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Escola Superior de Saúde

Maria Manuel Almeida Regêncio

Sons respiratórios computorizados em crianças com infeção respiratória do trato inferior: um estudo comparativo

Computerised respiratory sounds in infants with lower respiratory tract infections: a comparative study

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Computerised respiratory sounds in infants with lower respiratory tract infections: a comparative study

Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Fisioterapia, realizada sob a orientação científica da Doutora Alda Marques, Professora Adjunta da Escola Superior de Saúde da Universidade de Aveiro.

aos meus pais

o júri

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Palavras-chave Sons respiratórios normais; sons respiratórios adventícios; crianças; Infeção Respiratória Trato Inferior

Sumário

Enquadramento: As infeções respiratórias do trato inferior (IRTI) constituem o principal problema de saúde nos primeiros anos de vida das crianças. Desta forma, a investigação tem-se focado no desenvolvimento de medidas objetivas para o diagnóstico de IRTI, utilizando essencialmente as vantagens da auscultação convencional incorporadas numa análise computorizada e automática. Contudo, apesar da análise computorizada de sons respiratórios ser um método simples de deteção e caraterização dos sons respiratórios normais (SRN) e adventícios (SRA), desconhecem-se quais os valores de referência dos sons respiratórios em crianças, o que limita a sua aplicação na prática clínica

Objetivos: Caraterizar e comparar os SRN e os SRA em crianças saudáveis e com IRTI.

Métodos: Estudo descritivo, comparativo e transversal realizado em três instituições. Eram elegíveis crianças diagnosticadas pelo pediatra com IRTI e voluntários para crianças saudáveis. Foram recolhidos dados sócio demográficos, antropométricos e parâmetros cardiorrespiratórios. Os sons respiratórios foram registados com um estetoscópio digital. Foram analisados diversos parâmetros para os SRN: a frequência na intensidade máxima (Fmax), a intensidade máxima (Imax) e a média da intensidade ao longo de toda a faixa de frequência (Imean). Nos SRA foram analisados: a taxa de ocupação por wheezes (Wh%), a média wheezes (Wh), o número e o tipo Wh, a frequência e a localização Wh por região; o número crackles (Cr), o tipo e a frequência Cr, a duração da deflexão inicial, da maior deflexão e dos dois ciclos de deflexão dos Cr. Todos estes dados foram analisados por fase do ciclo respiratório (i.e., inspiração e expiração).

Resultados: Quarenta e nove crianças foram incluídas neste estudo: 25 saudáveis (G1) e 24 com IRTI (G2). A Fmax inspiratória (G1: M 116,1 Hz IQR [107,2-132,4] vs G2: M 118.9Hz IQR [113,2-128,7], p = 0,244) e expiratória (G1: M 107.3Hz IQR [102,9-116,9] vs G2: M 112.6Hz IQR [106,6-122,6], p = 0,083) foi superior nas crianças com IRTI relativamente às crianças saudáveis. A Wh% foi significativamente superior nas crianças com IRTI, relativamente às crianças saudáveis na inspiração (G1: M 0 IQR [0-0,1] vs G2: M 0,2 IQR [0-5,2] p = 0,032) e na expiração (G1: M 0 IQR [0-1,9] vs G2: M 1,5 IQR [0,2-6,7] p = 0,015).

Conclusão: Os sons respiratórios computorizados de crianças saudáveis e com IRTI apresentam diferenças. Os principais resultados indicam que os sons respiratórios normais apresentam uma Fmax maior em crianças com IRTI do que em saudáveis e que Wh% é a característica que mais difere entre os dois grupos.

Keywords Normal respiratory sounds; adventitious respiratory sounds; healthy; Lower respiratory tract infections

Abstract

Background: Lower respiratory tract infections (LRTI) are the main cause of health burden in the first years of age. To enhance the diagnosis and monitoring of infants with LRTI, researchers have been trying to use the large advantages of conventional auscultation. Computerised respiratory sound analysis (CORSA) is a simple method to detect and characterise Normal Respiratory Sounds (NRS) and Adventitious Respiratory Sounds (ARS). However, if this measure is to be used in the paediatric population, reference values have to be established first.

Aim: To compare and characterise NRS and ARS in healthy infants and infants with LRTI.

Methods: A cross-sectional descriptive-comparative study was conducted in three institutions. Infants were diagnosed by the paediatrician as presenting or not presenting an LRTI, healthy volunteers were recruited from the institutions. Socio-demographic, anthropometric and cardio-respiratory parameters were collected. Respiratory sounds were recorded with a digital stethoscope. Frequency at maximum intensity (Fmax), maximum intensity (Imax) and mean intensity (Imean) over the whole frequency range were collected to characterise NRS. Location, mean number, type, duration and frequency were collected to characterise ARS. All analysis was performed per breathing phase (i.e., inspiration and expiration).

Results: Forty nine infants enrolled in this study: 25 healthy infants (G1) and 24 infants with LRTI. Inspiratory Fmax (G1: M 116.1 Hz IQR [107.2-132.4] vs G2: M 118.9Hz IQR [113.2-128.7], p=0.244) and expiratory frequencies (G1: M 107.3Hz IQR [102.9-116.9] vs G2: M 112.6Hz IQR [106.6-122.6], p= 0.083) slightly higher than their healthy peers. Wheeze occupation rate was statistically significantly different between groups in inspiration (G1: M 0 IQR [0-0.1] vs G2: M 0.2 IQR [0-5.2] p= 0.032) and expiration (G1: M 0 IQR [0-1.9] vs G2: M 1.5 IQR [0.2-6.7] p= 0.015), being the infants with LRTI the ones presenting more wheezes.

Conclusion: Computerised respiratory sounds in healthy infants and infants with LRTI presented differences. The main findings indicated that NRS have Fmax higher in infants with LRTI than in healthy infant and Wh% was the characteristic that differ the most between infant with LRTI and healthy infant.

Abbreviations and/or acronyms

ARS – adventitious respiratory sounds
BMI – body mass index
CORSA – computerised respiratory sound analysis
f – frequency
Fmax - frequency at maximum intensity
IDW – initial deflection width
Imax – maximum intensity
Imean - mean intensity
LDW – largest deflection width
LRTI – lower respiratory tract infection
NRS – normal respiratory sounds
RSAT – respiratory sound annotation software
SpO2 – peripheral oxygen saturation
Wh% – wheeze occupation rate
WHO – World Health Organization
2CD – two cycle duration

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1. INTRODUCTION

Lower respiratory tract infections (LRTI) include a wide number of diseases, from acute bronchitis to pneumonia and involve the lower part of the respiratory system from the trachea to the lung parenchyma [1, 2]. These diseases are the main cause of health burden in the first years of age, representing approximately 14% of all hospitalisations in infants below 2 years old [3-5]. In Portugal, 0.3 per 100000 infant died and 2762 were hospitalised in 2013 due to LRTI [6]. These groups of diseases are also the major cause of missed work days by parents [7].

Risk factors for developing LRTI, in addition to host related conditions, include environmental conditions, day care centers, schools and hospitals [7]. The LRTI is defined by the presence of cardinal signs and symptoms such as cough, as the main symptom, sputum, respiratory discomfort/dyspnoea, wheezes and chest discomfort/pain [1, 8-10].

In infants, LRTI are commonly diagnosed by clinical findings where conventional chest auscultation is always included. Chest auscultation is one of the most important and established non-invasive methods, widely used in the assessment and monitoring of infant's respiratory diseases [11, 12]. However, its value has been questioned due to its greater disadvantage, subjectivity [13]. To confirm the diagnosis of pneumonia and monitoring its progress, one of the most common LRTI diseases, radiological findings are commonly accepted as the "gold standard" [2, 14]. Nevertheless, it presents several limitations, such as being unavailable in poor clinical settings, considerable doses of radiation and high levels of inter- and intra-observer subjectivity [15, 16]. Given the burden of LRTI worldwide, the World Health Organization (WHO) has developed a program for the control of respiratory infections with a case management algorithm that relies on symptoms of shortness of breath or cough, increased respiratory rate (≥50 cycles/ minute in infants) and chest in drawing for the diagnosis of paediatric pneumonia [14, 17] This algorithm, in addition to being more simple and economic than radiological methods, is also valuable in reducing mortality (~30%) and morbidity in pneumonia, however it does not address other respiratory diseases of high prevalence in infants, such as

bronchiolitis or asthma [18-21]. Hence, at this point, there is no clinical algorithm to accurately diagnose LRTI in infants and thus new solutions are warrant.

Recently, several measures have been suggested for improving diagnosis of LRTI. Lung ultrasound (LUS) has been suggested as a simple and reliable imaging tool (able to overcome the difficulties presented with radiological methods), to identify pleuro-pulmonary abnormalities, however, it may fail to detect consolidations that do not reach the pleura [22, 23]. The establishment of a definite microbiological diagnosis, using analysis of paired nasopharyngeal aspirate and induced sputum specimens have also been suggested, however observations do not support the routine use of induced sputum analysis for all infants and immediate results are not possible [24].

