International Journal of Cardiology 173 (2014) 92–99

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Spectral analysis of the heart sounds in children with and without pulmonary artery hypertension

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ARTICLE INFO

Article history:
Received 23 December 2013
Accepted 13 February 2014
Available online 24 February 2014

Keywords:
Machine learning
Phonocardiography
Auscultation
Stethoscope
Fast Fourier transform

ABSTRACT

Background: Pulmonary artery hypertension (PAH) is difficult to recognize clinically. Digital stethoscopes offer an opportunity to re-evaluate the diagnosis of PAH. We hypothesized that spectral analysis of heart sound frequencies using recordings from a digital stethoscope would differ between children with and without PAH.
Methods: We recorded heart sounds using a digital stethoscope from 27 subjects (12 males) with a median age of 7 years (3 months to 19 years) undergoing simultaneous cardiac catheterization. 13 subjects had a mean pulmonary artery pressure (mPAp) < 25 mm Hg (8–24 mm Hg). 14 subjects had a mPAp ≥ 25 mm Hg (25–97 mm Hg). We applied the fast Fourier transform, power spectral analysis, separability testing, and linear discriminant analysis with leave-one-out cross-validation to the heart sounds recorded from the cardiac apex and 2nd left intercostal space (LICS) to examine the frequency domain. The significance of the results was determined using a t-test and rank-sum test.
Results: The relative power of the frequencies 21–22 Hz of the heart sounds recorded at the 2nd LICS was decreased significantly in subjects mPAp ≥ 25 mm Hg versus < 25 mm Hg.
Conclusions: Heart sound signals of patients with PAH contain significantly less relative power in the band 21–22 Hz compared to subjects with normal PAp. Information contained in the frequency domain may be useful in diagnosing PAH and aid the development of auscultation based techniques for diagnosing PAH. In the future, utilizing the diagnostic information contained in heart sounds recordings may require analysis of both the time and frequency domains.

1. Introduction

Pulmonary artery hypertension (PAH) is a serious condition that imposes a global disease burden. Untreated, PAH has a high mortality whether the cause of the disease is idiopathic, genetic mutation or a complication of cardiac or pulmonary disease [1,2]. PAH is often diagnosed late because early clinical recognition is difficult even after the onset of symptoms [3]. There is, therefore, a need to explore or re-evaluate the clinical diagnosis of PAH.

The results of auscultation and phonocardiographic indicators of PAH have been described well together with plausible biological explanations for the findings [4,5]. Clinical indicators of PAH include increased loudness of the pulmonary component (P2) of the second heart sound (S2) and increased transmission of P2 to the cardiac apex. However, these descriptions have generally predated the use of new digital stethoscopes, which are readily available and have the capability of recording an acoustic tracing that can be optimized and analyzed later. There have been a few approaches to the non-invasive diagnosis of PAH that have been based on combining phonocardiography and mathematical analysis. These investigations, for the most part, have concentrated on the difficult task of identifying S2 and P2 reliably and precisely together with the splitting interval between the aortic component of S2 (A2) and P2 [6–9]. We undertook a pilot study to characterize the acoustic recordings of the heart sounds in children with and without PAH. Precise localization of S2, A2 and P2 was not part of our objective. Instead our goal was to explore the heart sound frequencies that might be associated with pulmonary artery hypertension.

We hypothesized that using recordings from a digital stethoscope we might demonstrate, through spectral analysis, heart sound frequencies

Abbreviations: A2, aortic component of second heart sound; LAp, left atrial pressure; LDA, linear discriminant analysis; 2nd LICS, 2nd left intercostal space; LOO, leave-one-out cross-validation; P2, pulmonary component of second heart sound; PA, pulmonary artery; PAH, pulmonary artery hypertension; PAp, pulmonary artery pressure; PAWp, pulmonary artery wedge pressure; PSD, power spectral density; QPI, pulmonary blood flow index; RAp, right atrial pressure; S2, second heart sound; VO_2, oxygen consumption.

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http://dx.doi.org/10.1016/j.ijcard.2014.02.025
0167-5273/

that would differ between subjects with and without pulmonary artery hypertension. Therefore, we sought to identify heart sound frequencies associated with the simultaneously measured pulmonary artery (PA) pressure at cardiac catheterization by spectral analysis obtained by digital stethoscope recordings from children with and without PAH.

2. Materials and methods

2.1. Ethics statement

The Research Ethics Board of the University of Alberta approved the study. All subjects or their parents gave informed and written consent to participate in the study. Informed assent was obtained from children who were sufficiently developmentally able.

2.2. Clinical data collection

We approached, for inclusion in the study, all children undergoing right heart cardiac catheterization that was required for management of their underlying condition. We excluded subjects with congenitally abnormal aortic, pulmonary and prosthetic valves.

