3]. A new approach to evaluate pulmonary vascular disease in an accurate, non-invasive manner is needed. Ideally, this approach would involve

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10877-019-00258-3) contains supplementary material, which is available to authorized users.

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characterization of the distal pulmonary vasculature to detect early changes. However, it has previously been thought that ultrasound technology cannot be used to directly monitor the pulmonary vasculature due to high signal attenuation and high degree of scattering of ultrasound waves by the pulmonary parenchyma and alveolar air [4].

A recently developed transthoracic pulsed spectral Doppler signal analysis system has demonstrated the ability to capture signals, termed lung Doppler signals (LDS), from the distal pulmonary vasculature [4, 5]. This technology measures dynamic properties of the pulmonary vascular bed based on the movement of the blood vessel-alveolar air interface throughout the cardiac cycle, as has previously been reported [5]. The LDS recording system analyzes the characteristics of the amplitude and power of LDS signals that corresponds to different phases of the cardiac cycle based on simultaneous electrocardiographic recordings, including systole (S), diastole (D) and atrial contraction (A). This LDS technology has previously been validated in healthy adults and adults with pulmonary hypertension (PH) and atrial arrhythmias, but has not been used in pediatric patients to date [6, 7].

To evaluate the potential diagnostic power of LDS for evaluating pulmonary vascular properties in children, it is first essential to define normative pediatric LDS profile values. Once this has been established, then pediatric normative data can be compared against healthy adults to delineate features that may reflect developmental changes in cardiopulmonary vascular properties. Thus, the purpose of this study was to characterize LDS in healthy children and compare these LDS profiles to healthy adults, with longer term goals of determining whether the technology could be used in the detection and ongoing assessment of PH in children.

2 Methods

2.1 Study design and study population

This prospective, two-center study included LDS data from healthy pediatric subjects 2–18 years of age without cardiopulmonary disease, collected between July 2013 and September 2017. This study was reviewed and approved by the Stanford University Institutional Research Board (IRB Protocol #25388; clinicaltrials.gov reference number NCT01225367). Informed consent was obtained from all subjects' guardians; informed assent was also obtained from pediatric subjects older than 7 years of age who were able to provide assent. Healthy pediatric subjects, including patient siblings, were recruited from outpatient pediatric cardiology clinics. No patient was brought to the clinic solely for the purpose of this study. Pediatric subjects were excluded if they had cardiopulmonary disease or severe chest wall deformity. Screening for cardiopulmonary disease involved physician review of subject medical history, vital signs, physical exam and radiographic imaging if available. Patients < 2 years of age were subsequently excluded due to poor quality of signals captured by existing available transducers. Trained research personnel collected subject data. Demographic and clinical data collected included age, gender, height, weight, race, current medications, vital signs and pulmonary exam findings. Pediatric LDS were compared against a previously described retrospective cohort of 72 healthy adults [6].

2.2 Study device

LDS recordings were performed using Transthoracic Parametric Doppler (TPD) (EchoSense, Haifa, Israel) consisting of a 2 MHz single element transducer (diameter 16 mm, focal length of 6 cm) (Viasys Healthcare, Madison, WI, USA) and a FDA-approved pulsed Doppler signal coupled with an ECG system (Norav, Delray Beach, FL, USA). Signal analysis and classification was performed by a proprietary software package (EchoSense, Haifa, Israel). The pulse repetition frequency was 3 kHz and a sample volume of 3 mm was used. The maximal transmitted power was 74 mW/cm^2, approximately 10% of the FDA allowed intensity.

2.3 LDS recording and signal processing

LDS were collected with subjects sitting upright, or lying supine if unable to sit upright, with continuous ECG monitoring. Recordings were sampled at the one-third mid-clavicular line on the right chest wall in three locations: second, fourth and sixth intercostal spaces at fixed depths throughout the lung parenchyma. Recordings were made by trained sonographers.