Another potential measure is computerised auscultation as it is objective (overcomes conventional auscultation subjectivity), requires minimal patient's collaboration, is economic, non-invasive and widely available. Sounds detected from the chest and mouth, are developed in the larger airways as a result of vibrations that are generated due to air velocity and turbulence, and may be classified as normal respiratory sounds (NRS) and adventitious respiratory sounds (ARS) [25]. Normal respiratory sounds are the respiratory associated sound heard over the chest and are most probably generated by air turbulence flow vortices [25]. Changes in the frequency and intensity of NRS may be related with changes in lung volume and in the velocity and direction of airflow [25] and thus, may be a good indicator of respiratory diseases [25-27].

Regarding to ARS, the most commonly studied are wheezes and crackles. Wheezes occur when there is a flow limitation [28]. Crackles are related with the sudden opening or closing of airways, during respiratory cycle, in pathological processes or presence of secretions [28, 29]. Crackles have been most commonly associated with pneumonia, whereas wheezes are often observed in patients with asthma and bronchiolitis [4, 30]. Using Computerised respiratory sound analysis (CORSA), a simple, objective and non-invasive method to detect, characterise and place NRS and ARS within the respiratory cycle [12, 31, 32] it may be possible to enhance diagnosis and monitoring of LRTI, especially in a non-collaborative population such as the paediatric population.

Recently, research has been directed to develop algorithms that allow real-time detection of sounds and interfaces to integrate these information in health professionals clinical and research practice [33, 34]. However, if this measure is to be used in the paediatric population, reference values have to be established to understand what is within or outside the norm [12]. Thus, this study aimed to characterise and compare computerised respiratory sounds in healthy infants and in infants with LRTI under the age of twenty four mouths.

2. METHODS

2.1. Ethics

All procedures were conducted in accordance with the ethical standards of the World Medical Association Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the Research Unit of Health Sciences at the School of Nursing in Coimbra, Portugal (P186-10/2013), and amended for the inclusion of one more hospital and different researchers (P186-12/02/2014) (Annex I). Prior to any data collection, written informed consents were collected from infant's legal representatives [35].

2.2. Study design and participants

This was a cross-sectional descriptive-comparative study conducted to characterise computerised respiratory sounds in paediatrics [36]. One hospital (Cliria Hospital SA), one clinical practice (*Fisiomanual*) and one school group (Oliveirinha school) were invited to participate and after an arranged meeting explaining the purposes of the study, all agreed to participate. Written permission to conduct the study was obtained from all institutions (Annex II).

Healthy infants (G1) and infants with LRTI (G2) aged 0 to 24 months old were recruited. Infants were eligible to participate in the study if they had been diagnosed with a LRTI by a paediatrician. Exclusion criteria were the presence of chronic respiratory diseases, cardiac diseases, neurological impairment and/or significant musculoskeletal disorders that could affect respiratory acoustics. Healthy volunteers were recruited from the three institutions, whilst attending paediatrics' routine appointments in their own doctors. Exclusion

criteria were the same used for infants with LRTI, plus having had an acute respiratory disease within the last month.

2.3. Data collection

Infant's socio-demographic, anthropometric and clinical data were collected with a structured questionnaire answered by parents [37] and completed using the medical notes. The questionnaire captured a holistic perspective of the infants and provided an individual assessment of each participant.

Socio-demographic data included gender and date of birth. Anthropometric data included weight and height measurements to calculate the body mass index. Clinical data included exposure to environmental risk factors, personal and family history of respiratory diseases.

A cardio-respiratory assessment was performed to collect data on i) parents reported respiratory symptoms, such as presence and type of cough (i.e., dry and productive), fever, wheezing and dyspnoea; ii) body inspection to search for cyanosis, changes in face, neck, limbs and chest; iii) tracheal deviations, intercostal, infracostal, suprasternal, supraclavicular and global indrawing, nasal flutter and weeping; iv) peripheral oxygen saturation levels (SpO2) and v) heart and respiratory rates [38].

Dyspnoea was assessed with the modified Wang Score (Annex III) [39]. Evaluation of dyspnoea allows health professionals to understand the perception of breathing discomfort of the subject. Nevertheless, direct reports for the quantification of breathlessness in paediatric subjects appears unsuitable due to difficulties in use verbal expressions and to the inability to express self-perception of breathlessness [40, 41]. Hence, in infants, dyspnoea is described by the physical signs of respiratory distress rather than the expressed perception of breathlessness [41]. The modified Wang Score is an assessment scoring system which comprises the assessment of five clinical signs: wheezing, retractions, peripheral oxygen saturation, respiratory rate and heart rate. Each category is scored as "0″ for normal, "1″ for moderate impairment, "2″ for mild impairment or "3" for severe impairment. Infants with a

normal functioning should have a cumulative score of 0, critically ill and severely distressed infants will have scores closer to 15 [42]. This score, used in the evaluation of neonates and infants, shows a good inter-observer agreement among caregivers [42, 43].

Respiratory sounds were collected using a digital stethoscope (Welch Allyn Master Elite Plus Stethoscope Model 5079-400, New York, USA) connected to an external sound card (Cakewalk UA-25EX UA-25, Boston, USA). The signal was converted with a 24-bit resolution at a sample rate of 44100 samples per second and recorded in .wav format on a laptop computer with the "LungSounds@UA" interface developed to collect respiratory sounds [44].

2.4. Procedures

The structured questionnaire was first applied to characterise the sample in terms of sociodemographic, anthropometric and general clinical characteristics. Then the cardiorespiratory assessment was performed. Most parameters described above were registered after direct observation. Whenever necessary a thermometer (Omron, Eco Temp Smart, MC-341-E) and a pulse oximeter (Nonin, WristOx2™, Model 3150) were used to monitor temperature, peripheral oxygen saturation and heart rate. Respiratory rate was monitored during at least one minute [45]. Dyspnoea was then registered.

Finally, respiratory sounds were collected. Infants' legal representatives were instructed to hold the infant in the upright position [4]. Six anatomical locations were recorded: anterior (at the second intercostal space in mid-clavicular, right and left), lateral (at the fourth or fifth intercostal space on the mid-axillary line, right and left) and posterior (laterally from the paravertebral line and below the scapular angle, right and left) locations [46], using reference points to ensure that the stethoscope was placed on the same anatomical location in each infant. Sounds were recorded during 20 seconds in each location with infants breathing at tidal volume. This recording time ensures that 7 to 10 respiratory cycles were recorded, according to CORSA short-term acquisition guidelines [47]

2.5. Data analysis

A sample size estimation using the GPower 3.1.7 software, was obtained performing a 2- tailed test, with 80% of power and a significance level of 0.05, using wheeze occupation rate (Wh%) values from a previous pilot study [48]. This variable was chosen as Wh% rate is strongly related with the degree of bronchial obstruction and thus, with the severity of the disease [49, 50]. Based on this power calculation a significant difference in Wh% would be detected with at least 60 participants per group.

Descriptive statistics were applied to characterise each group (i.e., socio-demographic and anthropometric data, cardio-respiratory parameters, dyspnoea and respiratory sounds). The distribution of the data was tested with the Shapiro-Wilk, used to low small sample sizes [51]. Independent sample t-tests were used to compare sample characterisation and cardio-respiratory parameters between groups (G1 vs G2).

To simplify the reading and understanding of the respiratory sounds data analysis, two sub-sections have been created (i.e., NRS and ARS).

2.5.1. Analysis of Normal Respiratory Sounds

Power spectra of the NRS signals was analysed based on the methodology proposed by Pasterkamp et al within a frequency band of 100 to 2000 Hz [52]. The sound signal was first analysed into segments of 2048 data points with a 50% overlap of points between successive segments. Then, each segment was windowed with a Hanning function before obtaining power spectral estimates using fast Fourier transformation [52]; crackles and wheezes were first detected and extracted from the signal and only then the characteristics of NRS were calculated, thus only “pure” sound spectrum was assessed. Finally, NRS parameters were automatically extracted from the sounds spectrum, i.e., frequency at maximum intensity (Fmax), maximum intensity (Imax) and mean intensity over the whole frequency range (Imean). All parameters were extracted per breathing phase (i.e., inspiration and expiration). These parameters were chosen as they provide important information about the respiratory system [53]. Mann Whitney U tests were applied to compare NRS

characteristics between groups, to determine whether there is a significant difference in the distributions of the two groups, since they did not follow a normal distribution [54, 55].

2.5.2. Analysis of Adventitious Respiratory Sounds

2.5.2.1. Wheezes Analysis

Wheezes were automatically detected using the interface - Respiratory Sound Annotation Software (RSAT) [56]. This interface uses the algorithm of Taplidou and Hadjileontiadis [57], which is based on the Short-time Fourier transformation [58] to detect wheezes. This algorithm has demonstrated a sensitivity of 99.2%, a specificity of 72.5% and a performance of 84.8% in the automatic detection of wheezes in adult patients with LRTI [59].

The mean number of wheezes was studied as it provides information on the possible presence of obstructive lung disease. The frequency and type of wheeze were analysed as these are important characterisation parameters to identify the source of the wheeze [46]. The wheeze's occupation rate was studied because the proportion of the respiratory cycle occupied by wheezes is associated with the degree of bronchial obstruction [31].

Descriptive statistics were used to asses and characterise the mean number, type (i.e., monophonic or polyphonic), frequency (*f*) and occupation rate (Wh%) of wheezes. These statistics were applied in infants presenting wheezes per respiratory phase and chest location. Mann Whitney U tests were applied to compare wheezes' parameters of healthy infants and infants with LRTI, to determine whether there is a significant difference in the distributions of the two groups, since they did not follow a normal distribution [54, 55].

