Ecole Doctorale BioSE (Biologie-Santé-Environnement)

Thèse

Présentée et soutenue publiquement pour l'obtention du titre de

DOCTEUR DE l'UNIVERSITE DE LORRAINE

Mention : « Sciences de la Vie et de la Santé »

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LUNG FUNCTION BY PLETHYSMOGRAPHY: A NEW METHOD IN VIETNAM FOR ASTHMA DIAGNOSIS

Date de soutenance: 22 Septembre, 2015

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EA 3450 DEVAH: Développement, Adaptation et Handicap. Régulations cardio-respiratoires et de la motricité.

FOREWORDS

I arrived in France on a very cold day, it was only minus eleven degree. However, all the time I was in this wonderful country, I felt really warm. What I've learned from France is the knowledge not only in medicine but also culture, humanity, love, nature, and scientific methodology. I really appreciate my professor and my colleagues in France.

ACKNOWLEDGEMENTS

From deepest of my heart, I would like to thank you Professor François MARCHAL, who is my greatest professor.

Special thanks to my beloved professor, Dr NGUYEN Thi Thanh Huong, the one who first guide me into doing research, the one who is always beside me for over this ten years, the one who has encouraged me live brave and strong since I was a young medical student. As I said in Stockholm, you're my second mother.

Dr Silvia VARECHOVA, my lovely teacher, friend and colleague. Thank you for lunches, dinners, and picnics that help me to be familiar with the life overseas. Thank you for encouraging me in my first presentation in France: "*Thanh, you can do it*".

Mr. Bruno DEMOULIN, my hero in France who first picked me up in Lorraine Train Station, who taught me French even I couldn't understand much, who prepared delicious lunch and dinner with wonderful "apple cake". Without your help, I might be lost the way in France.

I would like to thank **Professor Jacques REGNARD and Professor Sam BAYAT**, for their useful comments on this thesis and further study.

Mrs. NGUYEN Minh Ngoc, who set up the plethysmograph in Viet Nam. You're the one who inspired me to follow this study.

Professor PHAM Thi Minh Duc, a "strong" woman filled with knowledge and experience that I've admired a lot since I was a medical student.

Professor NGUYEN Van Tuan, my idol in science and even in life, who taught me understanding data and doing research, gave me a lot of knowledge and experience.

Thanks for Dr VU T.T. Lan, Dr NGUYEN .T. Yen, who put the first step of the cooperation between two Universities.

Professor Cyril SCHWEITZER, a person fulled with smile and knowledge, who encouraged me to be more confident.

Mrs. BONABEL Claude, a "flying woman" with kindness and friendship, who help me a lot to be familiar with the service in France.

Mrs. BEBON Françoise, everytime I see you, I feel warm and gentle. Thank you for all the morning started with crossing your door.

Thanks for **all the members of the service in France, especially for Sylvie Méline, Francine Cael, Marie-Jeanne Arnoux, Marianne Mougin, Myriam Chamagne, and Dominique Binot-Saintot, and in the Physiology Department of the Medical Faculty, Lorraine University**.

Especially thank to **Mrs. Françoise LORRAIN**, who helped me to deal with documents and protocol of registration at the University of Lorraine.

Thanks **Dr. Julia IOAN** for sharing the office room and helping me to work with French patients. Many thanks for Laurianne Coutier, my co-author.

The author gratefully thanks Association ***Hoa Trang Fleur Blanche*** for logistic assistance and financial support, especially thanks to the **Grant EA 3450** from Ministère de la Santé et de la Recherche Médicale.

Associate Professor LE Ngoc Hung, Dr LE Thanh Tung, Physiology department members including **Mrs. Hao, Mrs. Thao, Mrs. Ha A, Mrs. Ha B, Mrs. Van Du, Mr. Binh,** who have welcomed me as a member of the department since I was a student.

FSH student research group, FSH – AD group including **Dr TRAN Trang Anh**, Medical students: **VU Bich Phuong, DO Hai Dang** for good discussions on asthma.

Dr NGUYEN Thu Hoai, Dr PHAM Hong Duong, Dr NGUYEN Minh Sang, Dr NGUYEN Khac Toan, **the English club and colleagues** in Hanoi Medical University for data collecting and understanding. Many thanks for all volunteer subjects, without you there is no study.

Special thanks to **my family,** especially **my grandfather_** a non-stopping study person. Thanks to **mom and dad**, the **parents in law**, and **my great brother** and **my sister in law, my brother in law**. You're my life.

For my beloved wife and endless love of life, Dr PHI Quynh Anh who stands by me all the time. For my little son, I wish he would become a medical doctor in the future.

SUMMARY

Despite the increasing prevalence of asthma in Viet Nam, the country has limited means for respiratory function testing. A previous study using the forced oscillation technique suggested lower respiratory resistance between French and Vietnamese children at 10 years but not 6 years of age. If the hypothesis of a significant ethnic difference in airway caliber is correct, then similar differences should exist at adult age. To test the hypothesis, a plethysmographic study was set up to measure airway resistance and specific airway resistance in healthy young adults in France and Viet Nam. We took advantage of the study to provide reference values for lung volume in these populations.

Airway resistance is significantly larger in Vietnamese than in Caucasians but there is no difference in specific airway resistance. Altogether the study does not support the consequence of a putative ethnic difference in childhood airway caliber on airway resistance normalized for lung volume at adult age.

The standing height is the best predictor of the total lung capacity, while ethnicity is an important predictor of vital capacity and of the residual volume to total lung capacity ratio.

This is the first study which provides reference values for airway resistance, specific airway resistance and lung volumes by plethysmography in healthy young Vietnamese adults. Plethysmography was validated in the north of Viet Nam, and the study allowed initiating a young working group on asthma diagnosis in Vietnam.

Keywords: Asthma; Plethysmography, Specific Airway Resistance, Airway Resistance, Thoracic Gas Volume, Ethnicity, Panting; Turbulent, Laminar airflow, Healthy subjects, Thermal effect, Child.

Résumé

La fréquence de l'asthme augmente au Vietnam, mais les moyens de diagnostic et d'évaluation fonctionnelle sont limités. Une étude précédente utilisant la technique des oscillations forcées a montré une différence de résistance des voies aériennes entre enfants français et vietnamiens à l'âge de 10 ans mais pas à 6 ans. Si l'hypothèse d'une différence ethnique significative est correcte, alors des différences semblables devraient aussi exister à l'âge adulte. Pour tester l'hypothèse, une étude par pléthysmographie a été mise en place pour mesurer la résistance des voies aériennes et la résistance spécifique des voies aériennes chez de jeunes adultes sains en France et au Vietnam. Nous avons profité de l'étude pour établir des valeurs de référence pour les volumes pulmonaires dans ces populations.

La résistance des voies aériennes est significativement plus grande chez les sujets vietnamiens que chez les caucasiens, mais il n'y a aucune différence de résistance spécifique des voies aériennes. Au final, l'étude ne montre pas de différence de calibre des voies aériennes normalisé pour le volume pulmonaire liée l'ethnie, à l'âge adulte. La taille debout est le facteur prédictif le plus important pour la capacité pulmonaire totale, tandis que l'ethnicité est un facteur important pour la capacité vitale et le rapport du volume résiduel à la capacité pulmonaire totale.

Cette étude est la première qui fournit des valeurs de référence pour la résistance des voies aériennes, la résistance spécifique des voies aériennes et les volumes pulmonaires par pléthysmographie chez l'adulte vietnamien. La pléthysmographie a été validée à Hanoi et l'étude a permis la formation d'un nouveau groupe de travail sur le diagnostic et la prise en charge de l'asthme au Vietnam.

Mots-clés : Asthme ; Pléthysmographie ; Résistance spécifique des voies aériennes ; Résistance des voies aériennes ; Volume gazeux thoracique ; Appartenance ethnique ; Halètement ; écoulement laminaire, turbulent ; Sujets sains ; Effet thermique ; Enfant.

GLOSSARY

FEV1	**Force expiratory volume in the 1st second**
FOT	**Forced Oscillation Technique**
FRC	**Functional residual capacity**
Raw	**Airway resistance**
Rrs	**Respiratory resistance**
RV	**Residual Volume**
sRaw	**Specific airway resistance**
TGV	**Thoracic gas volume**
TLC	**Total lung capacity**
VC	**Vital capacity**

CONTENTS

This thesis is especially dedicated to

my wife and my little son

Lung Function by Plethysmography:

A New Method in Viet Nam for Asthma Diagnosis

1. INTRODUCTION

1.1. Asthma has urgent requirement for better diagnosis in Viet Nam

Respiratory diseases are most common causes of death (about 7%) all over the world, and 80% deaths by chronic respiratory diseases occur especially in developing countries (Cruz, 2007). Asthma is the most frequent chronic respiratory disease in children, in most countries. It may impact on somatic growth and interfere with school attendance and performance. The economic aspects of asthma (direct and in-direct costs) are particularly important in developing countries, and Viet Nam is a typical example (Cruz, 2007).

