Characterization of Impulse Oscillometric Measures of Respiratory Small Airway Function in Children

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Abstract. *Children suffering from asthma are often undiagnosed or misdiagnosed as their symptoms are similar to other respiratory conditions. Spirometry, the "golden" pulmonary function test used for asthma diagnosis, is often unsuitable for young children since it requires them to perform extreme inhalation and exhalation maneuvers. Impulse Oscillometry (IOS) is an effortless, child-friendly, sensitive, and reliable testing technique that could be used in the effective diagnosis of asthma. However, the IOS requires a deep understanding of the mechanical and/or equivalent electrical circuit models of the human respiratory system, which hinders its broad acceptance and utility in clinics. This paper presents a data characterization study based on the statistical assessment of the IOS parameters. The main focus is to investigate four different manifestations of pulmonary conditions in children due to peripheral obstruction: Asthma (A), Small Airway Impairment (SAI), Possible Small Airway Impairment (PSAI), and Normal (N). The objective of this investigation is to pave the way for the feature selection stage of our future computer-aided classification work to distinguish between lung dysfunction and healthy lung function in children by identifying those IOS parameters that are most sensitive to discriminate between the different respiratory conditions mentioned above. Our ultimate goal is to facilitate the interpretation of the impulse oscillometric test results and provide clinicians with a reliable and proven method for accurate classification of children's lung function for an early asthma detection, diagnosis, and control.*

Keywords

Asthma, Impulse Oscillometry (IOS), lung function, soft computing.

1. Introduction

Asthma causes the inflammation and narrowing conditions that significantly affect the lining of the small airways, which are the peripheral or distal airways with an inner diameter of about 0.5 to 2 mm [1]. The early manifestation of these conditions prior to an asthma diagnosis could be early Small Airway Disease (SAD) also known as Small Airway Impairment (SAI), which is a chronic obstructive bronchitis with narrowing of the bronchioles and small bronchi [1] and [2]. If inflammation persists during SAI, asthma will appear. Therefore, the early evaluation and treatment of the small airways might be even more effective when initiated earlier in the course of asthmatic disease [2] and [3].

The timely diagnosis of asthma is a challenging task since its symptoms are similar to other respiratory conditions. Additionally, the diseases affecting the small airways are difficult to detect by traditional diagnostic tests [4]. Early childhood is a critical period to assess pulmonary function since those suffering from asthma usually face the onset of their symptoms during this time [5] and [6]. Spirometry is a Pulmonary Function

Test (PFT) that quantifies the volume and flow of air inhaled and exhaled as a function of time, and it is the most common PFT used by primary medical practitioners to diagnose asthma. Spirometry requires significant cooperation from patients to perform extreme inhalation and exhalation maneuvers and is often unsuitable for young children who cannot follow exact instructions. Frequently, children of this age are underdiagnosed and poorly controlled [7], creating a substantial burden that includes a decreased quality of life[7], [8] and [9]. To this end, the IOS could be used as an alternative and objective method for asthma diagnosis and control in children. The IOS, which measures the respiratory impedance (pressure/flow as a function of frequency), is a child-friendly, noninvasive, and well validated technique requiring only the subject's passive cooperation with fast, easy, and reproducible measurements [10] and [11]. Despite its advantages, the high dimensionality of the IOS data and the complexity of the mathematical infrastructure necessary for their acquisition, make the analysis of test results difficult for clinicians. Thus, these challenges could be perceived as a barrier to the broad clinical acceptance of the IOS and use in spite of its patient friendliness and objectivity.

Recognizing the need to improve the clinical utility of the IOS, in this article we focus on the characterization of the IOS features as a preliminary step for our future computer-aided classification of lung function in children. The aim of this work is to identify those IOS features that demonstrate statistical significance pertaining to the differentiation between four different degrees of small airways obstruction which are the Asthma (A), Small Airway Impairment (SAI), Possible Small Airway Impairment (PSAI), and Normal (N) respiratory conditions.