The heart sounds were recorded using a 3M™ Littmann^{R} 3200 digital stethoscope (3M Inc., Denmark), using Zargis Cardioscan™ software (Zargis Medical Corp., Princeton, NJ, USA) to store recorded heart sounds in *.wav mono audio format. Heart sound recordings were obtained over 20 s with sampling frequencies of 4000 Hz. We recorded the heart sounds sequentially at the 2nd left intercostal space (2nd LICS) and the cardiac apex for 20 s. We used soft ware developed in MATLAB 2010b (The MathWorks, Inc., Natick, MA, USA) for signal analysis and optimization. Heart sounds were recorded simultaneously with the direct PA pressure measurements obtained during right heart catheterization in a standard manner using fluid filled catheters and transducers zeroed at the mid thoracic level. Other hemodynamic data including, heart rate, pulmonary artery wedge pressure (PAWp) or left atrial pressure (LAp) or left ventricular end diastolic pressure, right atrial pressure (RAp), oxygen consumption (VO_2) and systemic pressure and pulmonary blood flow were collected within 5–10 min of the acoustic recordings. Pulmonary blood flow indexed to body surface area (QPI) was measured either by thermodilution catheter or using the Fick equation with simultaneously measured oxygen consumption (VO_2). Oxygen consumption was measured by mass spectroscopy using the Ames 2000 or the Innocor (Innovision, Denmark). We calculated the pulmonary vascular resistance index (PVRI) from the formula mean PAp-mean PAWp or mean LAp/QPI. We measured QRS duration in lead V1 and PR interval in lead 2 from an electrocardiogram recorded on the day of the cardiac catheterization.

2.3. Definition of pulmonary artery hypertension

Pulmonary artery hypertension is defined as a mean PA pressure ≥ 25 mm Hg and a PAWp or LAp ≤15 mm Hg measured at heart catheterization in subjects at rest [10–12]. Therefore, we divided the recordings into 2 groups depending on whether the recording originated from subjects with a mean PA pressure < or ≥25 mm Hg. In all subjects the mean PAWp or LAp was <15 mm Hg.

2.4. Heart sound analysis

We analyzed the heart sound recordings with spectral feature extraction, in particular the relative power of the heart sound frequency bands. We performed separability tests to discover which recording site (the 2nd LICS or the apex) was more informative in diagnosing PAH. We applied linear discriminant analysis (LDA) to each spectral feature separately, with the aim of distinguishing subjects with and without PAH.

2.5. Spectral analysis

We applied fast Fourier transform on the heart sounds recorded from the cardiac apex and 2nd LICS to examine the frequency domain.

2.6. Spectral feature extraction

We investigated the power spectrum of heart sounds recorded at two positions (2nd LICS and apex). Power spectral density (PSD) analysis was undertaken. To answer the question which auscultation position and which frequency band provided the best detection of PAH, we explored systematically different heart sound frequency bands [F: (F + W)] Hz as follows:

Bandpass filter: a bandpass filter is applied to each heart sound recording to extract the heart sound data in a specific frequency band [F: (F + W)] Hz. We used Butterworth filters (3rd order) as they offer good transition band characteristics at low coefficient orders; as a result, they can be implemented efficiently.

Relative power (RP): the relative power of a certain frequency band (extracted in the previous step) is obtained by dividing the power of this frequency band by the power of the total frequency band:

$$RP_i = \frac{P_i(F, F+W)}{P_i(F_{min}, F_{max})}, \quad (1)$$

where P is the power of the frequency band [F, F + W] Hz and P (Fmin, Fmax) is the power of the wide frequency range [1,80] Hz at the auscultation position.

2.7. Separability test

The separability test was carried out to determine which auscultation position (2nd LICS or apex) was more informative for diagnosing PAH. After calculating the RP for all subjects within a certain frequency band [F: (F + W)] Hz, we computed the average RP for PAH subjects ($\mu \geq 25$) and subjects with normal pulmonary artery pressures ($\mu < 25$). The subscripts ≥ 25 and <25 indicate PAH subjects and subjects with normal PA pressure, respectively. Then we computed the standard deviation of RP within both populations, denoted by ($\sigma \geq 25$) and ($\sigma < 25$), respectively. The linear separability criterion J was computed as follows:

$$J(F, F+W) = \frac{|\mu \geq 25(F, F+W) - \mu < 25(F, F+W)|}{\sigma \geq 25(F, F+W) + \sigma < 25(F, F+W)}. \quad (2)$$

We calculate the index J (F, F + W) over a range of frequency bands, i.e., F = 1, 2,..., 79 Hz and W = 1, 2,..., 79 Hz, corresponding to 6241 different frequency bands within [1,80] Hz; we depict the value J as a function of F and W.

2.8. Linear discriminant analysis (LDA)

We assessed the classification performance with LDA through leave-one-out (LOO) cross-validation. We created each training set by taking all the samples except one with the corresponding test set being the sample left out. Thus, for n samples, we have n different training sets (each yielding a coefficient vector w) and n different test sets. We conducted this procedure for each spectral feature. We analyzed the discriminative power of each feature in terms of LDA classification error. We selected the spectral features

Table 1
Demographic data for subjects #1–14 with pulmonary artery hypertension and mean pulmonary artery pressure ≥ 25 mm Hg.