Asthma is defined in GINA criteria as a chronic airway disease which involves airway inflammation, intermittent obstruction, and hyper-responsiveness (figure 1) (Fitzgerald, 2014). It is necessary to quantitate impairment of forced expiratory volume in one second (FEV1) by spirometry, and to allow assessing treatment benefits as well as lung function follow-up.

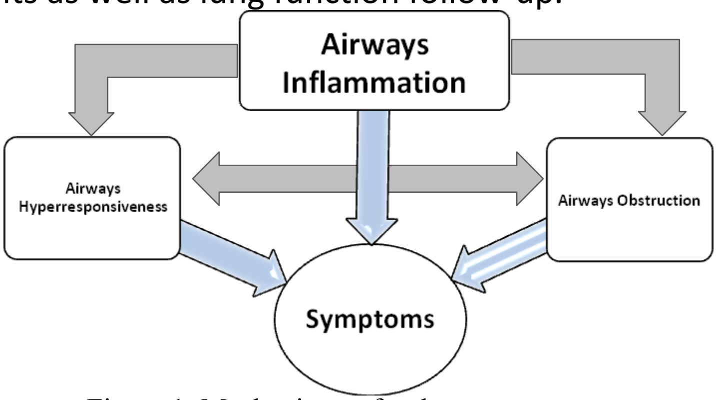


Figure 1: Mechanisms of asthma symptoms

According to the Global initiative for Asthma 2014, the common symptoms are: wheezing, chest tightness, coughing, and labored breathing. However, some patients have symptoms such as cough, but no objective evidence of airway obstruction or hyper-responsiveness. On the other hand, typical symptoms may be missing in asthmatic children. Therefore, the diagnosis of asthma is rendered difficult on the basis of only clinical symptoms.

Viet Nam is located in South-east Asia where poor control of asthma was reported in children and adult (Lai et al., 2003). Indeed, the study identified more than 60% of patients who did not undergo any lung function test during the past year.

A recent study however has determined an increasing prevalence of asthma in Vietnamese adults (Lam et al., 2011). Furthermore, a better identification of asthma prevalence around the world following ISAAC studies has indicated similar incidence of paediatric asthma in Viet Nam compared to European countries, in contrast to most developing countries that show comparatively low prevalence (Nga et al., 2003).

Therefore, Viet Nam needs the urgent development of lung function tests for asthma diagnosis and management. Also, a deeper understanding of asthma in Viet Nam is necessary to optimize diagnosis and treatment, particularly in the socio-economic context where long term therapy may be costly and should therefore be restricted to those patients that really need it.

1.2. Lack of awareness of lung function tests in Viet Nam

Two national conferences of physiology in 1968 and 1972 established for the first time normal lung function parameters by spirometry. In 2000, total lung capacity, functional residual capacity and residual volume were measured in healthy Vietnamese aged 20 to 40 using the Helium dilution technique in

Hanoi Medical University. Instead of “routine”, the results however have not been published in any international journal.

Pulmonologists in Hanoi based asthma diagnosis mainly on clinical symptoms and physical examination but do not routinely trust the identification of airway obstruction and reversibility by spirometry. The difficulty of applying lung function tests to diagnose asthma or other lung diseases may also be caused by lung function tests being available only in some central hospitals. In addition, parents may be afraid by the procedure to measure lung function in their child. Finally, the ability of children to cooperate with some of these tests may be limited as in other countries. In my opinion, all these reasons have limited the physician’s motivation to develop lung function testing. As a consequence, the accuracy of asthma diagnosis in Viet Nam is low and needs to be improved.

I have visited some respiratory centers in the north of Viet Nam and only a few have lung function testing available. Moreover, the reference data specific to the Vietnamese population is quite limited (table 1). In the biggest national hospital for children as well as in the Hospital of Hanoi Medical University, only spirometry is available with no Vietnamese reference data. The plethysmographic technique was brought to Hanoi by the end of 2009, with the help of the department of lung function testing in Nancy Children Hospital, and this is the machine that has been used in my study in the laboratory of Physiology, Hanoi Medical University. Unfortunately, spirometry was not available at the time the study was started, and therefore could not be applied. In 2011, a modern plethysmograph arrived in Bach Mai hospital – the biggest central university hospital particularly for pulmonology, but has not been used in daily activity until recently.

In a local hospital of Hanoi named Saint Paul, both spirometry and forced oscillation technique have been developed in collaboration with Nancy to study healthy and asthmatic children (Vu TL. et al., 2008; Vu TL et al., 2010; Nguyen .Y.T et al 20). One interesting hypothesis on airway growth was made in the conclusion of one study and contributed to the aim of the current investigation.

Table 1: The context of lung function test in the North of Viet Nam

Name of hospital	Technique	Reference data
The National Hospital of Pediatrics	Spirometry	Asian
The Hospital of Hanoi Medical University - CHU	Spirometry	Asian
The laboratory of Physiology – Hanoi Medical University (where the study was set up)	Spirometry (not available at studying time) Helium gas dilution Plethysmography (2009) (not apply in routine practice yet)	Asian No reference data
The Bach Mai National hospital – CHU	Spirometry Plethysmography (2011) (not apply in routine practice yet)	Asian No reference data
The Saint Paul Hospital – Local hospital of Ha Noi.	Spirometry Forced oscillation technique (FOT)	Asian

2. MOTIVATION

To characterize respiratory mechanics in healthy children in Hanoi, the respiratory resistance relationship to body height was characterized in the age ranged 6 to 10 years. The comparison with data from literature using the same technique suggested a difference in slope. The same respiratory resistance was found at height 110 cm, while a difference was suggested at 130 cm with larger value in Vietnamese subjects, suggesting smaller airways in older Vietnamese children (figure 2, Vu et al., 2008).

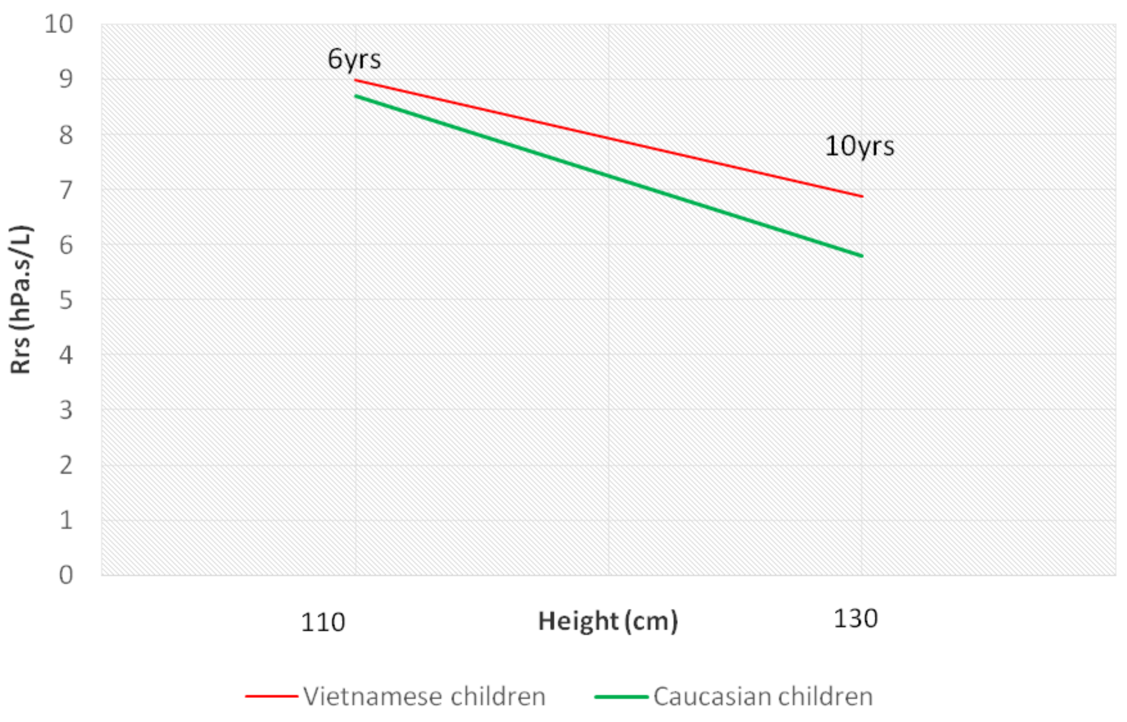


Figure 2: Same Rrs at height 110 cm but apparent difference at 130 cm between Vietnamese and Caucasian children

It was reasoned that should such a difference in airway calibre be consistent and significant later throughout growth, young healthy Caucasian and Vietnamese adults would demonstrate a similar trend. This hypothesis motivated the measurement of airway mechanics in healthy Caucasian and

Vietnamese young adults using similar technique. A repeated suggestion that lung function differs between Caucasian and Asiatic subjects (Ip et al., 2000a; Ip et al., 2000b; Strippoli et al., 2013; Yang et al., 1991) further encouraged the investigation. The question was: whether the suggested difference in airway calibre between the two paediatric populations in Vu et al’s study (Vu et al., 2008) would impact on plethysmographic measurement in young adults. The null hypothesis was that airway calibre would be similar in Vietnamese and Caucasians. The major end points were the airway resistance and the specific airway resistance, and lung volumes.