The statistics were applied in infants presenting wheezes per respiratory phase and chest location.

2.5.2.2. Crackles Analysis

Respiratory Sound Annotation Software was also used for automatic crackles detection [56], as it contains an algorithm based on the combination of

fractal dimension [60-62], box filtering techniques [63], and the crackle established criteria [64, 65].

The mean number of crackles was studied as this variable reflects the severity of the disease process [66]. The variable *f* allows identifying the crackle's source [67]. The type (i.e., fine or coarse), initial deflection width (IDW), largest deflection width (LDW) and two cycle duration (2CD) were collected to characterise crackles [46]. LDW was studied as it has been considered one of the best parameters for diagnostic and monitoring purposes [68].

Descriptive statistics were used to asses and characterise mean number, type, *f*, IDW, LDW and 2CD of crackles. Fisher's exact test was used to investigate the groups' differences on the number of infants presenting crackles, as it is used to assess the significance of a difference between the proportions in two groups; Mann Whitney U tests were applied to compare crackle's parameters of healthy infants and infants with LRTI, as it enables to determine whether there is a significant difference in the distributions of two groups when they do not follow a normal distribution [54, 55]. The statistics were applied in infants presenting crackles per respiratory phase and chest location.

Visual and hearing inspection of each sound file was performed by the researcher to confirm algorithms' annotation.

All sound files were processed based on published algorithms implemented in Matlab 2009 (The MathWorks, Inc, Natick, MA, USA). All statistical analysis was conducted in the SPSS Statistics version 19.0 for Windows. The level of significance considered was set at $p< 0.05$.

3. RESULTS

Sixty-one infants met the criteria to be included in the study. Eight legal representatives refused the participation of their infant due to: time constrictions (n=3) and infant's agitation (n=5). Four participants were later excluded from data analysis due to the poor quality of the sound recording (i.e., movement artefacts and voice sounds). In total 49 infants were enrolled in this study: 25

healthy infants (G1) and 24 infants with LRTI (G2) aged 0 to 2 years old (Figure 1).

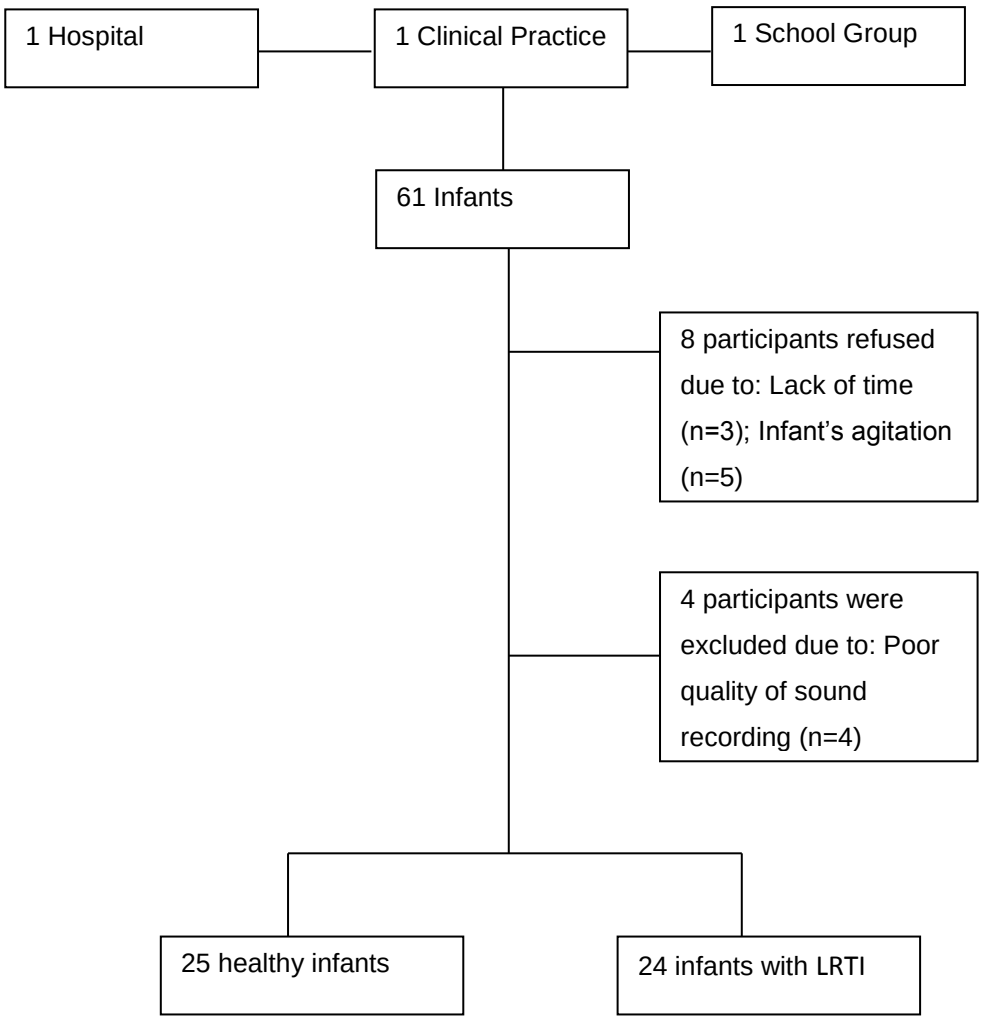

Figure 1 - Sample recruitment process

3.1. Sample characterisation

Infants mean age was 15.6±9.2 months (G1=14.3±9.9; G2=16.9±8.4). Twenty-five infants were healthy (12 male, 48%) and twenty-four presented LRTI (16 male, 66.7%). There were no significant differences between groups' general characteristics (Table 1).

Table 1 – Sample's Characterisation.

Variables	Groups	G1 Healthy (n=25)	G2 LRTI (n=24)	p-value
Gender	Female	13 (52)	8 (33.3)	0.191
	Male	12 (48)	16 (66.7)	
Age, months (Mean±SD)		14.3±9.9	16.9±8.4	0.271
BMI for age/percentile		68 (54)	54(70)	0.501
Environmental Risk Factors		13 (48)	10 (41.7)	0.473
	Carpets	8	7	
	Humidity	0	2	
	Animals	10	4	
Family Comorbidities		14 (56)	13 (54.2)	0.898
	Sinusitis (parents)	3	6	
	Rhinitis (parents)	5	5	
	Asthma (grandparents)	0	1	
	Asthma (parents)	4	2	
Parental Smoking		1 (4)	1 (4.2)	0.977

Results are presented as number (percentage), unless otherwise stated.

LRTI: lower respiratory tract infection; BMI: body mass index.

3.2. Cardio-respiratory assessment

Groups presented similar SpO_2 (G1: 97.4±2.7% vs G2: 95.7±2.4%; p=0.183) and respiratory rate (G1: 37.5±11.7 cpm vs G2: 39.1±11,6 cpm, p=0.586) (Table 2). Infants with LRTI had significantly higher heart rate (G1: 121.8±20.3 bpm vs G2: 132.3±17.3 bpm, p=0.027) and body temperature (G1: 36.2±0.4 ºC vs G2: 36.6±0.5 ºC; p=0.021) than healthy infants. The group with LRTI showed significantly more respiratory distress than the healthy group (G1: M 1 IQR 2 vs G2: M 2 IQR 3; p= 0.016) (Table 2).

The most common symptom in infants with LRTI was productive cough (G2: n=21, 87.5%), followed by fever (G2: n=14, 58.3%), increased respiratory rate (G2: n=11, 45.8%) and wheezing (G2: n=9, 37.5%) (Table 2).

Table 2- Sample's cardio-respiratory assessment

Variables	Groups	G1 Healthy (n=25)	G2 LRTI (n=24)	p-value
SpO2 (%)		96.3±2.7	97.3±2.5	0.183
Heart rate (bpm)		121.8±20.4	132.4±17.3	0.027*
Respiratory rate (cpm)		37.5±11.7	39.1±11.6	0.556
Body Temperature (ºC)		36.2±0.4	36.6±0.5	0.021*
Signs/ Symptoms [n(%)]		5 (20)	24 (100)	0.007*
	Cough (dry)	0	1	
	Cough (productive)	0	21	
	Fever	3	14	
	Increased RR	1	11	
	Wheezing	0	9	
	Rhinorrhea	0	1	
Wang Score (M [IQR])		1 [0.3-2.8]	2 [1-4]	0.016*

Results are presented as mean±standard deviation, unless otherwise stated.

LRTI: lower respiratory tract infection; SpO_2: peripheral oxygen saturation; bpm: beats per minute; cpm: cycles per minute; M: median; IQR: inter-quartile range; *p<0.05

3.3. Normal respiratory sounds

Considering all chest locations, infants with LRTI presented inspiratory (G1: M 116.1 Hz IQR [107.2-132.4] vs G2: M 118.9Hz IQR [113.2-128.7], p=0.244) and expiratory Fmax (G1: M 107.3Hz IQR [102.9-116.9] vs G2: M 112.6Hz IQR [106.6-122.6], p= 0.083) slightly higher than healthy peers, however this values were not significantly different. The Imax was significantly different in expiration (G1: M 49.9dB IQR [44.9-54.6] vs G2: M 50.8dB IQR [47.6-53.1], p=0.042), being higher in infants with LRTI.