Subject #	Age (years)	Height (m)	Weight (kg)	BSA ($m^{2)}$	BMI (kg/m^2)	Gender	Diagnosis
1	0.8	0.66	6.1	0.32	14.0	M	Repaired CDH
2	0.9	0.64	5.9	0.31	14.4	F	Unrepaired CHD
3	2	0.88	11.9	0.53	15.5	M	IPAH
4	3	0.90	12.3	0.55	15.2	M	Unrepaired CHD
5	7	1.23	23	0.89	15.2	F	IPAH
6	12	1.62	62	1.66	23.6	F	Repaired CHD
7	8	1.33	33.2	1.1	18.8	M	IPAH
8	9	1.34	29.9	1.06	16.7	F	Repaired CHD
9	12	1.62	62	1.66	23.6	F	Repaired CHD
10	12	1.49	59	1.53	26.6	M	IPAH
11	15	1.30	31.7	1.06	18.8	F	IPAH
12	12	1.54	77.6	1.76	32.7	F	Repaired CDH
13	11	1.55	54.8	1.53	22.8	M	IPAH
14	1.7	0.85	11.6	0.55	16.1	M	IPAH
Median	8.5	1.31	30.8	1.06	17.7	7M:7F	
Minimum	0.8	0.64	5.9	0.31	14		
Maximum	15	1.62	77.6	1.76	32.7		

Abbreviations: m = meters, kg = kilograms, BSA = body surface area, BMI = body mass index, M = male, F = female, CDH = congenital diaphragmatic hernia, CHD = congenital heart disease, IPAH = idiopathic pulmonary hypertension.

Table 2
Demographic data for subjects #15–27 with normal pulmonary artery pressures and mean pulmonary artery pressure <25 mm Hg.

Subject #	Age (years)	Height (m)	Weight (kg)	BSA ($m^{2)}$	BMI (kg/m^2)	Gender	Diagnosis
15	0.8	0.71	8.3	0.39	16.5	M	Unrepaired CHD
16	2	0.77	9.8	0.44	16.7	M	Repaired CHD
17	3	1.01	18.1	0.7	17.7	M	Unrepaired CHD
18	0.25	0.52	4.5	0.24	16.6	F	Repaired CHD
19	2	0.87	11.4	0.51	15.1	F	Unrepaired CHD
20	5	1.17	19	0.79	13.9	F	Post heart transplant
21	3	0.89	12.8	0.55	16.2	F	Post heart transplant
22	10	1.29	31.5	1.06	18.9	F	Post heart transplant
23	17	1.58	59	1.6	23.6	F	Repaired CHD
24	17	1.62	42	1.4	16.0	F	Repaired CHD
25	19	1.75	59	1.72	19.3	M	Post heart transplant
26	8	1.33	32.7	1.1	18.5	M	Unrepaired CHD
27	0.5	0.54	3.6	0.22	12.3	F	Repaired CHD
Median	3	1	18.1	0.7	16.6	5M:8F	
Minimum	0.25	0.52	3.6	0.22	12.3		
Maximum	19	1.75	59	1.72	23.6		

Abbreviations: m = meters, kg = kilograms, BSA = body surface area, BMI = body mass index, M = male, F = female, CDH = congenital diaphragmatic hernia, CHD = congenital heart disease.

through LOO. For each training set (containing all subjects except one), the spectral features were ranked according to the LDA classification error.

2.9. Statistical tests

We confirmed the relative power of frequencies between 21 and 22 Hz to discriminate between subjects with and without PAH by applying the t-test and the Wilcoxon–Mann–Whitney test (rank-sum test).

3. Results

We collected recordings from 27 subjects (12 males and 15 females) with a median age of 7 years (range: 3 months to 19 years). Thirteen subjects (Group 1) had a mean PAp < 25 mm Hg (range 8–24 mm Hg), and 14 subjects had a mean PAp ≥ 25 mm Hg (Group 2) (range 25–97 mm Hg). We did not exclude any recordings from the analysis. The clinical and hemodynamic details of the subjects are included in Tables 1–7. The only statistically significant differences between the two groups were hemodynamic measurements that reflected the presence or absence of PAH. There was no difference in the LAp, or PAWp, or QPI between the 2 groups. The 2 groups did not differ by age, weight, height, body surface area, or body mass index (Table 7).

3.1. Power spectral analysis

The average PSD obtained from the heart sound recordings at the 2nd LICS of subjects with normal PAp (<25 mm Hg) had increased power amplitude in the low frequency ranges of 15–25 Hz compared with the apex, as shown in Fig. 1. In other words, the energy amplitude of the mean PSD in patients with PAH was lower than in subjects with normal PAp.

3.2. Separability test

Fig. 2 represents the results of the separability test and reveals two different regions of interest (or high separability) from heart sound recordings at the 2nd LICS and the cardiac apex. The largest linear separation J between subjects with PAH and normal PAp is shown in the regions marked R1 and R2 in Fig. 2. The recordings made at the 2nd LICS show no separability between subjects with mean PAp < or

Table 3
Pulmonary vascular hemodynamic data. Subjects #1–14 with pulmonary artery hypertension and mean pulmonary artery pressure ≥25 mm Hg. (Note pulmonary artery pressures are those measured during auscultation. PVRI is calculated using mean PAp measured at the time of thermodilution or oxygen consumption measurement and oximetry.)