3. AIMS OF THE STUDY

The aim of the study was therefore to test the hypothesis that airway resistance and specific airway resistance are different between Vietnamese and Caucasian young adults. A secondary aim was to provide reference values for airway mechanics and lung volumes in Vietnamese subjects. Measurements were taken in Nancy and Hanoi where comparable measuring techniques were validated. For this, we took advantage of an ongoing collaboration between France and Vietnam to implement the lung function laboratory in Hanoi Medical University, Hanoi, Vietnam (HMU) with a body Plethysmography (the first plethysmograph in Hanoi) identical to that used in the paediatric lung function department in Nancy, France.

4. THE PRINCIPLE OF PLETHYSMOGRAPHY

4.1. What is plethysmography?

A plethysmograph is a virtually airtight body box that allows the subject to sit inside. Plethysmography measures static lung volumes, i.e.: those volumes that include residual volume (RV) - the gas volume that remains inside the lung at the end of a full expiration, i.e. Functional residual capacity (FRC), the lung volume at the end of a tidal expiration, and total lung capacity (TLC) the total volume of gas in the lung after a full inspiration.

In addition, plethysmography is a unique technique that provides an estimate of alveolar pressure, and therefore has the potential to measure specific airway resistance (sRaw) and calculate airway resistance (Raw) which are most valuable for asthma diagnosis (Goldman, 2005; Miller et al., 2005).

4.2. Lung volume measurement

Plethysmography was first described by Dubois in 1956 (Dubois et al., 1956) as a method to measure static lung volume. The principle is based on Boyle’s law that states that, under isothermal conditions, the volume of a gas enclosed in a rigid container decreases when pressure increases, and vice versa. Hence the product of volume and pressure is constant (Dubois et al., 1956) and may be written:

$$P.V = nRT \qquad [1]$$

(P = pressure of the gas, V = volume of the gas, n is Avogadro number, R is gas constant, T is gas temperature). When temperature is constant, the equation can then be rewritten as:

$$P1.V1 = P2.V2; \text{ or } P.V = (P + \Delta P) . (V + \Delta V) \qquad [2]$$

ΔP and, ΔV are respectively the change in pressure and volume during compression – decompression.

Equation [2] can be expanded:

$$P.V = P.V + P.\Delta V + \Delta P.V + \Delta P.\Delta V \quad [3]$$

Because ΔP and ΔV are small in comparison with P and V respectively, the product $\Delta P.\Delta V$ may be neglected, leading to:

$$\Delta V/ \Delta P= - V/P \quad [4]$$

$\Delta V/\Delta P$ is the compliance of the gas (or gas compressibility, Cg) that may also be defined as:

$$Cg = V/P \quad [5]$$

In plethysmography, V is the volume of gas compressed or decompressed inside the lung (thoracic gas volume, TGV) and P barometric pressure (PB) minus the pressure of water vapor at body temperature. Therefore:

$$Cg = TGV / (PB – 47) \quad [6]$$

Cg will be helpful in section 2.2 to characterize airway resistance.

- **Thoracic gas volume**

TGV is the absolute volume of gas inside the chest and is contributed to mostly by the volume of the alveoli. Compression and decompression of TGV is assumed to occur under isothermal conditions, so that equation [5] may be applied to TGV as follows:

$$\Delta V/ \Delta P = TGV/(P_B – 47) \quad [7]$$

Or

$$TGV = (\Delta V/\Delta P).(P_B - 47) \quad [8]$$

ΔP is easily measured at the mouth using a differential pressure transducer. The challenge of plethysmography is to measure ΔV which may be only a few hundreds of milliliters and should be the object of attentive metrological care.

- **Functional Residual Capacity and other lung volumes**

The expiratory position is identified at the beginning of the measurement, so that FRC may be calculated by correcting for the difference between TGV and the latter.

If the subject takes a vital capacity maneuver at the end of the measurement then TLC ad RV can be obtained (figure 2)

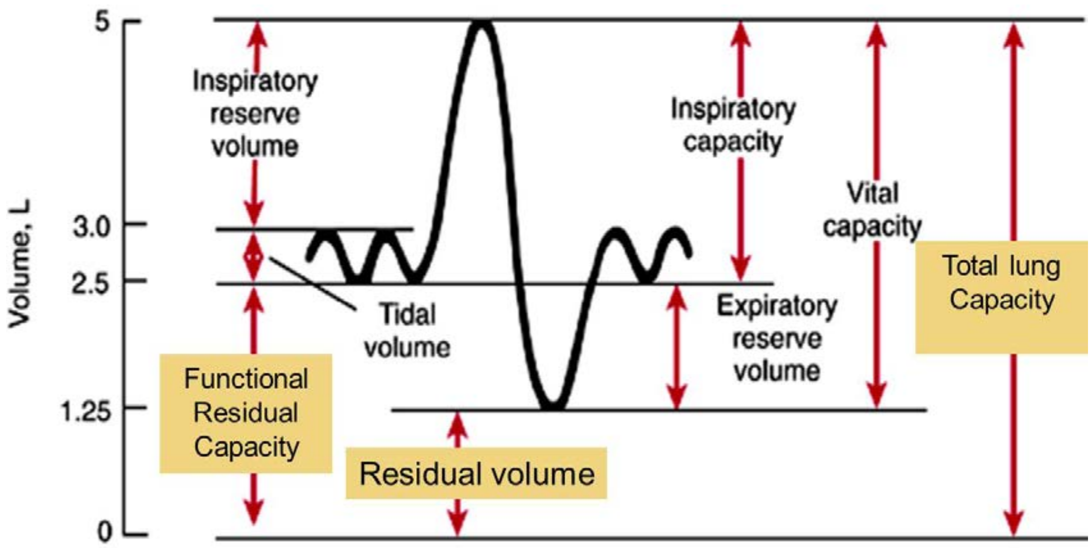


Figure 3: Lung volumes and capacities measured by Plethysmography are highlighted in yellow

4.3. Specific airway resistance and airway resistance measurement

Plethysmography also allows the measurement of airway resistance (Raw) and the specific airway resistance (sRaw) which are both important tools to diagnose asthma in children. Raw represents pressure losses due to flow in the airways. In a model where flow (V') regimen is laminar, Raw may be determined according to Poiseuille's law:

P_{alv} = Raw. V' [9]

Where Palv is alveolar pressure referenced to the pressure at the airway opening. When a subject breathes inside a plethysmograph, the pressure in the box reflects P_{alv} and the volume changes are related to gas compression and decompression (∆Vbox). The latter also depends on Cg, i.e. the larger the Cg the larger the ∆Vbox. Therefore:

$\Delta Vbox = P_{alv} . C_g$ [10]

Using eq 6 and 9, eq 10 may be altered:

$\Delta Vbox = Raw. V'.TGV/(P_B - 47)$ [11]

And the important relationship expressing sRaw (i.e., the product of Raw by TGV) is obtained as (16):

$sRaw = (\Delta Vbox / V').(P_B - 47)$ [12]

sRaw expresses the resistance of the airways per unit of lung volume. As Raw decreases when lung volume increases, sRaw is constant in a given individual (Dubois et al., 1956). Once sRaw and TGV have been measured, Raw may be easily calculated.

The theory however does not take into account the fact that ∆Vbox has a large component related to the change in temperature and humidity of the respired gas. The artifact has long been recognized and may be eliminated most simply during panting. In young children however where panting may be difficult to achieve, a numerical algorithm has been proposed to achieve the correction during tidal breathing, in replacement for the BTPS conditioning of the respired gas. During my stay in Nancy, I have been involved in studies showing that in those children able to perform the panting maneuver as reference measurement, the numerical correction lead to a significant overestimation of sRaw (Coutier et al., 2014a; Coutier et al., 2014b). These studies have been very helpful to me to become familiar with measurements in children and will be presented further in this document.

5. MATERIALS AND MEASUREMENT

5.1. Subjects

The study was designed as clinical cross-sectional investigations which involves both Caucasian and Vietnamese subjects.

Healthy young adults were recruited among students from HMU and from Université Lorraine, Faculté de Médecine, France (ULFM). Subjects were included on the basis of a medical history negative for tobacco smoking, past year asthma and past month respiratory tract infection. They were otherwise free from chronic respiratory or systemic disease. Physical respiratory and cardiac examinations were normal and the following information was collected: ethnicity, gender, age, standing height, sitting height, weight.

5.2. Equipment and study set up

Two Jaeger MedGraphics 1085 plethysmographs were customized in the department of physiology, ULFM. Body boxes were equipped with similar transducers, electronics, filtering, acquisition procedures and mathematical handling that have been previously described (Peslin et al., 1987). One equipment was set in the lung function department of HELFD, and the other plethysmograph was shipped to the department of physiology, HMU where it was serviced on site by the research engineer (Bruno DEMOULIN) that developed both measuring apparatus. The HMU body box was subjected to a mid-study on site visit, and remote on demand technical assistance was available via an internet connection. Daily quality control procedures included adjusting the gain of the pressure transducer against a water manometer, calibrating the pneumotachograph by the integral method and the plethysmograph signal using the built-in 50 mL reciprocating pump.