2. Materials and Methods

2.1. Impulse Oscillometry System and its Derived Parameters

The Impulse Oscillometry System (IOS) measures the respiratory (pulmonary) impedance (Z) which has two components: resistance (R) and reactance (X). In other words, Z is the sum of all the *resistive* and *reactive* forces that oppose the pressure impulses (oscillations) and are calculated from the ratio of pressure and flow at each frequency (5, 10, 15, 20, 25, and 35 Hz). Resistance is the in-phase component of respiratory impedance and reflects information about the forward pressure of the conducting airways. On the other hand, reactance is the out-of-phase component of respiratory impedance and reflects the capacitive (C) and inertive (I) properties of the airways [12]. Other IOS derived parameters include: the frequency-dependence of Resistance (fdR) which is calculated by subtracting R20 from R5 (R5–R20) and represents the small airways resistance, the resonant frequency (Fres) is the frequency at which the reactance is equal to zero, and the reactance area (AX), also known as the "Goldman Triangle" is the area under the reactance curve between 5 Hz and Fres and provides important information about small airways obstruction [12] and [13].

2.2. The IOS-Based Human Respiratory System Models

For more than a decade, previous research work in the Biomedical Engineering Research Laboratory at the University of Texas at El Paso (UTEP) has focused on the development, analysis, and validation of different equivalent electrical circuit models for human respiratory system impedance. This effort to date has demonstrated that the performance of the extended Resistance Inductance Capacitance (eRIC) model and the augmented RIC (aRIC) model (an improvement of the eRIC model) ranked in the middle of a series of traditional models developed over the past several decades in terms of total cumulative error. However, these recent models provide parameter estimates that are physiologically more realistic and in line with the expected values in normal subjects and those suffering from pulmonary dysfunction than previous models [13], [14] and [15].

The components of the eRIC model include the representation of large airway resistance "R", peripheral resistance "Rp", large airway inertance "I", and peripheral airway compliance "Cp". The aRIC model was developed and validated as an augmentation of the eRIC model. The additional element "Ce" in the aRIC model represents the extrathoracic compliance mainly due to the upper airways shunt effects. Figure 1 and Fig. 2 show the IOS-based equivalent electric circuit models of the human respiratory system developed and validated in our research laboratory [15].

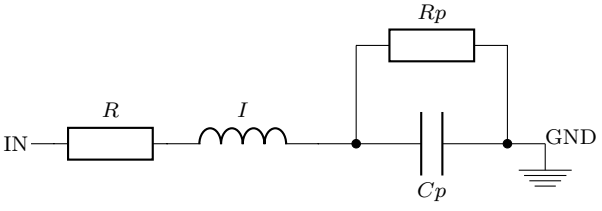

Fig. 1: eRIC Model of the human respiratory system.

Tab. 1: Study's population demographics.

Age (Years)	Body Mass Index (Kg·m^{-2})	Ethnicity	Gender	Age by Gender (Years)	Children Tested
Range: 5–17 Mean ± SD: 9.88 ± 3.62	Range: 12.7–37.6 Mean ± SD: 19.66 ± 4.73	Caucasian	Male	5–17	38
			Female	5–17	26
		Hispanic	Male	5–17	22
			Female	5–16	26
				Total	112

Tab. 2: Demographics for clinician's classification.

	Age (Years)			Body Mass Index (Kg·m^{-2})		
Classification	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**
Asthma (n=30)	5-13	8.1	2.5	14.35-37.57	18.89	5.35
SAI (n=54)	5-17	9.3	3.4	12.73-31.21	19.31	4.49
PSAI (n=17)	5-17	12.6	3.8	14.64-30.52	20.16	3.93
Normal (n=11)	11-17	13.4	2.5	16.14-30.15	22.79	4.55

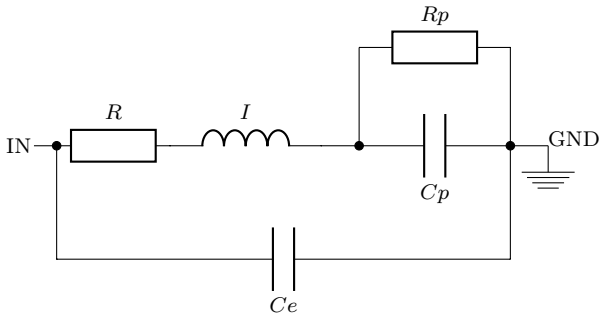

Fig. 2: aRIC Model of the human respiratory system.