Subject #	Mean PAp (mm Hg)	Systolic PAp (mm Hg)	Diastolic PAp (mm Hg)	Mean LAp/PAWp (mm Hg)	PVRI (WUm^2)	QPI ($L/min/m^2$)
1	29	48	13	6	4.8	4.8
2	25	38	12	2	5.2	4.4
3	64	89	34	9	13.1	4.2
4	66	92	47	7	10.7	5.5
5	25	31	19	7	5.5	3.3
6	97	140	66	10	27.2	3.2
7	37	49	26	10	9.3	2.9
8	30	46	14	5	7.4	3.4
9	85	119	57	6	27.2	2.9
10	63	95	37	7	19.3	2.9
11	55	99	37	6	16.7	2.9
12	32	45	22	14	6.9	2.6
13	73	103	53	12	17	3.3
14	53	14	33	3	7.5	4
Median	54	69	33	7	10	3.3
Minimum	25	14	12	2	4.8	2.6
Maximum	97	140	66	14	27.2	5.5

Abbreviations: PAp = pulmonary artery pressure, LAp = left atrial pressure, PAWp = pulmonary artery wedge pressure, PVRI = pulmonary vascular resistance index, WUm^2 = Wood units × meter squared, QPI = pulmonary blood flow index, $L/min/m^2$ = liters per minute per meter squared.

Table 4
Pulmonary vascular hemodynamic data. Subjects #15–27 with normal pulmonary artery pressures with a mean pulmonary artery pressure <25 mm Hg. (Note pulmonary artery pressures are those measured during auscultation. PVRI is calculated using mean pulmonary artery pressure measured at the time of thermodilution or oxygen consumption measurement and oximetry.)

Subject #	Mean PAp (mm Hg)	Systolic PAp (mm Hg)	Diastolic PAp (mm Hg)	Mean LAp/PAWp (mm Hg)	PVRI (WUm^2)	QPI ($L/min/m^2$)
15	20	29	17	11	2.8	3.2
16	20	32	11	8	3.1	3.9
17	15	25	10	4	0.8	14.4
18	15	25	7	6	2.0	4.4
19	24	34	15	9	4.8	3.1
20	14	27	7	7	N/A	N/A
21	20	30	12	10	2.6	3.8
22	8	11	5	5	1.3	2.3
23	17	31	9	7	2.8	3.6
24	12	22	4	5	1.6	4.5
25	14	20	8	10	1.5	2.7
26	17	24	11	11	0.6	3.7
27	15	23	7	1	5.6	2.3
Median	15	25	9	7	2.3	3.6
Minimum	8	11	4	1	0.6	2.3
Maximum	24	34	17	11	5.6	14.4

Abbreviations: PAp = pulmonary artery pressure, LAp = left atrial pressure, PAWp = pulmonary artery wedge pressure, PVRI = pulmonary vascular resistance index, WUm^2 = Wood units × meter squared, QPI = pulmonary blood flow index, $L/min/m^2$ = liters per minute per meter squared, N/A = not available.

≥25 mm Hg within the low or high frequency bands, although they show separability in the medium frequency band.

3.3. Linear discriminant analysis

To determine more precisely the frequency bands associated with PAH, we conducted LDA on the heart sounds recorded at the 2nd LICS and the cardiac apex. The frequency bands with the smallest LDA error were computed through LOO (labeled 1st, 2nd, and 3rd bands) (Table 8). We selected the most frequent spectral feature within the 3 optimal bands. As can be seen in Table 8, the frequency band 21–22 Hz in heart sounds recorded at the 2nd LICS is the most frequent in the top 3 bands, with lowest LDA error, for different training sets. However, bands 11–13 Hz and 61–62 Hz are almost equally frequent in the top 3 bands in the heart sounds recorded at the apex.

In the testing phase, we conducted LDA using 3 features (21–22 Hz of heart sounds recorded at the 2nd LICS and 11–13 Hz and 61–62 Hz of heart sounds recorded at the apex) assessed through LOO to report the true error of the optimal spectral band. The lowest classification error, between subjects with and without PAH, obtained through the LOO feature selection was 22.22% for the frequency band 21–21 Hz from heart sounds recorded at the 2nd LICS, as shown in Table 9.

The results in Table 9, reveal a statistically significant difference ($p < 0.05$) in the representation of the frequencies between 21 and 22 Hz in subjects with PAH compared to those with normal PAp. The boxplot of the relative power feature 21–22 Hz of the auscultation at the 2nd LICS shown in Fig. 3 is concordant with the findings in Fig. 1. The relative power of the frequency band 21–22 in subjects with PAH is lower than in subjects with normal PAp. Examples of heart sound recordings (filtered and unfiltered) at the cardiac apex in a patient with severe PAH and a subject with a normal PAp are shown in Fig. 4.

4. Discussion

The main finding of this study is that heart sounds recorded at 2nd LICS, but not at the cardiac apex, in the frequency band 21–22 Hz may distinguish children with PAH from subjects with normal PAp. There is a significant decrease in the relative power of 21–22 Hz in patients

Table 5
Systemic vascular hemodynamic and electrocardiographic data. Subjects #1–14 with pulmonary artery hypertension with a mean pulmonary artery pressure ≥25 mm Hg.