LDS were recorded and processed using the Echosense software package (Echosense, Haifa, Israel) featuring a pulmonary vasculature pattern recognition system as previously described [5, 6]. The LDS were displayed in real-time as a spectrogram, using a graphical display of velocity (with color reflecting signal power) versus time (Fig. 1). The spectrograms, which were synchronous with the cardiac cycle, consisted of three bidirectional main waves corresponding in time to systole (S), diastole (D) and the atrial contraction (A). The spectrograms were averaged over 20 cardiac cycles for each of the three intercostal locations. Spectral features, including velocity, slope, and reflected ultrasound power of each wave, were extracted and analyzed. This process was performed separately for positive and negative polarity signals. The time values were normalized to the heart rate by dividing by the R–R interval.

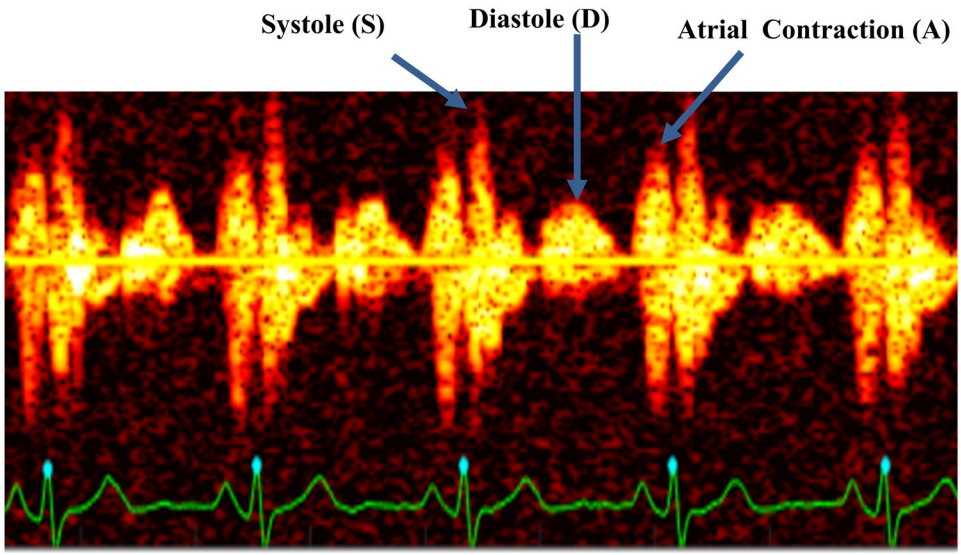


Fig. 1 Example of typical lung Doppler signals recorded by transthoracic parametric Doppler. LDS recorded by TPD with corresponding ECG synchronization. Signal amplitude indicates velocity and color represents power of the reflected ultrasound

2.4 Statistical analysis

The features of the spectra were automatically extracted by the software package and prepared for analysis and classification using a support vector machine (SVM), which utilized machine-learning methodology for distinguishing pediatric from adult subjects. The k-fold cross validation method was used to evaluate the SVM classification performance. In this analysis method, pediatric and adult subjects were divided into k subgroups of equal size. The classifier was trained on all except one sub-group and the results are validated on the excluded subgroup. This process is iterated k = 10 times and repeated n = 10 times.

Results are expressed as mean ± SD. The comparisons between pediatric and adult 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

Eighty-six children (mean age 9.1 ± 4.3 years) and 79 adults (mean age 59.7 ± 10.7 years) were included in the study. The participant demographics are presented in Table 1 and sample LDS tracings in Fig. 2. In all subjects, LDS recordings were performed without adverse event.

The normative LDS signals values for healthy children are shown in Table 2. When comparing pediatric to adult subjects, the highest discriminating LDS features were the duration of A signal, acceleration of A signal, time to peak S velocity, and the ratio of D:A peak velocity. Children have longer duration and decreased acceleration of atrial contraction (A signal) compared to healthy adults (46 ± 18 vs. 90 ± 34; p < 0.001). The time to peak systole (S signal) was longer (10.0 ± 3.5 vs. 11.7 ± 3.5; p < 0.001) and the velocity ratio between diastole (D signal) and atrial contraction (A signal) was higher in children compared to healthy adults (1.4 ± 0.5 vs. 0.4 ± 0.3; p < 0.001). Subgroup analyses between healthy younger (2–8 years; n = 43) and older (9–18 years; n = 57) children demonstrated statistically significant differences in a subset of LDS profiles including atrial acceleration (43.7 ± 33.9 vs. 47.7 ± 42.1; p = 0.04) and diastolic (D)-to-atrial (A) signal velocity (1.2 ± 0.5 vs. 1.5 ± 0.5; p = 0.01) (Fig. 3).