5.3. *Measurements*

The subject was placed inside the plethysmograph, a few minutes elapsed for pressure equilibration, and the relevant respiratory maneuvers where explained and trained. The subject was connected to the breathing apparatus through a bacterial filter (PALL filter pro-tec PF 30 SG, USA). Following a quiet tidal breathing period, during which the end expiratory position was determined, the subject was asked to pant at around 2 Hz, continue the efforts during closure of the shutter and finally perform a full inspiration followed by a full expiration (figure 4) sRaw, TGV and vital capacity (VC) were thus obtained consecutively, in that order. The plethysmograph signal versus flow or airway pressure relationships were examined visually X-Y immediately after the acquisition. Those maneuvers showing obvious signal distortion – mostly suggestive of glottis closure or swallowing - were excluded. At least 3 technically acceptable acquisitions were retained.

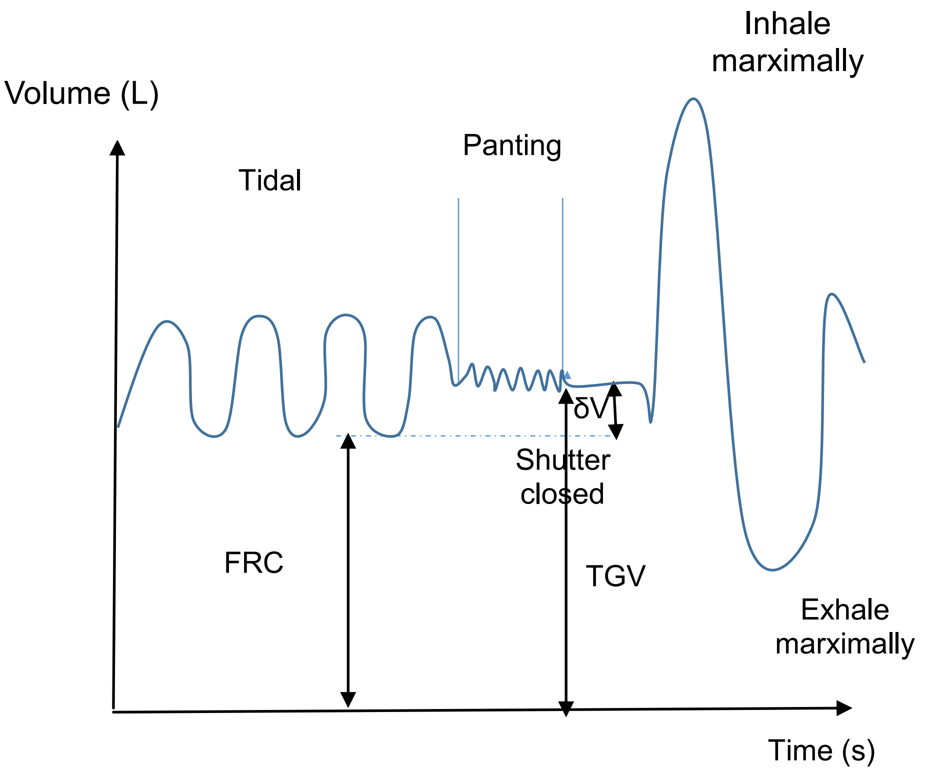


Figure 4: the maneuvers for sRaw and lung volume measurements

All recordings were stored on disk for later analysis and subjected to systematic check by M. Bruno DEMOULIN. The plethysmograph signal was drift-corrected (Peslin et al., 1987) and subjected to linear regression versus V' to compute sRaw, or versus airway pressure to compute TGV. The goodness of fit of each regression line was characterized by a correlation coefficient, usually better than 0.80 for sRaw and 0.97 for TGV. The latter was finally adjusted for the volume difference (δV, figure 4) between the end expiratory level and the occlusion level so as to determine the FRC which was used to compute Raw. From the FRC and VC, TLC, RV and the ratio RV/TLC were computed. Mean values were calculated and tabulated for each individual.

The HMU plethysmograph was set in a climate room, where ambient temperature and relative humidity were similar to those in HELFD (*i.e.:* 25°C and 60%).

5.4. *Ethical aspects*

The protocol was approved by ethical committees from both institutions, an informed consent obtained from the adult subjects or the children's parents.

5.5. *Statistics*

Student t test was used to compare mean values of the different biometric and lung function parameters. Single correlations between independent and dependent variables were calculated using Pearson's test. Multiple linear regression analyses were performed to determine the significant independent variables of sRaw, Raw, and lung volumes. We numbered gender “Male” = “1” and “Female = 2”, Ethnicity “Caucasian” = 1 and “Asian” = 2.

6. RESULTS

While Caucasian medical students all met the technical requirements for TGV and sRaw, Vietnamese subjects appeared less familiar and data from 45 subjects of a total of 140 were excluded from the analysis. Altogether 95 subjects in HMU (60 males, 35 females) and 101 in HELFD (41 males, 60 females) fulfilled inclusion criteria.

6.1. Comparison between two ethnicities

The comparison of biometrical characteristics between two ethnicities is described in the table 2 below.

Table 2: Biometrical characteristics of two groups

Population	**Vietnamese**		**French**		**p (V vs F)**
Gender	Male	Female	Male	Female	
N	60	35	41	60	
Age (year)	20.8 ± 1.65	20.7 ± 2.0	21.2 ± 2.1	21.4 ± 2.1	0.07
Standing height (cm)	168.3 ± 4.1	154.7 ± 5.6°	176.1 ± 5.3	164.4 ± 5.3°	< 0.0001
Sitting height (cm)	88.3 ± 4.0	83.8 ± 4.0°	92.5 ± 3.0	87.6 ± 3.0°	< 0.0001
Body weight (kg)	61.0 ± 8.4	49.1 ± 5.1°	70.0 ± 8.3	57.6 ± 8.7°	< 0.0001

Vs male: (°) $p < 0.0001$; (*) $p < 0.05$

The gender ratio was significantly different, with a larger proportion of males being recruited in Hanoi ($p = 0.002$) and the data are therefore presented while stratified for gender. Weight, standing and sitting height were significantly lower in Vietnamese than Caucasians and in females than in males (p < 0.0001). The gender related difference was apparently similar in both ethnic groups.

6.2. Raw and sRaw

Raw was significantly larger in Vietnamese than Caucasians and in females than males (p <0.05), with comparable effects of gender in both ethnic groups (table 3). Panting frequency was higher in Vietnamese than Caucasian subjects, and in females than males (table 3).

Table 3: Raw and sRaw

Gender	Male		Female	
Population	Vietnamese	Caucasian	Vietnamese	Caucasian
N	60	41	35	60
Age (year)	20.8 ± 1.65	21.2 ± 2.1	20.7 ± 2.0	21.4 ± 2.1
Raw (hPa.s/L)	1.75 ± 0.65	1.47 ± .58	2.53 ± 1.40°	1.95 ± .56°
sRaw (hPa.s)	5.19 ± 1.86	5.10 ± 1.90	5.38 ± 2.03	5.41 ± 1.65
Panting frequency (Hz)	3.3 ± 0.9	3.0 ± 0.8	3.1 ± 0.7*	2.7 ± 0.7*

Vs male: (°) p < 0.0001; (*) p< 0.05

Significant correlations were disclosed between Raw and standing height, sitting height, weight, FRC but not age or panting frequency. Pearson's correlation coefficients are listed in table 4.

	Table 4: Pearson's correlation coefficient of factors of Raw and sRaw									
	TGV	FRC	VC	RV	TLC	Standing Height	Sitting height	Weight	Age	Panting frequency
Raw	**-.392****	**-.506****	**-.453****	-.066	**-.419****	**-.411****	**-.264****	**-.270****	-.062	-.078
sRaw	.044	.094	**-.161***	**.254****	.003	-.078	-.039	-.083	-.031	-.117

(**) p < 0.0001; (*) p< 0.05

The multiple linear regression analysis indicated that FRC was in fact the only parameter significantly and independently related to Raw ($p < 0.0001$) (table 5).

Table 5: FRC is an independent parameter of Raw		
Variable	*Model of Raw*	
	P	Model
FRC	< 0.0001	6.35 – 0.47 x FRC (adjusted $R^2 = 0.27$)

The relationship between Raw and FRC presented in figure 5 indeed indicates data points for Vietnamese or French males and females roughly distributed along the same hyperbola.