Subject #	Mean BP (mm Hg)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Mean RAp (mm Hg)	Heart rate (beats/min)	QRS duration (ms)	PR interval (ms)
1	59	83	41	2	130	62	66
2	68	93	47	1	130	75	91
3	48	70	34	8	99	97	98
4	70	82	56	7	115	77	92
5	70	97	50	3	66	71	88
6	93	122	73	5	107	71	71
7	96	44	67	3	75	110	106
8	62	93	42	4	65	110	88
9	88	106	71	6	90	71	71
10	78	110	56	4	70	77	71
11	68	99	53	3	80	132	110
12	84	104	70	2	70	104	102
13	72	96	54	4	63	98	116
14	58	92	48	4	88	95	124
Median	70	94	53	4	84	86	91
Minimum	48	44	34	1	63	62	66
Maximum	96	122	73	8	130	132	124

Abbreviations: BP = systemic blood pressure, RAp = right atrial pressure, ms = milliseconds, min = minute.

Table 6
Systemic vascular hemodynamic and electrocardiographic data. Subjects #15–27 with normal pulmonary artery pressures with a mean pulmonary artery pressure <25 mm Hg.

Subject #	Mean BP (mm Hg)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Mean RAp (mm Hg)	Heart rate (beats/min)	QRS duration (ms)	PR interval (ms)
15	54	92	36	11	130	77	84
16	60	95	39	6	78	111	116
17	60	71	46	1	111	120	114
18	52	67	37	1	134	99	87
19	63	80	50	8	108	91	97
20	42	63	32	8	82	101	98
21	75	97	53	3	105	101	92
22	55	65	45	1	96	134	80
23	73	108	56	7	78	147	136
24	67	93	51	1	90	108	96
25	116	72	96	1	70	103	116
26	76	110	58	2	100	98	76
27	54	96	40	2	127	108	102
Median	60	92	46	2	100	103	97
Minimum	42	63	32	1	70	77	76
Maximum	116	110	96	11	134	147	136

Abbreviations: BP = systemic blood pressure, RAp = right atrial pressure, ms = milliseconds, min = minute.

Table 7
Comparison of clinical and hemodynamic data between subjects with pulmonary artery hypertension (mean PAp ≥ 25 mm Hg) and subjects with normal pulmonary artery pressures (mean PAp < 25 mm Hg).

Clinical and hemodynamic variables	p value
Age	0.5
Height	0.4
Weight	0.2
Body surface area	0.3
Body mass index	0.4
Systolic pulmonary artery pressure	<0.001*
Diastolic pulmonary artery pressure	<0.001*
Mean pulmonary artery pressure	<0.001*
Pulmonary vascular resistance index	<0.001*
Pulmonary blood flow index	0.9
Mean left atrial pressure	0.9
Mean right atrial pressure	0.5
Systolic blood pressure	0.2
Diastolic blood pressure	0.2
Mean blood pressure	0.1
Heart rate	0.2
Electrocardiogram QRS duration in lead V1	0.02*
Electrocardiogram PR interval in lead 2	0.4

* Signifies p< 0.05.

with PAH compared with subjects with normal PAp. The heart sounds were recorded with a handheld digital stethoscope. This resulted in a number of recordings, which were of insufficient fidelity and perhaps responsible for the 22% classification error (sensitivity of 79% and specificity of 77%). We anticipate that future studies with adhesive and high fidelity microphones will permit us to improve the misclassification rate by eliminating movement artifacts and reducing ambient noise.

We did not focus on the analysis of S2, specifically the pulmonary component of the S2, unlike previous investigations. Analysis of the S2, particularly differentiating the aortic and pulmonary components of the S2, as well as, the splitting interval remain challenging problems [8,13,14,6,7,9] Therefore, we did not analyze the time domain information but concentrated on using hidden information contained in the frequency domain. Our aim was to investigate the results with a readily available stethoscope and use machine learning techniques such as the LDA to classify the heart sounds as a composite signal without specific analysis of the S2 in the time domain. Our results suggest that the recording site that best distinguishes patients with a mean PAp ≥ 25 mm Hg from subjects with a mean PAp < 25 mm Hg is the 2nd LICS, which is the traditional area for auscultation of pulmonary artery events. This may add biological plausibility to our findings.