Table 1 Patient demographics

	Pediatric N = 86	Adult N = 79
Age (years)	9.1 ± 4.3	59.7 ± 10.7
2–8 [n (%)]	37 (43)	–
9–18 [n (%)]	49 (57)	–
Female [n (%)]	50 (58)	50 (63)
Weight (kg)	38 ± 18.5	73 ± 12
Height (cm)	130 ± 29	167 ± 9
BMI (kg/m^2)	21 ± 6	26 ± 3.2

Results are expressed as mean ± SD unless otherwise stated

The sensitivity and specificity of LDS to discriminate between healthy pediatric and adult subjects was 98.6% and 97.4%, respectively. The ROC curve for the detection of pediatric subjects versus healthy adults had an AUC of 0.98 (95% CI 0.96–0.99) (Supplement 1). Pediatric detection performance was subsequently analyzed in a sub-group of

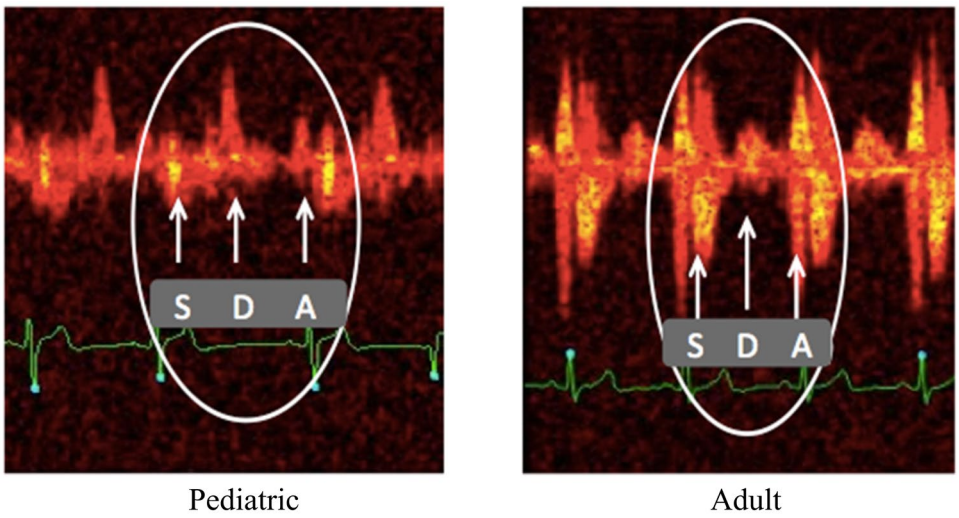


Fig. 2 Examples of lung Doppler signals in healthy pediatric versus adult subjects. S represents systole, D represents diastole and A represents atrial contraction

Table 2 Average LDS features in healthy pediatric versus adult subjects

LDS features	Pediatric (N = 86)	Adult (N = 79)	p-value
Peak velocities (cm/s)			
S	10.0 ± 3.5	11.7 ± 3.5	< 0.001
D	10.5 ± 3.3	9.6 ± 2.1	< 0.001
A	9.6 ± 4.4	12.4 ± 3.7	< 0.001
Acceleration slope (cm/s^2)			
S	162.5 ± 124.6	176.5 ± 119.2	0.874
A	45.9 ± 38.4	89.6 ± 33.7	< 0.001
Duration of signal (s)			
S	0.18 ± 0.06	0.16 ± 0.06	0.106
D	0.29 ± 0.12	0.18 ± 0.07	0.005
A	0.33 ± 0.17	0.16 ± 0.07	0.028
Time to peak			
S	0.14 ± 0.05	0.11 ± 0.03	< 0.001
D	0.60 ± 0.05	0.54 ± 0.06	0.003
A	0.89 ± 0.05	0.93 ± 0.02	< 0.001
Velocity ratio			
D:A	1.37 ± 0.52	0.94 ± 0.26	< 0.001

Results are expressed as mean ± SD unless otherwise stated

S represents systole, *D* represents diastole and *A* represents atrial contraction

pediatric subjects ages 2–8 years compared to pediatric subjects ages 9–18 years with no significant differences noted between the two groups.