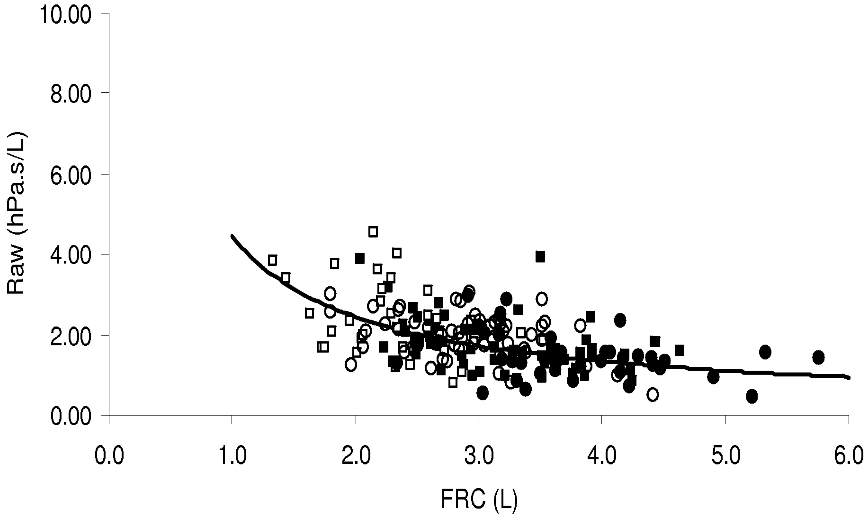


Figure 5: relationship between airway resistance (Raw) and Functional Residual Capacity (FRC) in healthy young adult males (closed symbols) and females (open symbols) from Hanoi, Viet Nam (squares) and Nancy, France (circles). Note distribution along a single hyperbola, in keeping with lack of gender or ethnic related difference in specific airway resistance

As expected from prior relationships, sRaw was found not to be different between males and females nor between Vietnamese and French (table 3). sRaw averaged 5.2 hPa.s in males and 5.4 hPa.s in females and was independent of almost all relevant variables, except FRC, which was found to show significant but weak relationship (table 6).

Table 6: Relationship between FRC and sRaw

Variable	sRaw	
	P	Model
FRC	0.04	11.69 + 0.58 x FRC (adjusted R^2 = 0.096)

6.3. *Lung volumes*

The values of TLC, RV and VC of Vietnamese in comparison with Caucasian subjects, are described in table 7.

Table 7: Lung volumes					
Population	**Vietnamese**		**French**		**p (V vs F)**
Gender	Male	Female	Male	Female	
N	60	35	41	60	
TLC (L)	5.62 ± 0.67	4.26 ± 0.63	6.81± 0.75	5.01 ± 0.57	0.0004
VC (L)	3.78± 0.66	2.78 ± 0.45	4.94 ± 0.68	3.72 ± 0.53	< 0.0001
RV (L)	1.84 ± 0.64	1.48 ± 0.43	1.87 ± 0.68	1.29 ± 0.34	0.0118
RV/TLC (%)	0.33 ± 0.10	0.34 ± 0.07	0.27 ± 0.08	0.26 ± 0.07	<0.0001

6.4. *Predictors of lung volumes*

Table 8 describes Pearson's correlation coefficients between lung volumes and independent variables. It may be seen that standing height and sitting height were both related to TLC, FRC and RV significantly.

Table 8: Pearson's correlation coefficient of factors of RV, FRC, TLC						
	Raw	sRaw	Standing Height	Sitting height	Weight	Age
RV	-.066	**.254****	**.370****	**.257****	**.160***	**-.193****
VC	-.453**	-.161*	.725**	.581**	.666**	.131
TLC	.003	**.818****	**.639****	**.650****	**-.419****	.004
(**) p < 0.0001; (*) p< 0.05						

The multiple linear regression analysis indicates the significant independent predictive variables which are described in figure predicting models to TLC, RV, and VC, with factors were ethnicity, gender, standing height or sitting height, age, and weight.

The predicting model of total lung capacity is described in the figure 6. In the multiple linear regression model to determine the predictors of total lung capacity, standing height was found the most important predictor of total lung capacity, together with gender and ethnicity were significant predictors. Interestingly, the sitting height disappeared from the model when we put it beside the standing height and other factors. The weight and age were not predictors of total lung capacity.

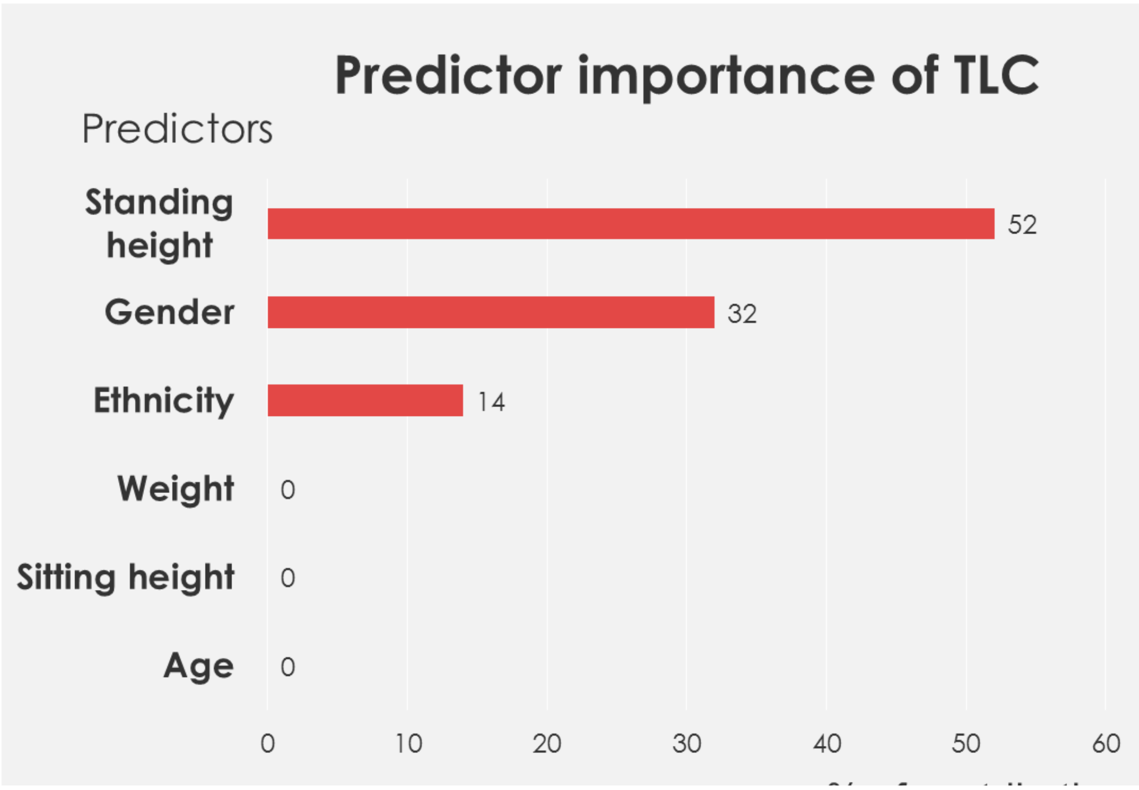


Figure 6: The model to predicting TLC in which standing height is the best predictor while sitting height disappeared.

Standing height also played the most important role to predict residual volume together with ethnicity and age. The weight, the gender and sitting height were not predictors of residual volume, while the age appears in the model in comparison with the model of TLC. The model is described in figure 7 as follows.

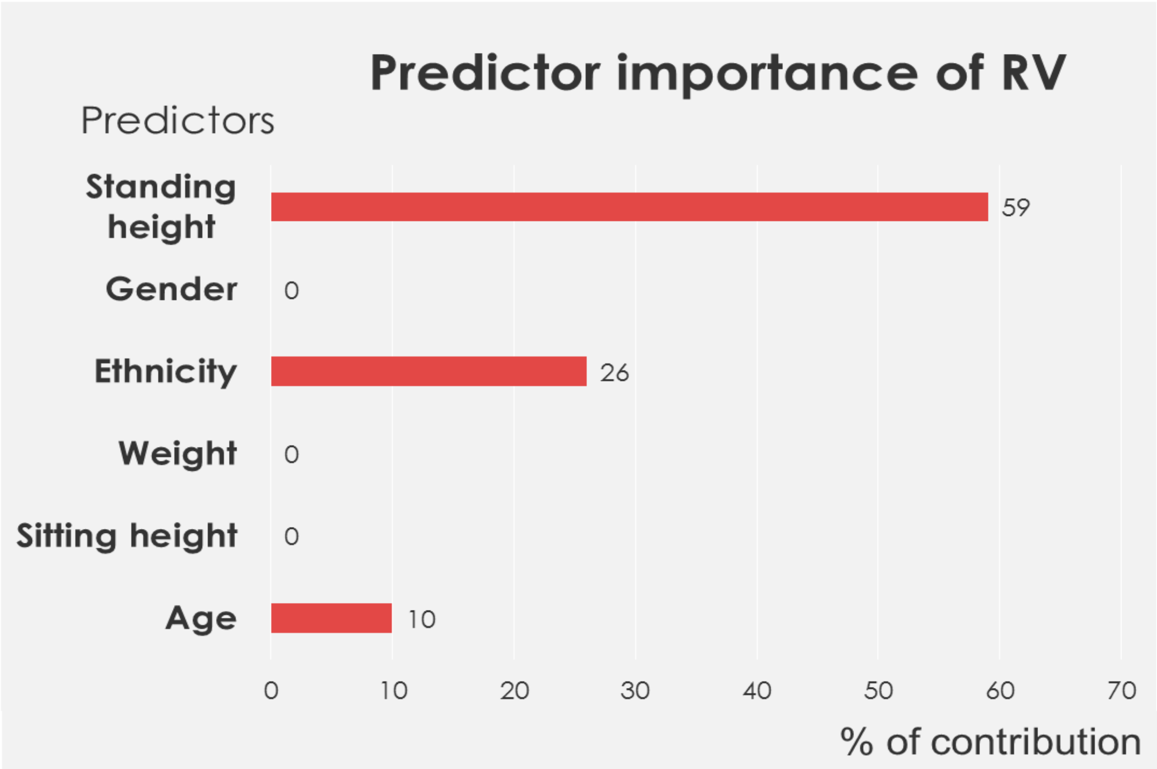


Figure 7: The model to predicting RV in which standing height is the best predictor while sitting height still disappeared.