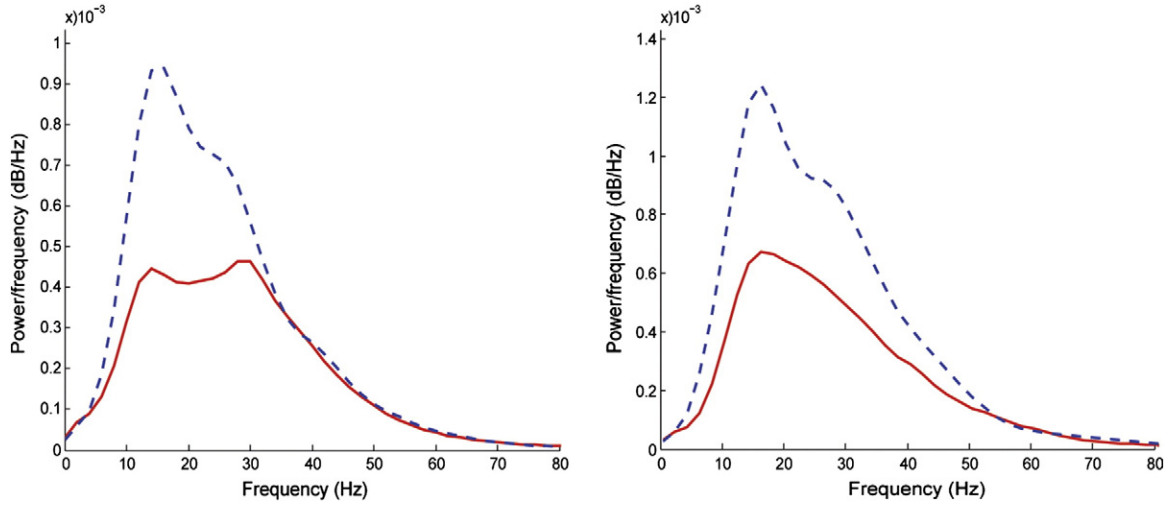

Fig. 1. Power spectral analysis of the heart sound recordings at the 2nd left intercostal space (left) and the cardiac apex (right). The dotted blue line represents the average power spectral density of subjects with mean PAp < 25 mm Hg (normal PAp) (n = 13), while the solid red line represents the average power spectral density of subjects with mean PAp ≥ 25 mm Hg (PAH) (n = 14).

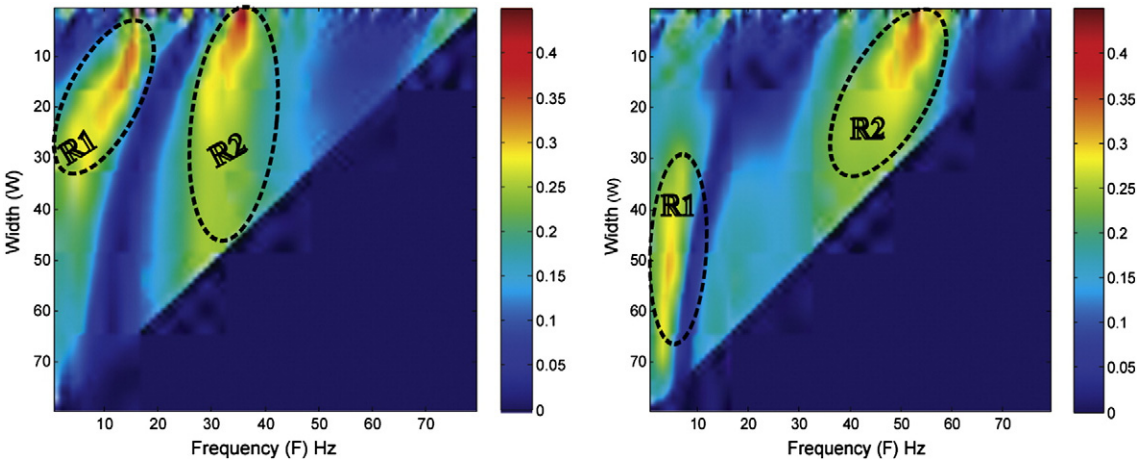

Fig. 2. Two-dimensional representations of the linear separation value J between subjects with PAH and subjects with normal PAp subjects for heart sounds measured at the 2nd left intercostal space (left) and the apex (right) auscultation positions. The x-axis represents the frequency (F), the y-axis represents the width (W), while the color indicates the linear separation value J. The heart sounds recorded at the cardiac apex (right) scored high index J values over the regions of (F,W), which means the heart sounds recorded at the apex are able to distinguish PAH from normal PAp. Moreover, recordings from the cardiac apex (right) contain two frequency regions in the (F,W) plane that may be used for distinguishing PAH from normal PAp.

The frequency band 21–22 Hz yielded the lowest LDA classification error within the entire 1–80 Hz range. Interestingly, Fig. 2 demonstrates two spectral regions (R1 and R2) that could be used as discriminative features for PAH. R1 and R2 are independent regions that reflect the changes in low frequency and high frequency, respectively. At the 2nd LICS, the optimal band 21–22 Hz was found in between R1 (≈10–20 Hz) and R3 (≈30–50 Hz). Interestingly, the frequency band 21–22 Hz yields the lowest classification error for most training sets (Table 8) and, therefore, results in stable classifiers. In addition, the frequency band 21–22 Hz was explicitly found to have the lowest LDA error during the training phase, as shown in iterations 1–27 in Table 8. To confirm our results, we assessed the discriminative power of the resulting spectral feature 21–22 Hz with two statistical tests. The p-value from the t-test is 0.044 (Fig. 3), while the p-value from the rank-sum test is 0.027, which suggests that 21–22 Hz is a promising feature for detecting PAH. In Fig. 4, we show heart sounds from a subject with PAH and control subject in the range 21–22 Hz.

Within the time frame of the study, it was only possible to include 27 subjects in the analysis. We conducted a post hoc power analysis, based on the results shown in Fig. 3, to ensure that the sample size was

Table 8
The linear discriminant analysis (LDA) error results (computed through leave one out cross validation (LOO)).