Considering the individual analysis of the six chest locations, significant differences were found between healthy infants and infants with LRTI at lateral and posterior right locations. At lateral right significant differences were found, being higher in the infants with LRTI, in inspiration for the Imax (G1: M 42.4 IQR [39.6-51.7]vs G2: M 50.1 IQR [46.5-56.1, p= 0.043) and Imean (G1: M 15.6 IQR

[12.9-20.3] vs G2: M 20.2 IQR [18.8-22.5], p= 0.046) and in expiration for Imax (G1: M 41.4 IQR [37.4-48.3] vs G2: M 50.071 IQR [46.5-56.0], p=0.018) and Imean (G1: M 14.1 IQR [10.3-17.9] vs G2: M 17.6 IQR [14.3-19.1], p=0.019). The posterior right location was significantly different, higher in infants with LRTI; in inspiration for the Imax (G1: M 45.9 IQR [44.2-49.3] vs G2: M 51.7 IQR [49.1-59.2], p=0.020) and Imean (G1: M 16.3 IQR [15.4-18.9] vs G2: M 21.3 IQR [15.6-23.1], p= 0.038); in expiration for the Imax (G1: M 45.394 IQR [43.6-49.8] vs G2: M 51.5 IQR [47.4-53.4], p=0.049) (Table 3).

Table 3- Normal respiratory sounds parameters during inspiration and expiration, at a frequency band width of 100-2000 Hz

Chest Locations	Position in the BC	Variables	G1 Healthy (n=25)	G2 LRTI (n=24)	p-value
All locations	Inspiration	Fmax (Hz)	116.1 [107.2-132.4]	118.9 [113.2-128.7]	0.244
		Imax (dB)	49.9 [44.9-54.6]	52.9 [49.7-56.1]	0.083
		Imean (dB)	17.8[13.7-21.6]	19.7 [15.6-22.2]	0.304
	Expiration	Fmax (Hz)	107.3 [102.9-116.9]	112.6 [106.6-122.6]	0.083
		Imax (dB)	49.9 [44.9-54.6]	50.8 [47.6-53.1]	0.042*
		Imean (dB)	14.3 [11.6-18.2]	16.9 [13.8-18.3]	0.117
Anterior Right	Inspiration	Fmax (Hz)	108.4 [102.9-127.1]	113.3 [105.5-141.7]	0.372
		Imax (dB)	46.6[44.7-52.9]	51.3 [48.3-54.6]	0.090
		Imean (dB)	18.3 [12.9-22.1]	19.7 [17.4-22.5]	0.310
	Expiration	Fmax (Hz)	105.1 [102.3-111.4]	107.5 [104.8-123.5]	0.240
		Imax (dB)	46.4 [44.7-52.9]	48.4 [45.7-52.6]	0.125
		Imean (dB)	13.8 [9.4-18.5]	17.4 [13.4-18.4]	0.184
Anterior Left	Inspiration	Fmax (Hz)	105.7 [103.2-118.9]	106.8[104.5-115.1]	0.855
		Imax (dB)	53.1 [48.4-58.2]	54.3 [46.7-61.2]	0.539
		Imean (dB)	17.8 [14.7-21.6]	22.2 [16.7-24.9]	0.159
	Expiration	Fmax (Hz)	103.2 [102.3-107.9]	104.3 [102.3-109.1]	0.692
		Imax (dB)	53.1 [49.1-55.3]	56.2 [46.3-60.8]	0.523
		Imean (dB)	15.2 [12.1-18.7]	17.6 [13.6-22.8]	0.186
Lateral Right	Inspiration	Fmax (Hz)	116.4 [103.7-153.7]	139.9 [105.6-179.1]	0.258
		Imax (dB)	42.439 [39.6-51.7]	50.1 [46.5-56.1]	0.043*
		Imean (dB)	15.6 [12.9-20.3]	20.2 [18.8-22.5]	0.046*
	Expiration	Fmax (Hz)	109.9 [102.7-128.1]	116.3 [104.9-137.8]	0.189
		Imax (dB)	41.4 [37.4-48.3]	50.1 [46.5-56.1]	0.018*
		Imean (dB)	14.1 [10.3-17.9]	17.6 [14.3-19.1]	0.019*
Lateral	Inspiration	Fmax (Hz)	105.7 [103.3-134.7]	115.7 [106.9-129.2]	0.273

Left		Imax (dB)	52.1 [45.5-56.1]	51.1 [44.3-54.5]	0.973
		Imean (dB)	19.9 [14.4-22.2]	18.6 [17.1-22.2]	0.956
	Expiration	Fmax (Hz)	112.4 [103.6-122.6]	107.7 [102.7-124.3]	0.510
		Imax (dB)	50.8 [44.7-55.5]	53.4 [46.1-57.6]	0.426
		Imean (dB)	14.9 [12.3-19.5]	16.8 [15.8-19.1]	0.365
Posterior Right	Inspiration	Fmax (Hz)	109.7[103.1-140.2]	112.4 [107.7-123.4]	0.585
		Imax (dB)	45.8 [44.2-49.3]	51.7 [49.1-59.2]	0.020*
		Imean (dB)	16.3 [15.4-18.9]	21.3 [15.6-23.1]	0.038*
	Expiration	Fmax (Hz)	105.1 [102.3-118.4]	114.2 [104.3-135.9]	0.286
		Imax (dB)	45.4 [43.6-49.8]	51.5 [47.4-53.3]	0.049*
		Imean (dB)	14.8 [10.8-15.9]	16.4 [13.3-17.6]	0.156
Posterior Left	Inspiration	Fmax (Hz)	125.7 [105.4-144.9]	115.7 [105.2-169.8]	0.904
		Imax (dB)	48.9 [45.9-55.2]	53.2[47.1 [55.4]	0.283
		Imean (dB)	18.1 [15.2-20.7]	20.8 [18.2-23.4]	0.137
	Expiration	Fmax (Hz)	107.8 [103.7]	104.7 [103.3-124.5]	0.534
		Imax (dB)	47.2 [43.5-51.2]	49.6 [47.3-52.3]	0.193
		Imean (dB)	14.2 [11.7-17.5]	17.4 [12.5-19.4]	0.301

Results are median [inter-quartile range], unless otherwise stated.

LRTI: lower respiratory tract infection; BC: breathing cycle Fmax: frequency at maximum intensity; Imax: maximum intensity; Imean: mean intensity; *p<0.05

3.4. Adventitious respiratory sounds

To simplify the interpretation of ARS results, two sub-sections have been created (i.e., “wheezes” and “crackles”).

3.4.1. Wheezes

Significant differences were not found between G1 and G2 for the number of infants with wheezes (Table 4). In general, few participants (n=17) presented this type of ARS. Considering all chest locations, infants with LRTI presented a significantly higher number of inspiratory (G1: M 0.0 IQR [0.0-0.1] vs G2: 0.1 IQR [0.0-0.1] p=0.031) and expiratory wheezes (G1: M 0.1 IQR [0.0-0.2] vs G2: M 0.1 IQR [0.1-0.3] p=0.400) than their healthy peers, however the latest did not reach statistical significance. They also presented, although not statistically significant, a higher number of expiratory monophonic wheezes (G1: M 0.1 IQR [0.0-0.2] vs G2: M 0.1 IQR [0.1-0.3] p=0.308). Wh% was also significantly higher in infants with LRTI than in healthy infants, both in inspiration (G1: M 0

IQR [0-0.1] vs G2: M 0.2 IQR [0-5.2] p= 0.032) and expiration (G1: M 0 IQR [0-1.9] vs G2: M 1.5 IQR [0.2-6.7] p= 0.015) .

The individual analysis of the six chest locations revealed significant differences in the expiratory Wh% at lateral right (G1: M 2.4 IQR [1.5-3.7] vs G2: M 8.1 IQR [3.9-28.5] p=0.028) and posterior left (G1: M 6.6 IQR [3.4-15.2] vs G2: M 19.2 IQR [14.7-62.2] p=0.022), where infants with LRTI presented higher Wh% than healthy infants. Comparisons for the wheezes' parameters were not possible to perform at the lateral right and left locations for inspiration, as wheezes were not present in healthy infants (Table 4).

Monophonic wheezes were the most common type of wheezes found in both healthy infants and infants with LRTI (Table 4).