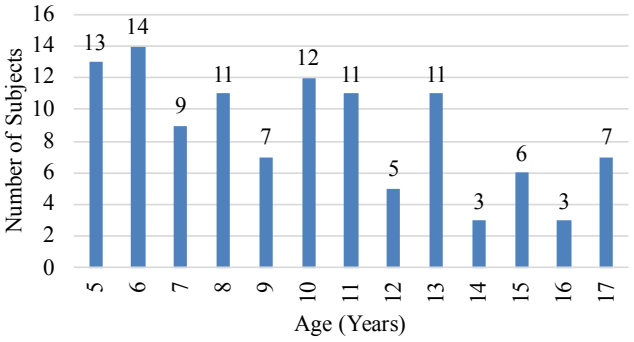

Fig. 3: Study demographics by age.

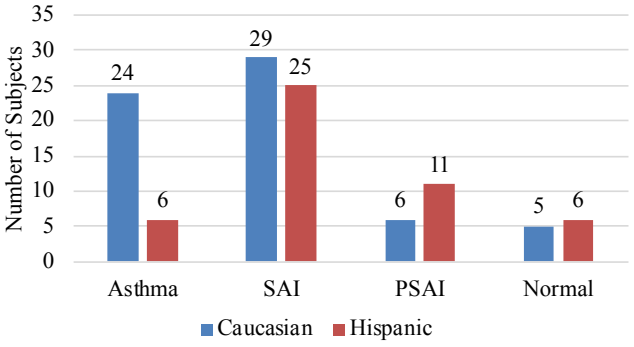

Fig. 4: Clinician's classification breakdown by ethnicity.

2.3. Subjects

The IOS dataset acquired as part of an NIH-funded study ("Asthma on the Border") was used for this study. The data were collected in El Paso, Texas with the approval of the University of Texas at El Paso Institutional Review Board (IRB). An informed consent form was given to every parent and their child, providing them with a detailed description of the study. This unique IOS database consists of 112 records of male and female Caucasian and Hispanic children from 5 to 17 years of age. The demographics of the studied population are further described in Tab. 1 and Fig. 3.

2.4. IOS Equipment and Data Acquisition

The equipment used for the study was a Jaeger MasterScreen IOS (manufacured by Viasys Healthcare, Höchberg, Germany). The system was calibrated every day before data collection using a 3-L syringe for volume calibrations and a reference resistance (0.2 kPa·L^{-1}·s^{-1}) for pressure calibrations. Children were asked to wear a nose clip, while breathing normally through a mouthpiece, and were instructed to close their lips tightly around it to avoid air leakage. During data collection, three to five IOS test replicates were performed on each subject to ensure reproducible tests without artifacts. In each IOS test, impulses were

Tab. 3: Mean and coeficient of variation of each IOS parameter.