Standing height however play less important in predicting the vital capacity, while ethnicity is the best one.

The sitting height is still disappeared, along with age in the model to predict vital capacity. The weight gives more importance in this model.

The predicting model of vital capacity is in the figure 8.

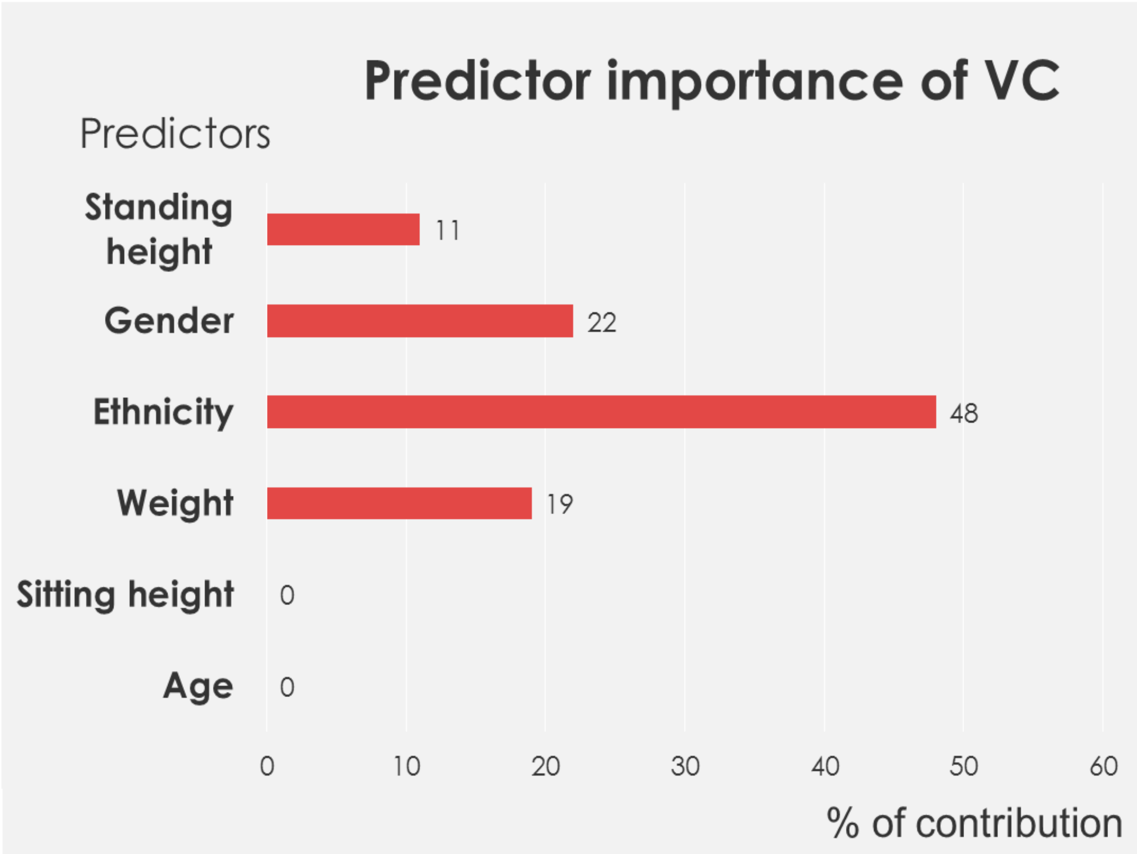


Figure 8: Ethnicity was the best predictor of VC while standing height play less important role in this model. Sitting height and age were not predictors of VC.

The predictors of total lung capacity of in each ethnicity were the same, with standing height is the best predictor and gender (figure 9).

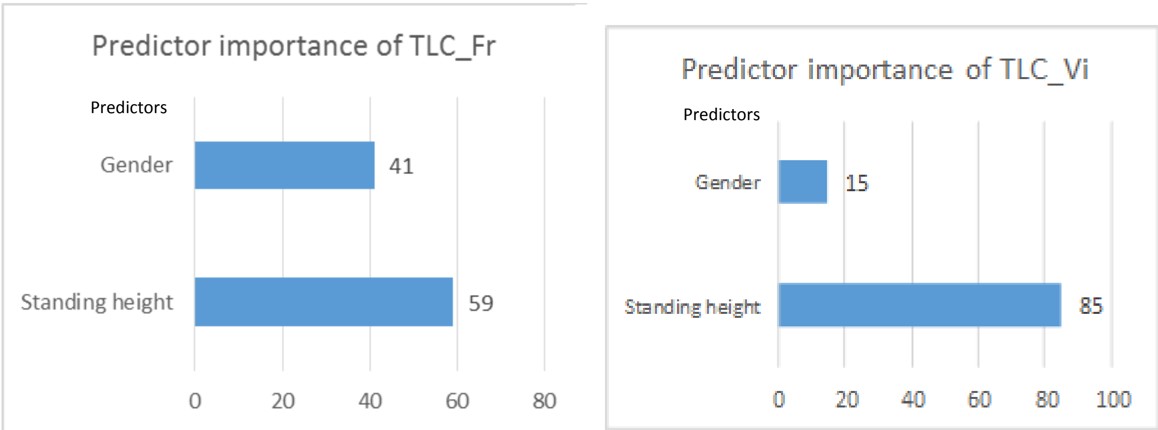


Figure 9: Predictors of total lung capacity in each ethnicity indicated that standing height is the best predictor of TLC in each ethnicity.

Figure 10 presents the predicting model of thoracic distention ratio that is obtained by RV divided to TLC (RV/TLC ratio) in which ethnicity was the best predictor, together with weight, age, and standing height appeared in this model. The gender and the sitting height were not the predictors in this model.

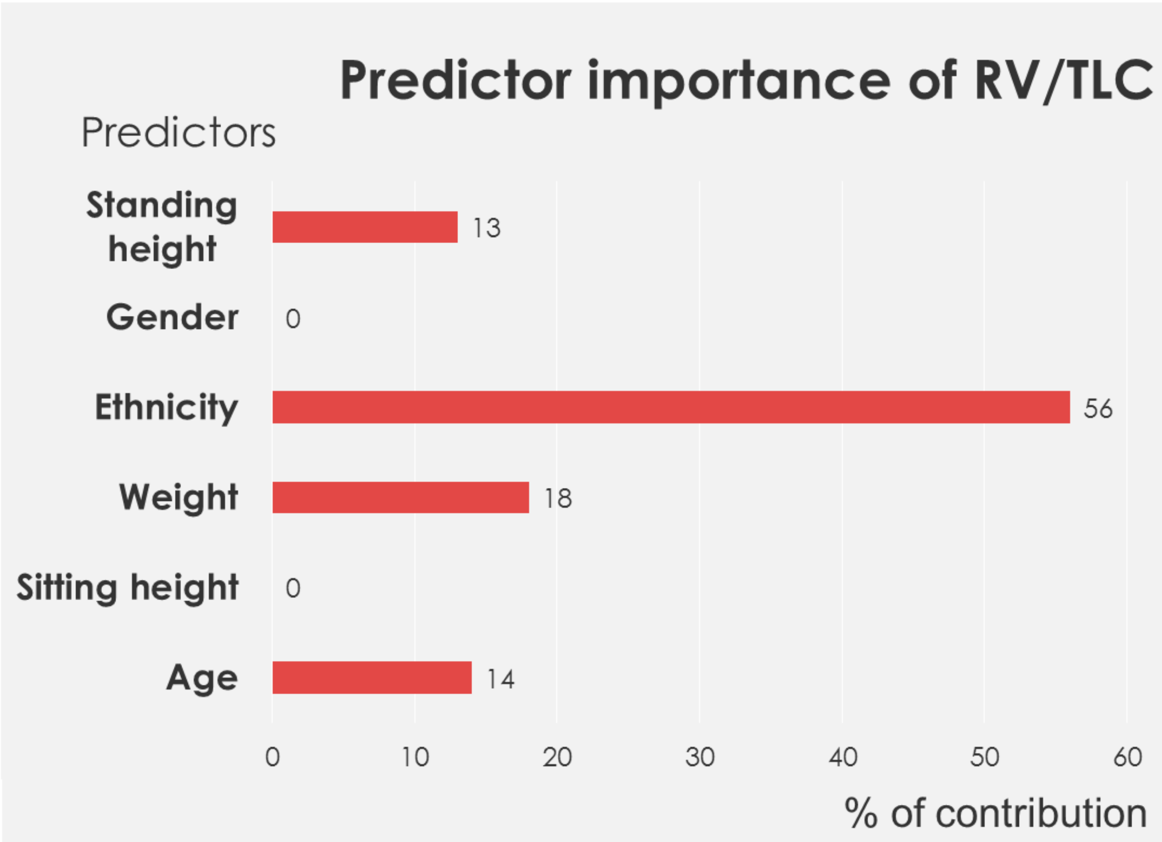


Figure 10: Predictors of thoracic distention ratio (RV/TLC %) with ethnicity was the best predictor of this ratio.