4 Discussion

Using a novel, non-invasive pulse-Doppler ultrasound system, we found healthy children without cardiopulmonary disease have distinct LDS features (throughout the cardiac cycle) when compared to healthy adults. This technology is feasible in pediatric subjects and requires minimal time for data acquisition. Based on the normative pediatric data established in our study, future studies are needed to determine whether this novel, non-invasive technology can detect PH in children based on differences in recorded LDS.

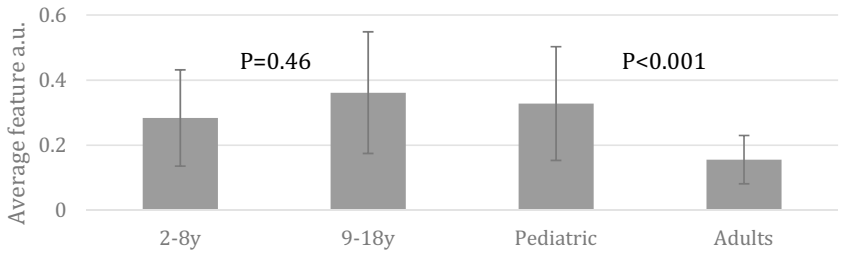
The rationale for validating LDS technology in pediatric populations compared to adults arises from knowledge that pulmonary vasculature develops throughout childhood, particularly during the first decade of life [8–11]. Specific morphologic changes that occur during childhood development of the pulmonary arterial vasculature include decreased muscularization of peripheral arterial walls with decreasing wall thickness. Additionally, the ratio of alveoli to arteries decreases throughout childhood. Throughout this period, pulmonary venous wall thickness does not change [12]. Thus, studying LDS data in children compared to adults is essential for establishing normative pediatric values due to pulmonary vascular differences.

In our study, children were found to have decreased atrial contraction signal acceleration along with a higher peak diastole-to-atrial contraction velocity ratio. These findings represent lower atrial contraction power in children relative to adults due to age-related differences in left-sided myocardial compliance and pulmonary vascular tone [13–15]. Furthermore, these LDS features were significantly different between younger and older children, supporting the theory that LDS demonstrate differences in pulmonary vascular development during early childhood as described above. In addition, time to peak systolic velocity is longer in children is likely related to the shorter cardiac cycle length and relative longer time spent in diastole due to greater chronotropic response and higher heart rates in children compared to adults [16].

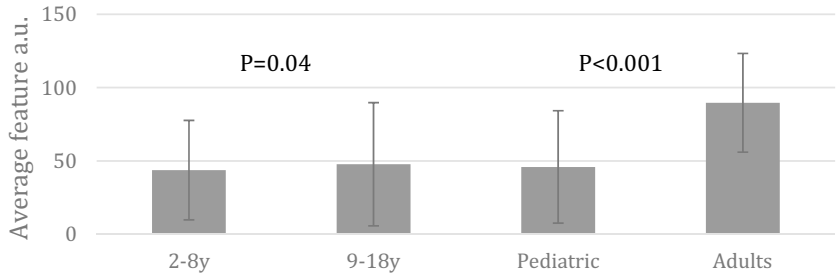
One potential application for this technology is for the assessment of pulmonary hypertension in children. PH alters