Table 4 - Wheezes' parameters in healthy infants and infants with LRTI during inspiration and expiration

Chest Locations	Position in the BC	Variables	G1 Healthy (n=25)	G2 LRTI (n=24)	p-value
All Locations	**Inspiration**	No of infant with Wh [n(%)]	6(24)	11(46)	
		No. of Wh	0.0 [0.0-0.1]	0.1 [0.0-0.4]	0.031*
		No. of monophonic Wh	0.0 [0.0-0.1]	0.1 [0.0-0.4]	0.039*
		No. of polyphonic Wh	0	0 [0-0.1]	0.289
		Wh%	0 [0-0.1]	0.2 [0-5.2]	0.032*
		f	189.1 [128.5-351.1]	186.3 [137.3-339.9]	0.880
	Expiration	No of infant with Wh [n(%)]	12(48)	17(71)	
		No. of Wh	0.1 [0.0-0.2]	0.1 [0.1-0.3]	0.400
		No. of monophonic Wh	0.1 [0.0-0.2]	0.1 [0.1-0.3]	0.308
		No. of polyphonic Wh	0	0 [0-0.0]	0.600
		Wh%	0 [0-1.9]	1.5 [0.2-6.7]	0.015*
		f	232.1 [162.8-319.6]	166.1 [136.9-579.0]	0.451
Anterior Right	**Inspiration**	No of infant with Wh	3(12)	4(17)	

		[n(%)]			
		No. of Wh	0.1 [0.0-0.1]	0.2 [0.1-0.6]	0.050*
		No. of monophonic Wh	0.1 [0.0-0.1]	0.2 [0.1-0.5]	0.050*
		No. of polyphonic Wh	0	0 [0-0.1]	0.386
		Wh%	3.1 [2.3-3.1]	4.4 [2.6-12.1]	0.480
		f	191.1 [102.3-191.1]	219.0 [155.1-409.9]	0.986
	Expiration	No of infant with Wh [n(%)]	2(8)	7(29)	
		No. of Wh	0.2 [0.0-0.2]	0.3 [0.2-0.6]	0.557
		No. of monophonic Wh	0.2 [0.0-0.2]	0.2 [0.2-0.6]	0.557
		No. of polyphonic Wh	0	0	0.593
		Wh%	5.5 [1.2-5.5]	5.6 [1.9-18.4]	0.558
		f	133.1 [113.1-133.1]	250.4 [143.1-930.4]	0.242
Anterior Left	**Inspiration**	No of infant with Wh [n(%)]	2(8)	4(17)	
		No. of Wh	0.4 [0.1-0.4]	0.1 [0.1-0.5]	0.812
		No. of monophonic Wh	0.4 [0.1-0.4]	0.1 [0.1-0.5]	0.812
		No. of polyphonic Wh	0	0	1.000
		Wh%	13.7 [2.3-13.7]	2.9 [2.1-19.7]	0.814
		f	133.2 [129.2-133.2]	176.3 [115.1-230.5]	0.481
	Expiration	No of infant with Wh [n(%)]	8(32)	8(33)	
		No. of Wh	0.1 [0.1-0.3]	0.1 [0.1-0.6]	0.440
		No. of monophonic Wh	0.1 [0.0-0.3]	0.1 [0-0.3]	0.903
		No. of polyphonic Wh	0	0 [0-0.1]	0.324
		Wh%	2.3 [1.6-6.7]	3.9 [1.2-9.7]	0.462
		f	160.2 [143.5-314.9]	143.7 [118.9-405.3]	0.967
Lateral Right	**Inspiration**	No of infant with Wh [n(%)]	0(0)	3(13)	
		No. of Wh	N/A	0.1[0.1-0.1]	N/A
		No. of	N/A	0.1 [0.1-0.1]	N/A

		monophonic Wh			
		No. of polyphonic Wh	N/A	0	N/A
		Wh%	N/A	3.9 [1.7-3.9]	N/A
		f	N/A	215.3 [123.7-215.3]	N/A
	Expiration	No of infant with Wh [n(%)]	5(20)	5(21)	
		No. of Wh	0.1 [0.1-0.1]	0.3 [0.1-0.7]	0.093
		No. of monophonic Wh	0.1 [0.1-0.1]	0.1 [0.0-0.4]	0.528
		No. of polyphonic Wh	0	0 [0-0.5]	0.317
		Wh%	2.4 [1.5-3.7]	8.1 [3.9-28.5]	0.028*
		f	357.5 [226.4-520.5]	230.9 [162.2-1041.1]	0.754
Lateral Left	**Inspiration**	No of infant with Wh [n(%)]	0(0)	2(8)	
		No. of Wh	N/A	0.3 [0.1-0.3]	N/A
		No. of monophonic Wh	N/A	0.3 [0.1-0.3]	N/A
		No. of polyphonic Wh	N/A	0	N/A
		Wh%	N/A	6.5 [4.9-6.5]	N/A
		f	N/A	760.6 [304.7-760.6]	N/A
	Expiration	No of infant with Wh [n(%)]	7(28)	5(21)	
		No. of Wh	0.1 [0.1-0.1]	0.2 [0.1-0.4]	0.087
		No. of monophonic Wh	0.1 [0.1-0.1]	0.1 [0.1-0.3]	0.465
		No. of polyphonic Wh	0	0 [0-0.1]	0.081
		Wh%	2.4 [1.9-2.8]	2.9 [2.2-14.5]	0.223
		f	193.8 [137.3-462.9]	460.9 [144.1-1121.2]	0.465
Posterior Right	**Inspiration**	No of infant with Wh [n(%)]	1(4)	3(13)	
		No. of Wh	0.1 [0.1-0.1]	0.9 [0.1-0.9]	0.655
		No. of monophonic Wh	0.1 [0.1-0.1]	0.5 [0-0.5]	0.655
		No. of	0.1 [0.1-0.1]	0.3 [0.1-0.3]	0.180

		polyphonic Wh			
		Wh%	7.2 [7.2-7.2]	17.2 [11.1-17.2]	0.180
		f	218.1 [218.1-218.1]	265.3 [114.4-265.3]	0.655
	Expiration	No of infant with Wh [n(%)]	3(12)	7(29)	
		No. of Wh	0.1 [0.1-0.1]	0.4 [0.1-0.6]	0.170
		No. of monophonic Wh	0.1 [0.0-0.1]	0.30 [0.1-0.6]	0.134
		No. of polyphonic Wh	0	0 [0-0.1]	0.708
		Wh%	3.3 [1.5-3.3]	8.7 [1.2-15.6]	0.305
		f	218.5 [203.7-218.5]	166.1 [129.2-425.3]	0.569
Posterior Left	**Inspiration**	No of infant with Wh [n(%)]	1(4)	2(8)	
		No. of Wh	0	0.5 [0.3-0.5]	0.221
		No. of monophonic Wh	0	0.5 [0.3-0.5]	0.221
		No. of polyphonic Wh	0	0	1.000
		Wh%	2.7 [2.7-2.7]	31.3 [6.5-31.3]	0.221
		f	302.1 [302.1-302.1]	175.2 [164.2-175.2]	0.221
	Expiration	No of infant with Wh [n(%)]	7(28)	6(25)	
		No. of Wh	0.2 [0.1-0.6]	0.6 [0.5-1.1]	0.045*
		No. of monophonic Wh	0.2 [0.1-0.5]	0.3 [0.1-0.9]	0.519
		No. of polyphonic Wh	0.1 [0-0.1]	0.2 [0-0.5]	0.498
		Wh%	6.6 [3.4-15.2]	19.2 [14.7-62.2]	0.022*
		f	179.7 [120.7-193.8]	139.8 [119.1-261.4]	0.567

Results are presented as median [inter-quartile range], unless otherwise stated.

LRTI: lower respiratory tract infection; BC: breathing cycle; N/A: not applicable; Wh: Wheezes; WH%: wheeze occupation rate; *f*: frequency; *p<0.05

3.4.2. Crackles

Considering all chest locations, infants with LRTI had a higher number of inspiratory crackles (G1: M 0.2 IQR [0.1-0.3] vs G2: M 0.5 IQR [0.1-1.2], p=0.027) than healthy infants.

The individual analysis of the six chest locations showed significant differences in the expiratory frequency at anterior right site (G1: M 210.2 IQR [202.7-210.2] vs G2: M 143.9 IQR [135.3-163.4], p=0.032). Comparisons of crackles' parameters were not possible to perform at anterior right, lateral right and left and posterior right locations for inspiration and anterior left for inspiration and expiration, because healthy infants did not present crackles in these chest locations (Table 5).

Significant differences were not found between G1 and G2 for the number of infants with crackles and crackles' number, type and 2CD, per respiratory phase.

Table 6 - Crackles' parameters in healthy infants and infants with LRTI during inspiration and expiration.