7. DISCUSSION

In this study, Raw and absolute lung volumes are smaller than in Caucasians, but there is no difference in sRaw.

7.1. Ethnicity and airway resistance

The difference in Raw between the two ethnicities is original and was not previously identified in the literature. The finding is particularly valuable in view of the particular protocol that involved similar equipment in two laboratories in different countries. Even though efforts have been made to standardize protocols in the two laboratories, slight differences in measuring conditions were observed. The larger Raw in Vietnamese could be explained by the higher panting frequency in Vietnamese subjects. In these conditions, higher, and therefore more turbulent flows are likely to occur. As a result, the computed airway resistance will be larger, according to Rohrer's model described in figure 11. In laminar conditions observed at low flow, the slope of the relationship between pressure loss and flow is smaller than during turbulent conditions because of non linearities.

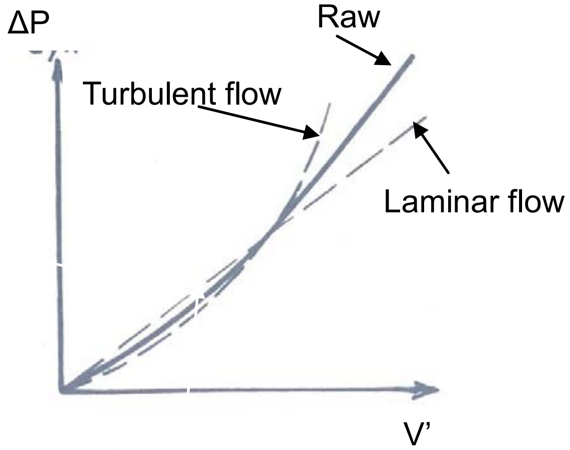


Figure 11: larger flow causes higher Raw because of turbulent regimen.

In a study of Peslin et al (1996), the breathing frequency was found significantly related to airway resistance, with higher frequency causing higher Raw and sRaw (fig 12). The contribution of the difference in panting frequency in the current study may therefore not be fully eliminated. However, the multiple linear regression model showed that there was no statistically significant role of frequency in determining airway resistance. In addition, the relationship between frequency and airway resistance in the study of Peslin et al was partly related to the thermal effect which did not interfere in the current frequency range.

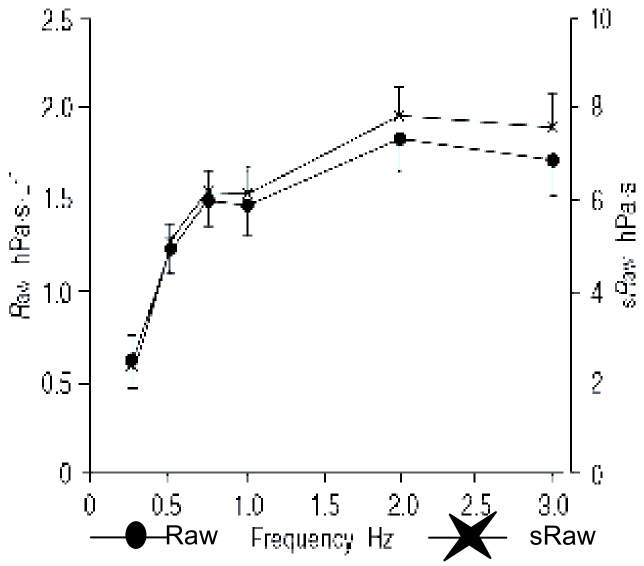


Figure 12: Higher breathing frequency is associated with higher airway. Peslin R. et al (1996).

A major finding was that Raw was found to relate to FRC similarly in both two laboratories, and sRaw was independent on gender and ethnicity. The hyperbolic relationship between airway resistance and lung volume has been characterized using multiple data points at different volumes in some healthy individuals (Briscoe and Dubois, 1958). In the current report, a unique relationship may also be demonstrated from single measurement at FRC in a number of subjects with different ethnical and socio-economic backgrounds.

The current results do not support the hypothesis that the apparently different respiratory resistance - body height relationship reported between Vietnamese and Caucasian children (Vu et al., 2008) impacts airway size at adult age - once it is normalized for lung volume. The airway size – lung volume relationship is determined by the tethering of lung tissue onto the intra-parenchymal airways, and generally expresses the interaction between elastic lung recoil and airway distensibility. Measurements during growth have demonstrated lung compliance to be linearly related to FRC in children beyond 4 years of age, with slope - i.e. the specific lung compliance - approximating 0.04 – 0.06 hPa^{-1} (Polgar, 1971). In young adults the elastic recoil of the lung was found to be similar in Asiatic and Caucasian subjects, not surprisingly since the specific lung compliance was shown to be rather constant among mammals of different species (Chan et al., 1995). As a result, the lung tissue pull on airway wall should be similar in both ethnic groups. Airway, bronchial and/or tracheal distensibility have been studied in healthy young adults using different methodological approaches (Brown et al., 2007; Hoffstein et al., 1987; Kelly et al., 2012; Noble et al., 2010), but we are aware of little data on ethnicity - dependence of this mechanical property. Comparative measurements in asthmatics and controls demonstrated that airway smooth muscle tone and airway wall remodeling were major determinants for the increased airway wall stiffness in asthma (Brown et al., 2007; Kelly et al., 2012). Unless difference in airway smooth muscle mechanical properties exists between healthy Caucasian and Asiatic subjects, airway distensibility is unlikely to vary with ethnicity. Interestingly, while reviewing lung function data of healthy young adults enrolled in a study in respiratory effects of ambient ozone concentration, no difference in sRaw was reported between Caucasian Americans and African Americans, in contrast with differences observed in lung volume and expiratory flows (McDonnell and Seal, 1991).

sRaw averages about 5.3 hPa.sec, and, in contrast to Raw, does not significantly depend on standing or sitting height, gender or ethnicity. Interestingly, the fact that comparable measurements were obtained in ethnical group in its own native environment indicates that environmental factors do not significantly impact on the airway resistance – lung volume relationship in young adults.

While the Raw – FRC relationship was found comparable in Caucasian and Asiatic young adults of both genders, the multiple regression analysis disclosed a weak but significant positive relationship between sRaw and FRC. When analyzing the coupling between lung and airway size, Mead used the ratio of the upstream airway conductance to vital capacity during forced expiration. The theoretical analysis showed the ratio – that has dimension of a specific airway conductance - would be predicted to decrease slightly with vital capacity if turbulent flow was accounted for (Mead, 1980). We are aware that the specific airway conductance was defined with respect to vital capacity, so that transposition to the current study - where sRaw is related to the volume at which it is measured - should be made with caution (Mead, 1980). Nevertheless, it is interesting that the current positive association between sRaw and FRC may relate to rheological conditions, especially as turbulent flow is majored during panting. It must also be noted that the statistical relationship is weak and explain only 9.6% (p=0.04) of the value of sRaw according to the equation in table 5.

Our previous suggestion that the relationship between respiratory resistance and height may differ between Asiatic and Caucasian school children (Vu et al., 2008) may stem from the differential rate of growth in airway size and lung volume. The rapid increase in lung volume with ongoing alveolar multiplication, contrasting with the slower development of the more mature bronchial tree has indeed been reported in infancy, resulting in an increase in sRaw during that period of life (Doershuk et al., 1974; Stocks, 1977). Furthermore, the lung volume-corrected maximal mid expiratory flow has been observed to decrease from 8 to 12 years of age, a further indication that the airway caliber would continue to grow at a slower rate than lung volume (Hibbert et al., 1984). To the best of our knowledge, whether the differential rate of growth between airways and lung parenchyma during childhood has ethnic specificities is not known. It is noteworthy however that the relationship between FEV1 and body height in 10 years old children exhibited a lower slope in Chinese compared with Caucasian (Yang et al., 1991). Finally it may be added that in our previous study (Vu et al., 2008), the respiratory resistance measured using the forced oscillation technique at 8 Hz encompasses a number of properties not strictly related to intrathoracic airways size, such as mechanical characteristics of lung and chest wall tissues or the parallel impedance of the airway wall.