		Mean				Coeficient of Variation (%)			
IOSParameter	**Units**	**Asthma**	**SAI**	**PSAI**	**Normal**	**Asthma**	**SAI**	**PSAI**	**Normal**
R5	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.823	0.654	0.493	0.4	20.2	22.2	23	22.8
R10	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.629	0.519	0.41	0.348	18.2	21.5	22.5	24.8
R15	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.504	0.43	0.374	0.342	19.7	24.7	22.4	24.9
R20	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.45	0.402	0.354	0.332	19.1	24.2	23.6	22.3
R25	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.498	0.447	0.369	0.342	17.2	21.5	25.4	21.2
R35	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.65	0.551	0.461	0.417	18	19.7	24.4	23.1
X5	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	-0.362	-0.263	-0.168	-0.106	32.2	34.3	42.7	37.9
X10	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	-0.24	-0.156	-0.072	-0.023	32.2	42.3	61.5	65.9
X15	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	-0.163	-0.091	-0.026	0.018	35.6	49.7	130.8	128.6
X20	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	-0.025	0.021	0.04	0.062	172.4	214.7	62.1	41.9
X25	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.1	0.111	0.114	0.12	42.1	41.8	29.2	22.4
X35	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.199	0.206	0.21	0.206	22.5	22.4	18.7	23.9
R5–R20	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.373	0.253	0.139	0.068	31.3	35.5	48.5	49.8
Fres	Hz	20.914	19.334	16.697	13.145	8	12.6	11.6	18.9
AX	$kPa{\cdot}l^{-1}{\cdot}$	3.015	1.887	0.866	0.366	32.5	39.5	58	32.9
eRIC R	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.423	0.389	0.347	0.329	18.6	23.5	24.5	22.8
eRIC Rp	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.836	0.637	0.444	0.497	31.5	37.6	48.3	103.4
eRIC I	$kPa{\cdot}l^{-1}{\cdot}s^{-2}$	0.001	0.001	0.001	0.001	28.6	30.8	31.6	16
eRIC Cp	$l{\cdot}kPa^{-1}$	0.04	0.063	0.112	0.188	32.9	44.2	34.2	34.8
aRIC R	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.371	0.34	0.324	0.31	27.1	33.1	28.2	26.4
aRIC Rp	$kPa{\cdot}l^{-1}{\cdot}s^{-1}$	0.795	0.597	0.408	0.309	28.9	31.7	41.3	34.6
aRIC I	$kPa{\cdot}l^{-1}{\cdot}s^{-2}$	0.002	0.002	0.001	0.001	39.3	45.1	45.2	24.2
aRIC Cp	$l{\cdot}kPa^{-1}$	0.032	0.051	0.1	0.152	40.7	59	41.5	20.4
aRIC Ce	$l{\cdot}kPa^{-1}$	0.003	0.003	0.002	0.002	68.1	74.1	95.9	96.3

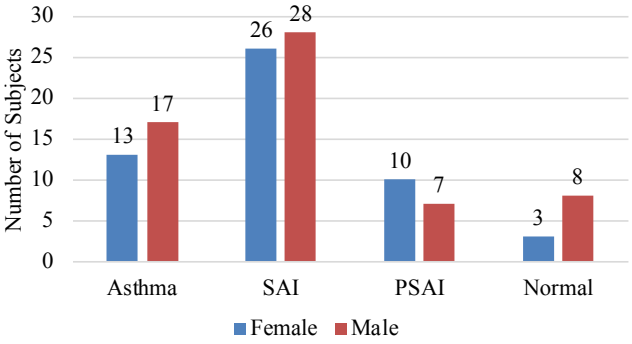

Fig. 5: Clinician's classification breakdown by gender.

applied for a period of 30 to 45 seconds. The data were then carefully reviewed (quality-assured) offline by our expert clinician to ensure that they were artifact free (no air leaks, no swallowing effects, no breath holding, no vocalization), segments containing artifacts were rejected and were not used for the present study. After the review of every test, each child's data were classified into one of four conditions based on the clinician's expertise and experience: Normal (N), Possible Small Airway Impairment (PSAI), Small Airway Impairment (SAI), or Asthmatic (A). Table 2, Fig. 4 and Fig. 5 detail the demographics by class.