Iteration	Apex			2nd LICS		
	First band (error)	Second band (error)	Third band (error)	First band (error)	Second band (error)	Third band (error)
1	61–62 (19%)	61–63 (23%)	11–13 (27%)	21–22 (19%)	13–25 (27%)	13–28 (27%)
2	11–13 (27%)	12–13 (27%)	12–79 (27%)	21–22 (23%)	13–25 (27%)	13–28 (27%)
3	9–12 (23%)	9–13 (23%)	11–13 (23%)	21–22 (23%)	15–29 (27%)	32–44 (27%)
4	61–62 (19%)	9–12 (23%)	9–13 (23%)	21–22 (23%)	18–20 (27%)	32–43 (27%)
5	11–13 (27%)	12–70 (27%)	12–71 (27%)	21–22 (23%)	32–44 (27%)	33–43 (27%)
6	61–62 (19%)	11–71 (23%)	11–72 (23%)	21–22 (23%)	34–42 (23%)	14–16 (27%)
7	11–13 (27%)	12–73 (27%)	12–74 (27%)	21–22 (23%)	32–44 (27%)	33–43 (27%)
8	61–62 (19%)	11–72 (23%)	11–73 (23%)	21–22 (23%)	33–43 (23%)	34–42 (23%)
9	11–13 (27%)	57–59 (27%)	61–62 (27%)	21–22 (23%)	13–25 (27%)	13–26 (27%)
10	11–13 (27%)	57–59 (27%)	61–62 (27%)	21–22 (23%)	15–29 (27%)	32–44 (27%)
11	12–13 (23%)	11–13 (27%)	12–69 (27%)	21–22 (19%)	32–45 (23%)	33–43 (23%)
12	11–13 (27%)	12–13 (27%)	12–69 (27%)	21–22 (23%)	35–40 (23%)	36–39 (23%)
13	9–13 (23%)	1–12 (27%)	2–12 (27%)	21–22 (23%)	14–31 (27%)	31–45 (27%)
14	11–13 (27%)	57–59 (27%)	61–62 (27%)	21–22 (23%)	18–20 (27%)	32–42 (27%)
15	9–13 (26%)	11–13 (27%)	12–13 (27%)	21–22 (23%)	14–16 (27%)	32–44 (27%)
16	9–12 (26%)	9–13 (27%)	11–13 (27%)	21–22 (19%)	32–45 (27%)	33–43 (27%)
17	1–11 (27%)	2–11 (27%)	3–11 (27%)	21–22 (19%)	18–20 (23%)	31–45 (23%)
18	61–62 (23%)	9–13 (27%)	11–13 (27%)	21–22 (19%)	18–20 (23%)	34–43 (23%)
19	11–13 (27%)	12–70 (27%)	12–71 (27%)	14–16 (27%)	21–22 (27%)	32–45 (27%)
20	61–62 (23%)	9–13 (27%)	11–13 (27%)	21–22 (23%)	34–43 (23%)	13–29 (27%)
21	11–13 (23%)	1–11 (27%)	4–11 (27%)	18–20 (23%)	21–22 (23%)	32–42 (23%)
22	11–13 (23%)	1–8 (27%)	1–11 (27%)	21–22 (23%)	15–29 (27%)	30–49 (27%)
23	57–59 (23%)	61–62 (23%)	9–13 (27%)	21–22 (23%)	3–72 (27%)	3–73 (27%)
24	11–13 (23%)	9–13 (27%)	9–14 (27%)	21–22 (23%)	34–43 (23%)	32–45 (27%)
25	57–59 (23%)	61–62 (23%)	9–12 (27%)	21–22 (19%)	13–29 (27%)	13–30 (27%)
26	9–12 (27%)	9–13 (27%)	11–13 (27%)	21–22 (23%)	31–45 (23%)	32–43 (23%)
27	11–13 (23%)	57–59 (23%)	61–62 (23%)	18–20 (23%)	21–22 (23%)	31–45 (23%)

Table 9
A comparison between optimal frequency bands.

	Cardiac apex		2nd LICS
Frequency band	11–13 Hz	61–62 Hz	21–22 Hz
LOO LDA error (%)	25.9	25.9	22.22
p-Value (t-test)	0.427	0.032	0.044
p-Value(rank sum)	0.234	0.182	0.027

Abbreviations: LOO = leave-one-out cross validation, LDA = linear discriminant analysis.

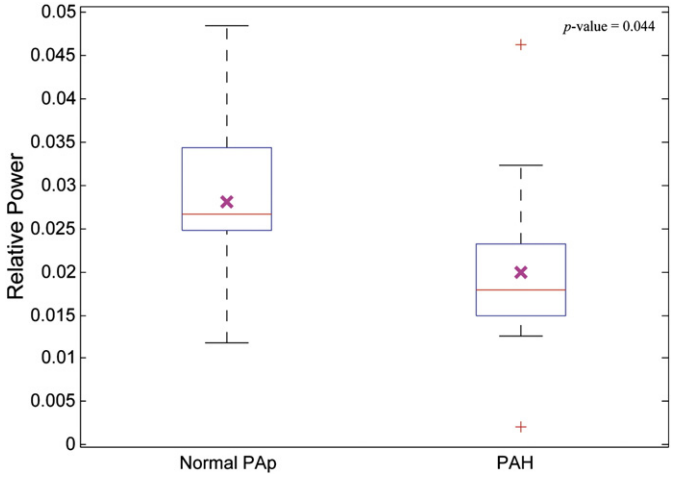

Fig. 3. Boxplot of the relative power feature 21–22 Hz of the heart sounds recorded at the 2nd left intercostal space. The left box represents the relative power of 21–22 Hz from heart sound recordings from subjects with mean PAp 8–24 mm Hg i.e. normal PAp (n = 13), while the right box represents the relative power of 21–22 Hz from heart sound recordings from subjects with mean PAp 25–97 mm Hg (PAH) (n = 14). The cross in each box refers to the statistical mean, while the red line refers to the statistical median. A two-sample t-test was performed, and a significant difference was detected between subjects with a normal PAp and PAH ($p < 0.05$).