Chest Locations	Position in the BC	Variables	G1 Healthy (n=25)	G2 LRTI (n=24)	p-value
All Locations	**Inspiration**	No of infant with Cr [n(%)]	16(64)	18(75)	
		No. of Cr	0.2 [0.1-0.3]	0.5 [0.1-1.2]	0.027*
		No. of coarse Cr	0.1 [0.1-0.2]	0.3 [0.1-0.7]	0.043*
		No. of fine Cr	0.1[0.0-0.1]	0.1 [0-0.3]	0.402
		IDW	3.4 [2.9-4.1]	3.3 [2.6-4.8]	1.000
		LDW	2.8 [2.5-3.1]	2.8 [2.5-3.3]	0.991
		2CD	13.2 [11.6-14.6]	13.4 [10.4-15.4]	0.863
		f	157.2 [134.6-220.7]	148.9 [97.5-190.1]	0.518
	Expiration	No of infant with Cr [n(%)]	17(68)	20(83)	
		No. of Cr	0.5 [0.4-0.9]	0.8 [0.3-1.3]	0.393
		No. of coarse Cr	0.4 [0.2-0.7]	0.5 [0.1-1.1]	0.522
		No. of fine Cr	0.1 [0.1-0.2]	0.2 [0-0.4]	0.866

		IDW	3.5 [3.2-4.2]	4.1 [3.3-4.7]	0.180
		LDW	2.8 [2.6-3.1]	2.7 [2.5-3.3]	0.692
		2CD	12.3 [11.2-13.4]	13.1 [11.4-14.9]	0.272
		f	189.2 [123.3-276.9]	140.4 [98.9-169.1]	0.059
Anterior Right	**Inspiration**	No of infant with Cr [n(%)]	0(0)	4(17)	
		No. of Cr	N/A	1.9 [1.3-4.3]	N/A
		No. of coarse Cr	N/A	0.9 [0.5-1.9]	N/A
		No. of fine Cr	N/A	0.9 [0.2-3.1]	N/A
		IDW	N/A	2.7 [2.2-5.7]	N/A
		LDW	N/A	2.8 [2.3-3.2]	N/A
		2CD	N/A	10.1 [8.9-14.8]	N/A
		f	N/A	154.9[104.2-177.6]	N/A
	Expiration	No of infant with Cr [n(%)]	2(8)	10(42)	
		No. of Cr	1.2 [1.2-1.2]	1.7 [1.2-2.3]	0.283
		No. of coarse Cr	0.9 [0.9-0.9]	1.3 [1.1-1.9]	0.105
		No. of fine Cr	0.3 [0.2-0.3]	0.3[0.1-0.5]	0.747
		IDW	3.2 [2.9-3.2]	3.8 [3.5-4.1]	0.133
		LDW	2.8 [2.7-2.8]	3.1 [2.8-3.2]	0.283
		2CD	12.4 [11.4-12.4]	13.4 [12.1-14.5]	0.390
		f	210.2 [202.7-210.2]	143.9 [135.3-163.4]	0.032*
Anterior Left	**Inspiration**	No of infant with Cr [n(%)]	0(0)	3(13)	
		No. of Cr	N/A	1.4 [1.2-1.4]	N/A
		No. of coarse Cr	N/A	0.9 [0.8-0.9]	N/A
		No. of fine Cr	N/A	0.6[0.3-0.6]	N/A
		IDW	N/A	3.3 [2.9-3.3]	N/A
		LDW	N/A	3.0 [2.3-3.0]	N/A
		2CD	N/A	13.1 [1.1-13.1]	N/A
		f	N/A	137.9 [135.9-137.9]	N/A
	Expiration	No of infant with Cr [n(%)]	0(0)	5(21)	
		No. of Cr	N/A	3.3 [2.1-4.7]	N/A
		No. of coarse Cr	N/A	2.0 [1.2-4.2]	N/A
		No. of fine Cr	N/A	0.6 [0.5-1.3]	N/A
		IDW	N/A	3.5 [3.1-4.1	N/A
		LDW	N/A	2.9 [2.4-3.1]	N/A
		2CD	N/A	12.9 [11.2-14.8]	N/A

		f	N/A		N/A
Lateral Right	**Inspiration**	No of infant with Cr [n(%)]	0(0)	3(13)	
		No. of Cr	N/A	3.0 [1.6-3.0]	N/A
		No. of coarse Cr	N/A	1.4 [1.3-1.4]	N/A
		No. of fine Cr	N/A	0.4 [0-0.4]	N/A
		IDW	N/A	4.1 [3.4-4.1]	N/A
		LDW	N/A	3.1 [2.2-3.1]	N/A
		2CD	N/A	14.1 [9.1-14.1]	N/A
		f	N/A	144.9 [106.5-144.9]	N/A
	Expiration	No of infant with Cr [n(%)]	6(24)	3(13)	
		No. of Cr	1.4 [1.2-1.9]	2.3 [1.1-2.3]	0.606
		No. of coarse Cr	1.2 [0.9-1.6]	0.6 [0.3-0.6]	0.517
		No. of fine Cr	0.3 [0.1-0.4]	0.7 [0-0.7]	0.606
		IDW	3.6 [2.9-4.2]	1.7 [1.4-1.7]	0.439
		LDW	2.9 [2.4-3.2]	2.2 [1.8-2.2]	0.606
		2CD	13.6 [11.1-14.4]	7.5 [6.9-7.5]	0.439
		f	148.3 [127.2-296.2]	234.3 [105.1-234.3]	0.796
Lateral Left	**Inspiration**	No of infant with Cr [n(%)]	0(0)	2(8)	
		No. of Cr	N/A	1.6[1.3-1.6]	N/A
		No. of coarse Cr	N/A	0.8 [0.2-0.8]	N/A
		No. of fine Cr	N/A	0.9 [0-0.9]	N/A
		IDW	N/A	3.2 [2.1-3.2]	N/A
		LDW	N/A	2.7 [2.1-2.7]	N/A
		2CD	N/A	11.2 [7.5-11.2]	N/A
		f	N/A	205.2 [134.5-205.2]	N/A
	Expiration	No of infant with Cr [n(%)]	2(8)	4(17)	
		No. of Cr	1.3 [1.2-1.3]	2.8 [1.1-7.9]	1.000
		No. of coarse Cr	1.1 [0.8-1.1]	2.3 [1.1-7.4]	0.355
		No. of fine Cr	0.3 [0.1-0.3]	0.3 [0.1-0.8]	0.643
		IDW	3.5 [3.1-3.5]	4.2 [4.0-4.5]	0.355
		LDW	2.8 [2.5-2.8]	3.3 [3.1-3.5]	0.165
		2CD	12.5 [11.2-12.5	15.1 [13.1-15.4]	0.165
		f	203.3 [143.9-203.3]	126.6 [120.3-132.7]	0.064
Posterior Right	**Inspiration**	No of infant with Cr	0(0)	2(8)	

		[n(%)]			
		No. of Cr	N/A	2.3 [2.3-2.3]	N/A
		No. of coarse Cr	N/A	1.1 [0.8-1.1]	N/A
		No. of fine Cr	N/A	1.3 [1.0-1.3]	N/A
		IDW	N/A	3.3[2.4-3.3]	N/A
		LDW	N/A	2.3 [2.1-2.3]	N/A
		2CD	N/A	10.3 [9.4-10.3]	N/A
		f	N/A	174.2 [149.1-174.2]	N/A
	Expiration	No of infant with Cr [n(%)]	3(12)	3(13)	
		No. of Cr	1.3 [1.1-1.3]	1.9 [1.3-1.9]	0.513
		No. of coarse Cr	0.9 [0.6-0.9]	1.5 [1.0-1.5]	0.513
		No. of fine Cr	0.4 [0.1-0.4]	0.4 [0.3-0.4]	0.827
		IDW	3.3 [2.6-3.3]	3.5 [3.3-3.5]	0.275
		LDW	3.1 [2.3-3.1]	2.3 [1.7-2.3]	0.127
		2CD	13.3 [10.5-13.3]	11.5 [8.2-11.5]	0.275
		f	137.8 [120.6-137.8]	224.9 [147.9-224.9]	0.127
Posterior Left	**Inspiration**	No of infant with Cr [n(%)]	14(56)	9(38)	
		No. of Cr	0.3 [0.1-0.7]	0.6[0.3-1.4]	0.207
		No. of coarse Cr	0.2 [0.1]	0.4 [0.1-0.8]	0.395
		No. of fine Cr	0.1 [0-0.2]	0.8 [0-0.4]	0.645
		IDW	3.6 [2.4-4.2]	2.8 [2.1-4.6]	0.682
		LDW	3.3 [2.9-3.5]	2.8 [2.4-3.3]	0.219
		2CD	13.9 [12.9-15.9]	149.9 [114.9-167.9]	0.329
		f	139.2 [124.8-148.1]	149.9 [114.9-167.9]	0.461
	Expiration	No of infant with Cr [n(%)]	14(56)	17(71)	
		No. of Cr	0.5 [0.4-0.9]	0.9[0.2-1.2]	0.475
		No. of coarse Cr	0.4 [0.2-0.7]	0.5 [0.1-1.1]	0.662
		No. of fine Cr	0.2 [0.1-0.2]	0.1 [0-0.4]	0.937
		IDW	3.4 [3.2-3.9]	4.1 [3.3-4.7]	0.169
		LDW	2.7 [2.5-2.9]	2.7 [2.4-3.2]	0.662
		2CD	12.2 [10.9-13.2]	12.8 [11.2-14.8]	0.421
		f	209.4 [155.5-288.8]	145.9 [99.1-175.8]	0.057

Results are presented as median [inter-quartile range], unless otherwise stated.

LRTI: lower respiratory tract infection; BC: Breathing cycle; N/A: not applicable; Cr: Crackles; IDW: initial deflection width; LDW: largest deflection width; 2CD: two cycle duration; *f*: frequency; *p<0.05

4. DISCUSSION

This study has shown that computerised respiratory sounds in healthy infants and infants with LRTI present differences. The main findings indicated that i) NRS have an Fmax higher in infants with LRTI than in healthy infants and ii) Wh% was the characteristic that differed the most between infants with LRTI and healthy infants.

Regarding groups' general characteristics, no significant differences were found in the cardio-respiratory assessment for respiratory rate and SpO_2. Increased respiratory rate has been reported as a signal commonly observed in patients with LRTI [69]. Nevertheless, the low severity of the LRTI in the sample included in this study and the reduced number of infants with pneumonia may explain the lack of differences found in these parameters between the two groups.