The collected data from IOS testing included resistance and reactance measurements at frequencies 5, 10, 15, 20, 25, and 35 Hz, resonant frequency (Fres), and the reactance area (AX). Additionally, R5–R20 (fdR), the eRIC, and the aRIC parameters were calculated. The methodology for parameters estimation of the eRIC and aRIC respiratory models are further described by Diong et al. in [14] and [15], respectively. In total, 24 IOS derived features for each child were considered. Table 3 lists all parameters obtained for the present study and shows the mean and coefficient of variation of each IOS parameter per each of the studied conditions.

2.5. IOS Data Characterization for Dimensionality Reduction

The high dimensionality of the IOS parameters, as well as the dispersion of the data generated for the different classes produce an overlapping effect. This makes computer-aided classification of multiple classes with different degrees of severity in peripheral obstruction difficult. The complexity of the data used for this investigation plotted in terms of the respiratory impedance components R and X, as a function of the Frequency (F) is shown in Fig. 6.

It is observed that the data from the different classes overlap, thus making the class differentiation a challenging task. Therefore, a deep analysis of the IOS parameters is required to find discriminating features that could help in the accurate classification of classes with different degrees of distal obstruction. To this end, statistical analysis was performed using the MINITAB 18 Statistical Software (Minitab, Inc., State College, USA). ANOVA One-way (Analysis of Variance) was the test used to determine statistical differences be-

Tab. 4: IOS Resistance Parameters Comparison-Matrix.

IOS Parameter	Asthma vs. SAI	Asthma vs. PSAI	Asthma vs. Normal	SAI vs. PSAI	SAI vs. Normal	PSAI vs. Normal
R5	0	0	0	0	0	0.031
R10	0	0	0	0.001	0	**0.086**
R15	0.002	0	0	**0.055**	0.012	**0.324**
R20	0.027	0.001	0	**0.073**	0.029	**0.49**
R25	0.018	0	0	0.005	0.001	**0.422**
R35	0	0	0	0.004	0	**0.289**

Tab. 5: IOS Reactance Parameters Comparison-Matrix.

IOS Parameter	Asthma vs. SAI	Asthma vs. PSAI	Asthma vs. Normal	SAI vs. PSAI	SAI vs. Normal	PSAI vs. Normal
X5	0	0	0	0	0	0.015
X10	0	0	0	0	0	0.002
X15	0	0	0	0	0	0.001
X20	0	0	0	**0.105**	0.005	0.003
X25	**0.28**	**0.239**	**0.149**	**0.802**	**0.54**	**0.627**
X35	**0.497**	**0.428**	**0.687**	**0.79**	**0.974**	**0.821**

Tab. 6: IOS Derived Parameters Comparison-Matrix.

IOS Parameter	Asthma vs. SAI	Asthma vs. PSAI	Asthma vs. Normal	SAI vs. PSAI	SAI vs. Normal	PSAI vs. Normal
R5–R20	0	0	0	0	0	0.003
Fres	0.002	0	0	0	0	0
AX	0	0	0	0	0	0.003

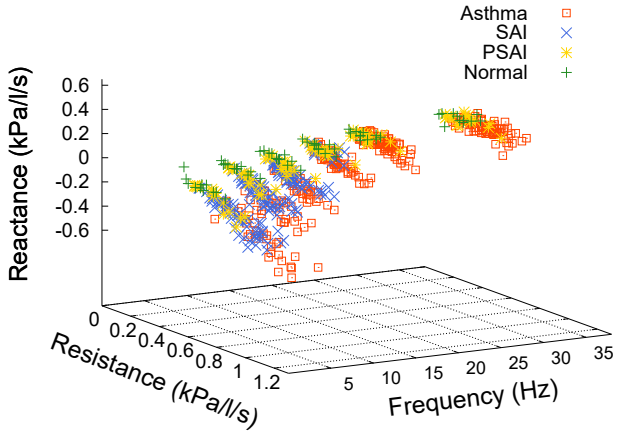

Fig. 6: 3D Plot of Resistance and Reactance vs. Frequency.

tween data sets. The statistical analysis was performed using a confidence level of 95 %.