sufficient for our analysis. The mean and standard deviation of the null hypothesis of the control group (subjects with normal PAp) are 0.0281 and 0.0096, respectively; while, the mean under the alternative hypothesis (subjects with PAH) was 0.02. The power calculation using the t-test showed that a representative sample size of the population should be greater than 17 subjects, which indicates that our sample size (27 subjects) is sufficient to draw meaningful conclusions.

Our approach differs from other investigations that have concentrated on the time domain features of the S2. Improved discrimination between children with and without PAH requires higher-fidelity recordings with reduced noise, especially from recordings made at the cardiac apex. The frequency band 21–22 Hz from the 2nd LICS heart sounds yielded the lowest classification error for most training sets, and therefore, appears to provide a stable feature.

4.1. Study limitations

A larger sample size and a more diverse data set are needed in order to generalize and confirm the findings of this study. The use of higher-fidelity adhesive microphones with simultaneous recording of heart sounds from different sites may improve the classification error. Prospective evaluation of the frequencies with the analyzer blinded to the PAp will also be required to validate these findings.

5. Conclusion

Our data, obtained very simply with a handheld digital stethoscope, suggests that heart sound signals recorded at the cardiac apex and 2nd LICS of patients with PAH contain significantly less relative power in the medium-frequency band 21–22 Hz compared to subjects with normal pulmonary artery pressure. We demonstrated also that information contained in the frequency domain may be useful in diagnosing PAH. We suggest that the information contained within the frequency domain may add important diagnostic potential to the development of auscultation-based techniques for diagnosing PAH. In the future, improving the diagnostic information contained in acoustic recordings may require analysis of both the time and frequency domains of the heart sounds.

Acknowledgments

The investigators gratefully acknowledge grant funding from the Women's and Children's Health Research Institute, the Alberta Innovates Centre for Machine Learning and the Cardiovascular Medical Research and Education Fund for Pulmonary Hypertension.

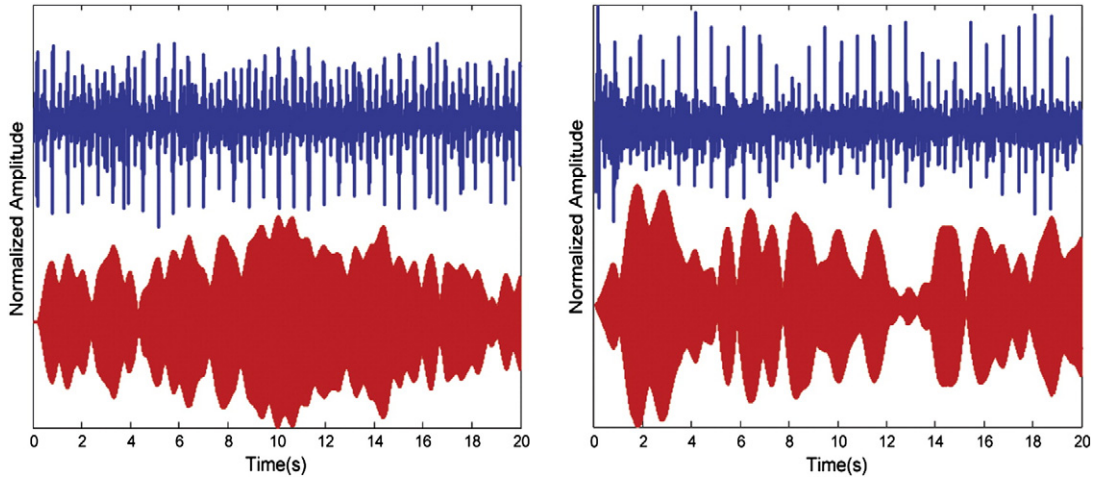

Fig. 4. An example of the effect of filtering heart sounds recorded at the 2nd left intercostal space with the optimized frequency band 21–22 Hz in a subject with normal PAp (mean PAp = 8 mm Hg) on the left and severe PAH (mean PAp = 97 mm Hg) on the right. The y-axis represents normalized amplitude of the heart sounds and the x-axis represents time in seconds. The blue signal represents the original (unfiltered) heart sounds, while the red signal represents the filtered heart sounds recorded at the 2nd left intercostal space. In the patient with severe PAH, there are fewer amplitude deflections in the 21–22 Hz frequency range than in the subject with normal PAp. Signal amplitudes have been normalized and manipulated to fit the two signals in one figure.

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