The NRS were analysed in a frequency band between 100 to 2000 Hz, and for both groups the main respiratory sound energy was found at about 100 Hz. Although no significant differences were found for NRS parameters, some trends appeared to exist. In infants with LRTI, respiratory sounds intensity showed a maximum during inspiration at about 118 Hz and in expiration approximately at 112 Hz. These values were slightly higher than those found in healthy infants Fmax during inspiration occurred at 116Hz and during expiration at 107 Hz). The literature has already demonstrated that the Fmax, in acute asthmatic infants, increased when compared with values of healthy infants [70, 71]. This might suggest that, similar to infants with asthma, infants with LRTI also present some degree of air flow obstruction resulting from bronchoconstriction. Nevertheless, more studies in infants with LRTI are needed to confirm this finding. According to the literature, healthy infants present respiratory sound power between 100 and 300 Hz [4],which is in line with the results of the present study.

Considering all chest locations, the normal respiratory sound intensity in infants with LRTI (both at inspiration and expiration) presented an Imean between 16 to 19 dB respectively, similarly to those found in healthy infants

(inspiration of 17 dB, expiration of 16 dB). It has been recognised that most of the respiratory sound intensity is between 17.7 ± 3.9 dB in infants [52, 72]. These results showed that infants with LRTI presented a higher respiratory sound intensity than their healthy peers. The sample studied presented a low severity of the LRTI, which may justify the lack of significant differences in the Fmax, Imax and Imean of respiratory sounds. When chest locations were analysed individually, significant differences were found in the Imean of respiratory sound between healthy infants and infants with LRTI at lateral and posterior right locations. All significant differences were at the right locations; this could be potentially related with local of injuries, however this information could not be collected because infants did not perform radiological techniques. Future studies could establish this relationship.

Also, to analyse NRS, crackles and wheezes were first detected and extracted from the signal and only then the characteristics of NRS were calculated, thus only “pure” sound spectrum was assessed.

The ARS were found in healthy infants and infants with LRTI; however ARS parameters varied between groups. Wheezes were observed in approximately half of the number of infants (70%) with more expression in the LRTI group (≈ +20%). Wheezes are generated by the oscillation of narrowed airway walls due to flow constrictions [4, 28] and have been extensively used as an indicator of airway obstruction in infants [27, 57]. Infants with LRTI showed a higher number of wheezes and Wh% in expiration than their peers. It is known that Wh% has a relationship with the number of wheezes detected [73] and that the severity of airway obstruction determines wheeze’s number, thus Wh% are related with the severity of the disease [49, 50]. In the present study, infants with LRTI present 2.8-31.3% Wh%. These values and the fact that wheezes were mainly expiratory, monophonic and with low frequency, supports the results of mild severity (score≤3) found with the modified Wang Score and confirmed by the literature in infants with LRTI in the community [74].

The number of crackles, both inspiratory and expiratory, was higher in infants with LRTI than in healthy infants. Crackles are explosive and discontinuous sounds which can occur in both respiratory phases [75] and the

number of crackles presented in a respiratory cycle is an important indicator of the severity of respiratory pathologies [65, 66]. In infants with LRTI, inspiratory crackles may have occurred by the sudden open of the closed airways, due to changing in the elastic stress and expiratory crackles may have been caused by sudden airway closure, in more proximal locations [66, 74, 76-79]. In healthy infants the presence of crackles may be justified by the airways collapse at higher volumes [12, 65, 66, 76].

The mean number of crackles, per respiratory cycle, found in infants with LRTI was between 0.17 and 0.78, lower than the results of the available studies assessing crackles parameters in infants [42, 48]. Differences between healthy and infants with LRTI, in the mean number of crackles, were observed in both respiratory phases of the present study. Crackles are a common ARS in infants with pneumonia [80], however they are not frequently present in other common LRTI such as bronchiolitis and wheezing syndrome [69, 81]. In this study only 12.5% (n=3) of the infants present pneumonia, thus few infants with LRTI presented crackles.

Crackles' analysis is based in their position in the respiratory cycle and duration which informs about the lung pathological process and the place within the lungs of crackles occurrence [65, 66]. Both groups had more crackles in distal locations, and coarse crackles were the most common type of crackles founded. In healthy infants, the presence of some crackles were probably explained by the gas passing through airways during intermittently opening and closing airways [28, 65].

5. LIMITATIONS AND FUTURE WORK

In this study the analysis of NRS, frequencies and intensities of the ARS was not considered, which could have influenced the results of the statistical analyses. In some studies with respiratory sounds, this separation does not happen[82]. These can explain the absence of differences in this study. Therefore, it is recommended studies with both methods of analyse.

The frequency band used to analyse NRS ranged between 100 to 2000 Hz. It is known that respiratory sound intensities start to appear bellow 100Hz of

frequency [82], and thus there is a risk that some information bellow 100Hz may have been lost. Nevertheless, previous studies have shown that the frequency sound power in infant are mainly above 100 Hz [65], meaning that the major component of the NRS (i.e., where the main intensities fall) have been captured and thus the contentment of the information lost may be residual.

The severity of LRTI was assessed using the modified Wang Score, a scale designed to assess bronchiolitis severity. However this score is based on five clinical signals that also often present in LRTI, and therefore, it is believed that an adequate assessment of the respiratory distress was performed. Moreover, there is no specific scale designed to assess respiratory distress in infants with LRTI. Therefore, new methods to assess respiratory distress in LRTI are recommended.

The sample in terms of LRTI severity found with the modified Wang Score was very similar. The sample was composed mainly of infants with mild severity (score ≤3), which implies that not all ranges of respiratory sounds were assessed and the differences between infant's sounds were not significant. Therefore, it is highly recommended that future studies investigate all ranges of severity.

The sample size used in this study was not enough to characterised respiratory sounds in healthy and infants with LRTI below 2 years old (type II error). Sample size estimation had determined that a significant difference needed a minimum of 60 infants in each group, which was not possible to obtain within the timeframe of this study. However, this study is part of a larger study to characterize computerised RS in paediatrics and therefore this is a contribution.

6. CONCLUSIONS

Computerised respiratory sounds in healthy infants and infants with LRTI presented differences. The main findings indicated that NRS have a Fmax higher in infants with LRTI than in healthy infants and that Wh% was the characteristic that differed the most between infant with LRTI and healthy infant.

Currently, there are no reference values for characterisation of sounds in healthy infants and those with LRTI; no clinical algorithm to accurately diagnose LRTI in infant, however solutions have been studied. Computerised respiratory sounds are an objective and simple measure which developments will improve the inclusion of sounds in the clinical practice and therefore further enhance them as a measure of evaluation.

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Annex I – Ethics' approval

COMISSÃO DE ÉTICA

da **Unidade Investigação em Ciências da Saúde - Enfermagem** (UICISA: E)

da **Escola Superior de Enfermagem de Coimbra** (ESEnfC)

Parecer Nº P186-10/2013

Título do Projecto: Estabelecimento de valores de referência para sons pulmonares adventícios e o teste de marcha com carga progressiva modificado em crianças saudáveis e com patologia respiratória

Identificação do Proponente

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Filiação Institucional: Escola Superior de Saúde da Universidade de Aveiro

Investigador Responsável/Orientador: Profª Alda Sofia Pires de Dias Marques

Relator: José Carlos Amado Martins

Parecer

Trata-se de estudo descritivo, correlacional, tendo como objetivo principal: "estabelecer valores de referência para os sons pulmonares adventícios e para o teste de marcha com carga progressiva em crianças com patologia respiratória e saudáveis, contribuindo assim para melhor compreensão das patologias, e consequentemente, melhorar o diagnóstico, monitorização e tratamento de crianças com problemas respiratórios".

Será utilizada amostra de conveniência, com crianças (idade<18 anos), com diagnóstico de patologia respiratória pediátrica e crianças saudáveis. Os critérios de inclusão/exclusão são definidos. Colheita de dados de dezembro de 2013 a dezembro de 2016.

A caracterização decorrerá no Hospital Santa Maria (Porto), Banda Filarmónica Ovarense (Ovar), Clube do Povo de Esgueira (Aveiro) e Clínica Estrela Esteves Unipessoal (Aveiro), instituições com as quais existe protocolo de colaboração com a Universidade de Aveiro e que já aprovaram o estudo, sendo apresentados comprovativos.

São definidas as medidas e testes a utilizar que têm um carácter não invasivo.

É garantida a confidencialidade e o anonimato da informação em todo o processo de recolha e análise. Será solicitado o consentimento do responsável legal de cada criança e à própria criança, em função do seu grau de maturidade. São apresentados os documentos para informação e obtenção do consentimento na forma escrita, que cumprem os requisitos éticos.

Não são previstos desvantagens ou riscos para os participantes.

Tendo em consideração o exposto, é entendimento desta Comissão que, em termos éticos, nada há a opor ao desenvolvimento da investigação.

O relator: 

Data: 20/11/2013 O Presidente da Comissão de Ética:

FCT Fundação para a Ciência e a Tecnologia

A Pedido do Senhor Presidente da
Comissão de Ética da UICISA: E

Informamos que se juntou à equipa de investigadores do projeto **Estabelecimento de valores de referência para sons pulmonares adventícios e o teste de marcha com carga progressiva modificado em crianças saudáveis e com patologia respiratória**, as Senhoras Sara Daniela Quina Rodrigues e Maria Manuel Almeida Regêncio.