In this analysis, each IOS parameter for each class was compared against the same IOS parameter for a different class, until the parameter was compared for all classes. A comparison-matrix for each of the main IOS parameters was completed, where the p-values obtained for each of the comparisons were listed in the corresponding matrix. Please refer to Tab. 4 for the resistance parameters comparison, Tab. 5 for the reactance parameters, Tab. 6 for other IOS derived parameters, Tab. 7 for the eRIC, and Tab. 8 for the aRIC human respiratory model parameters. For an IOS parameter to be considered potentially discriminative all of its p-values must be less than 0.05. The corresponding tables have any cells where the p-values are greater than 0.05 highlighted in bold, which render that specific IOS feature undiscriminative.

3. Results

For resistance, it is observed in Tab. 4 that the resistance parameters R5, R10, R15, R20, R25, and R35 are potentially discriminative to differentiate between all classes except SAI vs. PSAI and PSAI vs. Normal; where R15 and R20 cannot differentiate between SAI vs. PSAI, and R10, R15, R20, R25, and R35 cannot differentiate between PSAI vs. Normal. Therefore, the only resistance parameter found to be potentially discriminative for all conditions was R5.

For reactance, it is observed in Tab. 5 that the reactance parameters X5, X10, X15 are potentially discriminative to differentiate all classes, while X20 differentiates all classes except SAI vs. PSAI. X25 and X35 do not differentiate any of the classes. Therefore, the reactance parameters found to be potentially discriminative for all conditions were X5, X10, and X15.

Tab. 7: eRIC Parameters Comparison-Matrix.

eRIC Parameter	Asthma vs. SAI	Asthma vs. PSAI	Asthma vs. Normal	SAI vs. PSAI	SAI vs. Normal	PSAI vs. Normal
R	**0.091**	0.003	0.003	**0.097**	**0.073**	**0.669**
Rp	0.001	0	0	0.004	0	**0.205**
I	0.026	0	0	0.019	0.011	**0.463**
Cp	0	0	0	0	0	0.001

Tab. 8: aRIC Parameters Comparison-Matrix.

aRIC Parameter	Asthma vs. SAI	Asthma vs. PSAI	Asthma vs. Normal	SAI vs. PSAI	SAI vs. Normal	PSAI vs. Normal
R	**0.208**	**0.121**	**0.082**	**0.611**	**0.418**	**0.689**
Rp	0	0	0	0	0	**0.094**
I	**0.053**	0	0	0.008	0.004	**0.334**
Cp	0.001	0	0	0	0	0.002
Ce	**0.738**	**0.112**	**0.455**	**0.07**	**0.347**	**0.61**

Tab. 9: Ranking of Potentially Discriminative IOS Parameters.

	Coeficient of Variation (%)					
IOS Parameter	**Asthma**	**SAI**	**PSAI**	**Normal**	**CV Avg**	**Ranking**
Fres	8	12.6	11.6	18.9	12.8	1
R5	20.2	22.2	23	22.8	22	2
eRIC Cp	32.9	44.2	34.2	34.8	36.5	3
X5	32.2	34.3	42.7	37.9	36.8	4
aRIC Cp	40.7	59	41.5	20.4	40.4	5
AX	32.5	39.5	58	32.9	40.7	6
R5-R20	31.3	35.5	48.5	49.8	41.3	7
X10	32.2	42.3	61.5	65.9	50.5	8
X15	35.6	49.7	130.8	128.6	86.2	9

For the other IOS derived parameters category, which included R5–R20 (fdR), Fres, and AX, it is observed in Tab. 6 that for all instances these parameters are potentially discriminative since all p-values were nearly equal to zero in all cases.

For the eRIC parameters, it is observed in Tab. 7 that the "Cp" parameter is potentially discriminative to differentiate all classes, while "Rp" and "I" differentiate all classes except PSAI vs. Normal, and the "Rc" parameter does not differentiate any of the classes. Therefore, the only eRIC parameter found to be potentially discriminative for all conditions was "Cp".