Fig. 3 **a**–**d** Lung Doppler signal features by age

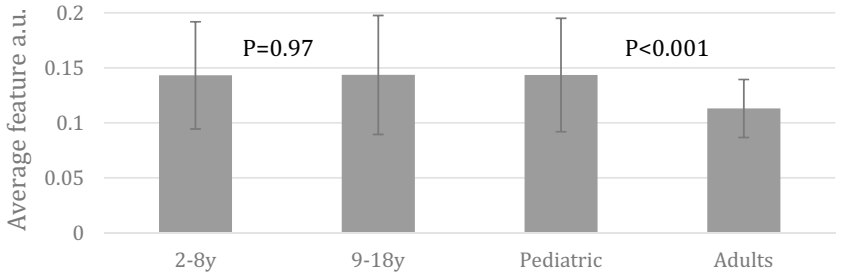
(A) Duration of atrial contraction.



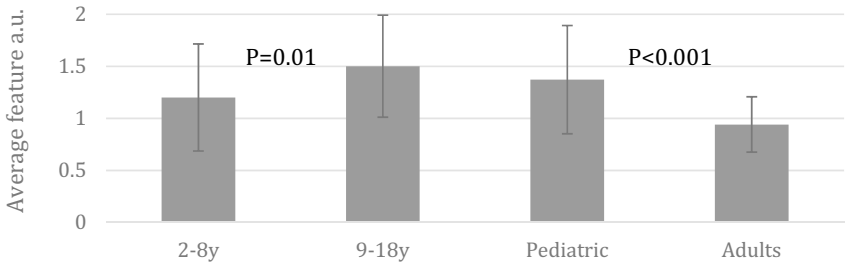
(B) Acceleration of atrial contraction.



(C) Time to peak systole.



(D) Peak velocity ratio of diastole-to-atrial contraction.



the vascular compliance of the lung parenchyma resulting from the elevation of distending transmural pressure [6]. Pulmonary artery stiffness assessed by cardiac catheterization has been shown to predict advanced PH and mortality at 20 years follow-up [17]. However, performing invasive diagnostic cardiac catheterization testing in children presents multiple challenges including need for sedation with associated cardiovascular risks. Alternatively, non-invasive imaging modalities such as transthoracic echocardiogram are conventionally used to assess upstream hemodynamic changes in right ventricular pressure estimates and systolic function. However, meta-analysis comparing echocardiography to

RHC for assessing PH in adults demonstrated 63% accuracy [1]. Given the important prognostic utility of pulmonary artery stiffness in pediatric PH, the LDS technology may provide a complementary, non-invasive technique to assess this hemodynamic parameter that correlates with invasive hemodynamic measurements. Such high correlation (85% sensitivity and specificity) in detection of PH in adults with PH with LDS technology has already been demonstrated [6].

Additionally, LDS technology has a relatively short learning curve required to obtain high quality LDS. It requires only brief data acquisition time (approximately 5 min) and the device is small and portable (approximately the size of a briefcase). All of these factors make this technology an appealing complementary approach to non-invasive evaluation in high-risk PH patients.

4.1 Study limitations

Data acquisition in children < 2 years of age was inconsistent. Current transducers are not optimized for the small chest-lung distances, and the high heart rates in this age group make discerning individual signal waves challenging. Future applications of this technology to this young population would require modifications of ultrasound probes to minimize the signal depth window. In addition, significant pulmonary parenchymal disease may also interfere with signal acquisition due to high attenuation of ultrasound beams, and may pose problems acquiring data in children with chronic lung disease.

5 Conclusion

LDS recorded by our transpulmonary Doppler technology captures pulmonary vascular signals that are both sensitive and specific to healthy children without cardiopulmonary disease when compared to healthy adults. This technology is feasible in pediatric subjects and requires minimal time for data acquisition. Based on the normative pediatric data established in our study, future studies are needed to determine whether this novel, non-invasive technology can detect PH in children based on differences in recorded LDS.

Compliance with ethical standards

Conflict of interest Danielle S. Burstein, Rachel K. Hopper, Elisa K. McCarthy, Keeley Hall and Jeffrey A. Feinstein have no conflict of interest. Rachel Schatzberger is an employee of Echosense Ltd. Yoram Palti is an officer and shareholder of Echosense Ltd.

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