Com os melhores cumprimentos

Cristina Louçano, Lic.
Administrative Assistant
Unidade de Investigação em Ciências da Saúde: Enfermagem
| Escola Superior de Enfermagem de Coimbra
| Polo C – Rua José Alberto Reis – Coimbra |
| investiga@esenfc.pt | +351 239 487 217 |

Exima Direção Clínica

Da

Cliria, Hospital Privado de Aveiro

A Comissão de Ética reuniu no dia 12 do corrente mês de fevereiro de 2014 com as ausências justificadas do Dr. António Simões, Dra. Filipa Loreto e Dr. Miguel Varela.

Analisou um pedido de colheita de dados para um estudo científico intitulado "sons pulmonares adventícios em crianças saudáveis e com patologia respiratória", formulado pela Dra. Ana Oliveira, aluna a frequentar o Mestrado em Fisioterapia da Escola Superior de Saúde da Universidade de Aveiro, sob a orientação científica da Dra. Alda Sofia Pires de Dias Marques, para ser efetuado nas consultas de pediatria da Cliria, Hospital Privado de Aveiro.

O estudo insere-se no mestrado de fisioterapia.

Tem o consentimento informado obtido pelos tutores das crianças.

Tem autorização dos médicos pediátricos colaborantes.

A investigadora, em reunião da comissão, prestou todos os esclarecimentos suscitados de ordem ética sobre os princípios, meios e fins do estudo.

A comissão é de parecer que estão salvaguardados os princípios éticos inerentes a este estudo pelo que entende nada a haver eticamente que impeça a sua realização.

Aveiro, 12 de fevereiro de 2014

Pel' Comissão de Ética

Cliria - Hospital Privado de Aveiro, S.

(Amorim Figueiredo)

Annex II – Institutions' approval

Autorização Institucional

Eu, MANUEL BALTAZAR FERREIRA MONTELA

responsável pela instituição FISIOMANUAL LDA. declaro que fui informado dos objetivos do estudo científico intitulado: Sons pulmonares adventícios em crianças saudáveis e com patologia respiratória", e concordo em autorizar a execução da mesma nesta instituição. Caso necessário, a qualquer momento como instituição CO-PARTICIPANTE desta investigação poderemos revogar a autorização, se comprovada atividades que causem algum prejuízo a esta instituição ou ainda, a qualquer dado que comprometa o sigilo da participação dos integrantes desta instituição. Declaro também, que não recebemos qualquer pagamento por esta autorização bem como os participantes também não receberão qualquer tipo de pagamento.

Representante da Instituição	30/10/14 Data	Assinatura
Investigadora	30/10/14 Data	Assinatura

Annex III – Modified Wang Score

Modified Wang Score

Pont.	Frequência respiratória (cpm)	Sibilâncias	Retrações	Saturação periférica de Oxigénio (SpO_2)	Frequencia cardíaca (bpm)
0	<30	Nenhuma	Nenhuma	≥95%	<140
1	31-45	Audíveis no final da expiração e apenas com estetoscópio	Apenas intercostal	92-94%	140-159
2	46-60	Audíveis durante toda a expiração ou sem o estetoscópio durante a expiração	Traqueoesternal	90-91%	160-179
3	>60	Audíveis durante a inspiração e a expiração sem estetoscópio	Severa e com adejo nasal	< 90%	≥ 180

Fonte: Wang EE, Milner RA, Navas L, Maj H (1992). Observer agreement for respiratory signs and oxymetry in infants hospitalized with lower respiratory infections. Am Rev Respir Dis;145(1):106-109

Appendix I – Information sheets (health institutions)

Folha de informação ao representante legal

A aluna Maria Manuel Almeida Regêncio a frequentar o Mestrado em Fisioterapia da Escola Superior de Saúde da Universidade de Aveiro, sob a orientação científica da Professora Doutora Alda Sofia Pires de Dias Marques, vem por este meio solicitar-lhe a autorização para a participação do seu representando legal no estudo clínico intitulado: "Sons pulmonares adventícios em crianças saudáveis e com patologia respiratória".

É importante que compreenda porque é que a investigação está a ser realizada e o que é que a mesma envolve. Por favor, leia a informação com atenção e discuta a participação do seu representando. Se houver algo que não esteja claro para si ou necessitar de informação adicional, por favor não hesite em contactar a aluna ou a sua orientadora (contactos no final deste documento).

Muito obrigado desde já por ler a informação.

Qual é o propósito do estudo?

Este estudo visa contribuir para o estabelecimento de valores de referência para os sons pulmonares adventícios (SPA) em crianças saudáveis e com patologia respiratória.

Para que seja possível determinar valores de referência de SPA em crianças com patologias respiratórias e em crianças saudáveis, que podem afetar a precisão do diagnóstico clínico e a prescrição e monitorização do tratamento, venho então solicitar-lhe autorização para que o seu representando legal participe neste estudo que será realizado no Cliria - Hospital Privado de Aveiro, SA

Porque foi o meu representando escolhido?

O seu representando foi escolhido porque deu entrada na Cliria - Hospital Privado de Aveiro, SA e tem idade inferior a 24 meses.

Tenho de aceitar a participação do meu representando?

A decisão de autorizar a participação do seu representando ou não, é completamente sua. No entanto, é totalmente livre de desistir a qualquer momento, sem que para tal tenha de dar qualquer justificação. A decisão de desistir ou de não participar, não afetará a qualidade dos serviços de saúde prestados a si ou ao seu representando agora ou no futuro.

O que acontecerá se autorizar a participação do meu representando?

Se decidir participar vai-lhe ser pedido que assine dois formulários de consentimento informado, um para si e outro para a aluna de mestrado. Após receber o consentimento informado devidamente assinado, será feita uma avaliação do estado de saúde geral do seu representando. De seguida, um oxímetro de pulso, equipamento semelhante a um relógio, ser-lhe-á colocado no pulso para medir a quantidade de oxigénio que o seu sangue está a

transportar e a frequência cardíaca. Por último, serão gravados os sons que os seus pulmões estão a fazer naquele momento, durante aproximadamente 20 segundos, com um estetoscópio digital ligado a um computador portátil.
A aplicação do protocolo terá a duração de aproximadamente 15 minutos e nenhum dos testes realizados provoca qualquer desconforto para a criança.

Quais são os efeitos secundários dos procedimentos do estudo?
Não existem efeitos secundários de participar no estudo.

A participação será confidencial?
Toda a informação recolhida no decurso do estudo será mantida estritamente confidencial.
Os dados recolhidos serão salvaguardados com um código e palavra-passe, para que ninguém os possa identificar. Apenas a aluna responsável pelo projeto e a sua orientadora terão acesso aos dados.

O que acontecerá aos resultados do estudo?
Os resultados do estudo serão analisados e incorporados num dissertação de Mestrado e alguns serão publicados em Jornais e/ou conferências de finalidade científica. No entanto, em nenhum momento o seu representando será identificado/a.

Contacto para mais informações sobre o estudo
Se pretender obter mais informações sobre o estudo, pode telefonar ou escrever para:
Alda Marques, Maria Regêncio
Escola Superior de Saúde da Universidade de Aveiro,
Universidade de Aveiro,
Campus de Santiago,
Edifício III, 3810-193, Aveiro
Telefone: 913937469, 234 247 113 ou 234 372 462
e-*mail: mariaregencio@ua.pt; amarques@ua.pt*

Muito obrigado por ter lido esta informação

Appendix II – Informed Consent

CONSENTIMENTO INFORMADO

Título do Projeto: Sons pulmonares adventícios em crianças saudáveis e com patologia respiratória

Nome da Orientadora: Prof. Doutora Alda Sofia Pires de Dias Marques

Nome da aluna de Mestrado: Maria Manuel Almeida Regêncio

Por favor leia e marque com uma cruz (X) os quadrados seguintes.

1. Eu confirmo que percebi a informação que me foi dada e tive a oportunidade de questionar e de me esclarecer. ☐

2. Eu percebo a participação do meu encarregando é voluntária e que ele é livre de desistir, em qualquer altura, sem dar nenhuma explicação, sem que isso afete qualquer serviço de saúde que lhe é prestado. ☐

3. Eu compreendo que os dados recolhidos durante a investigação são confidenciais e que só os investigadores responsáveis pelo projeto têm acesso a eles. E dou portanto, autorização para que os mesmos tenham acesso a esta informação. ☐

4. Eu compreendo que os resultados do estudo serão publicados numa dissertação de mestrado e jornais e/ou conferências de finalidade científica sem que haja qualquer quebra de confidencialidade e anonimato. E dou portanto, autorização para a utilização dos dados para esses fins. ☐

5. Eu confirmo que o meu encarregando foi questionado acerca da sua vontade em participar no estudo e que nenhuma avaliação foi realizada contra a sua vontade, sendo assim respeitada a sua autonomia. ☐

6. Eu concordo então em participar no estudo. ☐

_____	_____	_____	_____
Nome do Participante	Representante Legal	Data	Assinatura

_____	_____	_____
Investigadora	Data	Assinatura