For the aRIC parameters, it is observed in Tab. 8 that the "Cp" parameter is potentially discriminative to differentiate all classes. "Rp" differentiates all classes except PSAI vs. Normal, while "I" differentiates between all classes except Asthma vs. SAI and PSAI vs. Normal. The "Rc" and "Ce" parameters do not differentiate any of the classes. Therefore, the only aRIC parameter found to be potentially discriminative for all conditions was "Cp".

Table 9 summarizes the IOS derived-parameters that have discriminative capacity to statistically differentiate all four classes based on their means. It is also important to understand the dispersion of the data for each parameter, since less variation will imply less data overlapping between groups. Therefore, these IOS parameters were ranked based on the dispersion of their data measured in terms of the average of the coefficient of variation for the different classes. Table 9 shows the ranking based on the coefficient of variation.

4. Discussion

Based on the analysis performed, nine parameters were found sensitive to discriminate between the Asthma, SAI, PSAI and Normal pulmonary conditions. Unlike previous studies, we demonstrated that these parameters statistically differentiate between four levels of peripheral lung function instead of just two (asthmatics and non-asthmatics) as previously presented by other studies [2], [16], [17], [18] and [19].

From the analysis of the resistance parameters, R5 was found to be discriminative, this finding is supported by previous studies that have found R5 to be statistically significant to differentiate IOS bronchodilator responses for asthmatic and non-asthmatic children. In addition to R5, R10 has also been found to be an important parameter to differentiate between these two groups. However, in our study it was confirmed that R10 has no discriminative capacity to dis-

tinguish between PSAI and Normal conditions [16], [17], [18], [20] and [21].

Regarding reactance, we found X5, X10, and X15 to be discriminative parameters, in previous studies X5 and X10 have been observed to be sensitive to differentiate IOS bronchodilator responses for asthmatic and non-asthmatic children [16], [17], [20] and [21]. In addition, X5 has been shown to correlate with improvement in the peripheral lung function due to the use of systemic drugs [19].

R5–R20 (fdR), Fres, and AX have also been found to be sensitive measures to detect lung function changes in children in previous studies [2], [3], [13], [20], [21], [22] and [23].

The findings related to the equivalent electrical circuit model parameters for the human respiratory system are supported by previous studies performed by our research group. Where, the baseline IOS measures and estimated model parameters have previously been analyzed to evaluate their discriminative capacity to track changes in lung function in children [2], [13] and [22]. In these studies, IOS measures and estimated model parameters of Asthma, SAI, PSAI, and Normal children were statistically analyzed to evaluate their discriminative capacity by comparing pre and post-bronchodilator responses for each group. According to these studies, the data for Asthma and SAI seemed to fall into one category (Small Airway Impaired), while PSAI and Normal could be grouped into a different one (Healthy). A statistical assessment was then performed to identify the IOS and estimated model parameters that were discriminative to distinguish between the two groups, it was concluded that AX and the eRIC "Cp" estimated model parameter were the most sensible and reliable measures to statistically distinguish between the two groups [2]. With the present study, we were able to confirm that the eRIC "Cp" estimated model parameter not only differentiates between two conditions but also differentiates between the four conditions presented in here. In addition to the eRIC "Cp", the aRIC "Cp" estimated model parameter was also found discriminative to distinguish between the four groups.

5. Conclusions

In this work, we were able to identify the IOS parameters that statistically differentiate between four levels of peripheral lung function in children (Asthma, SAI, PSAI and Normal). Out of the 24 IOS parameters studied, only 9 were found to be sensitive to differentiate between the four respiratory conditions studied in this paper. The discriminative IOS parameters identified and listed from higher to lower sensitivity (based on the dispersion of their data) were: Fres, R5, Cp from the eRIC model, X5, Cp from the aRIC model, AX, R5–R20, X10, and X15. These parameters could be used as input features in further computer-aided classification work to best distinguish normal lung function and different degrees of small airways obstruction in children.

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