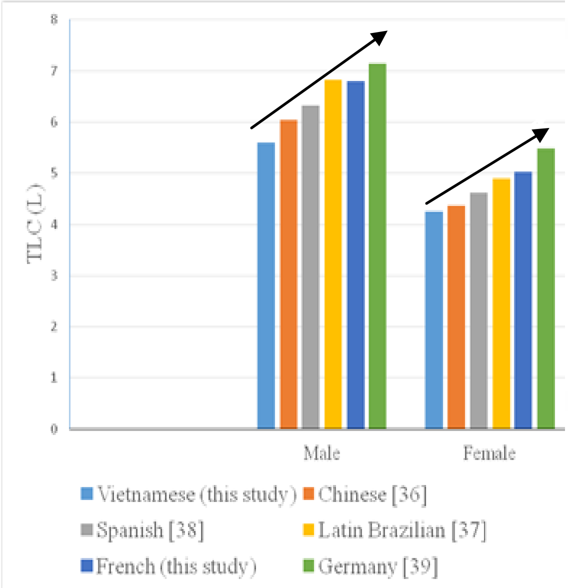
It concluded that the specific airway resistance offers similar characteristics in healthy Asiatic and Caucasian young adults while measured in Vietnam and France, respectively. As a consequence, the apparently lower slope of the respiratory resistance to body height relationship suggested in Asiatic compared with Caucasian children at school age does no impact airway size - once it has been normalized for lung volume - at adult age.

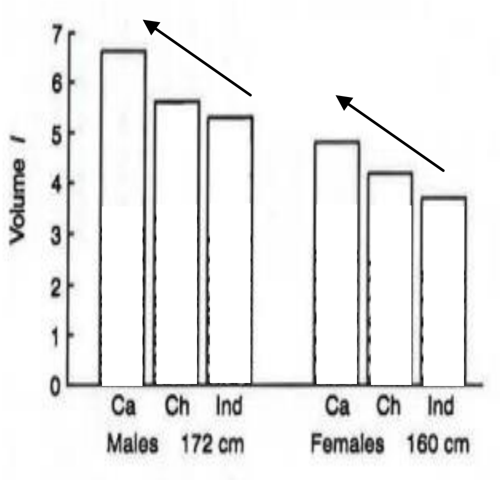
7.2. Lung volumes

Reference values are important to consider normality of measured lung volumes in an individual. Ideally, they should be obtained in the relevant particular ethnical population. This study provides the first description of lung volumes in Vietnamese young healthy adults.

TLC depends on airspace volume, rib cage dimensions and the ability to expand the lungs and it was found significantly higher in Caucasians than Vietnamese. The statistical model to predict TLC was based on ethnicity, gender, age, standing height, sitting height, and weight. Figure 5 indicates that TLC is significantly related to ethnicity, standing height and gender. The model could explain 71.3 % of the variation in TLC. Surprisingly, sitting height was not a significant predictive variable of any lung volume, as it would have been expected a closer proxy to chest wall dimensions than standing height. A possible explanation may relate to the larger variability in the measurement of sitting than standing height. It must also be emphazised that the age and stature ranges were rather small, and the current findings would perhaps not apply in a population including children and adults.

Studies on TLC from various countries are presented in figure 13. TLC of Vietnamese young adults appear to be close to those reported in Chinese, both being also lower than in subjects of Spanish, Latin Brazilian, French or German origin. The trend for TLC to be smaller in female than male also appeared in figure 13.





Means of total lung capacity of Caucasian, Chinese and Indian males at 172 cm of body height, and females of 160 cm, both of age 30 years old.

Figure 13: TLC of Vietnamese (light blue column) and French (dark blue column) young healthy adults from 18 to 25 yrs in comparison with Chinese (Ren et al., 2012), Latin Brazilian (Neder et al., 1999), Spanish (Cordero et al., 1999), and German (Koch et al., 2013) at the same range of age in two genders. It is noted that TLC of Asian (Vietnamese and Chinese) were lower than of Caucasian subjects. The same observation was obtained in the study of (Yang et al., 1991) where TLC was higher in Caucasian than in Chinese and lowest in Indian. A lower value in female than male was also reported.

Static lung volumes are also related to the compliance of the lung – i.e., its distensibility – but the latter may be expected to be similar between Asians and Caucasians, based on prior measurements of specific lung elastance in these two populations (Chan et al., 1995). In addition, a smaller inspiratory muscle strength may account for the difference in TLC, but there is no current data to support the hypothesis.

Altogether, the fact that standing height is the major determinant of TLC in both groups suggests that lung size eventually is the major explanation to the difference in TLC among ethnicities. A plethysmographic study in Chinese and Caucasian children and adolescents measured in Hong Kong (Ip et al., 2000) also concluded that standing height was the best predictor of TLC. A study of

Donnelly et al., 1991 determined what factors best determine lung volume, among standing height, chest dimensions - including widths at base, middle and apex - and length of the lung. Interestingly, the multiple regression showed that chest middle width together with standing height but not the length of lung finally appeared as significant predictors of TLC, explaining 86% of the variation. In our study, the standing height alone was found to explain 52% of the variation while, again, sitting height - which is expected to be mostly descriptive of the length of lung – was excluded from the prediction model.

Surprisingly, and in contrast with recent reports (Quanjer et al., 2012), ethnicity was found more predictive of VC than standing height, although the significance of standing height was larger in Caucasians. The reason might be related to the rather small age and height span of the subjects as stated previously, therefore a methodological bias rather than a true physiological finding. On the other hand, a difference of muscle strength may be present between ethnicities, with smaller strength in Vietnamese subjects. It is interesting that the RV/TLC ratio is mainly determined by ethnicity, and it may be speculated that the higher ratio in Vietnamese could be related to a less powerful expiratory effort that in turn would contribute to a smaller VC.

A limitation to our study relates to the fact that forced expiration could not be studied, to provide forced vital capacity and forced expiratory volume in 1 second and therefore allow a more meaningful comparison with recent compilation of spirometric data across the world (Quanjer et al., 2012) Nevertheless, we found evidence from the literature that useful clinical information may rely upon the RV/TLC ratio (Joseph, 2011) as a complement to FEV1/FVC for asthma diagnosis. For instance, FEV1/FVC may be more related to the larger airways caliber and central airway obstruction and

RV/TLC to smaller airways and gas trapping. FEV1/FVC is widely measured in the context of asthma all around the world (Quanjer et al., 2012) as the methodology is easy to apply but further studies on RV/TLC ratio would certainly be beneficial to a sharper assessment of asthmatic subjects.

To summarise this section, these are the first data of lung volumes by plethysmography in healthy young Vietnamese adults, which is promising for asthma management and diagnosis in this population. Ethnicity is an independent factor for VC but standing height is the most important predictor of TLC in both two ethnicities. The different RV/TLC ratio between the two groups may relate to a lower expiratory effort in Vietnamese subjects. Further study for fully understanding the lung volume growth in Vietnamese population is required.

8. PROSPECTIVES

Body plethysmography has been found feasible in our set up and the method will now be applied to children as well. The possibility to measure sRaw during tidal breathing is attractive as requiring little cooperation, but the thermal artefact has been demonstrated to be an important source of error (REF) so that the training of children with the panting manoeuvre is an attractive alternative. Indeed, in the study of Coutier et al., 2014b panting has been determined as useful a method in school children.

Plethysmographic sRaw discriminates asthmatics from healthy controls in children (Marchal et al., 2005), (Mahut et al., 2010), (Wanger, 2011), (Criee et al., 2011) and deserves further evaluation in Viet Nam.

To further investigate on Vietnamese children, I would like to propose a project protocol with 4 main steps: Educating, Training, Researching, and Expanding. The education will be provided to medical students, doctors and population, and training to the technicians. The research then be performed on volunteer children and parents. Finally, we will expand the protocol of plethsymography to the other respiratory centers. I would like to do further study on Vietnamese children in order to apply the Plethysmography technique along with other techniques, such as spirometry, and forced oscillation technique, to complete the research protocol on both adult and children. I also understand about the importance of bronchodilation test, such as with ventolin, and bronchoconstriction test, such as methacholine and mannitol, for asthma diagnosis and management.

Forced oscillation technique seems to be easier to children since it requires little corporation: the measurement is performed during tidal breathing of subjects. The spirometry is the most popular and useful technique because while the measurement is not much difficult, the machine is small and its price is not expensive. To complete the research protocol, we will use these two techniques together with plethysmography on asthma diagnosis for children.

Bronchodilator test has not been applied routinely in clinical practice, while it is recommended in almost of international asthma diagnosis protocol. A fact that broncho-provocation test has not been available in Viet Nam during the studying time. We interviewed some pulmonologists and received the answer that there are three reasons of this condition: firstly, we lack of the machine to divide and mix the methacholine into such a minor dose written in the protocol of technique. Secondly, it has had no study of methacholine or mannitol on Vietnamese population yet until now. And thirdly, about exercise test, the concern is not enough to build up a costly climate room with the standard equipment.

A small and young research group named FSH-AD, which stands for "Friendship and Science for Health – Asthma Diagnosis", was founded in 2013 by the principle investigator of this thesis, which includes two medical students and one peadiatrist in attempt to develop this study on Vietnamese children. We are developing a study proposal for early asthma diagnosis in children after series of discussions and trainings on several topics: "What is medical research?" "Good Clinical Practice – GCP training course", "Clinical application of FOT, Spirometry, Plethysmography", "Asthma diagnosis up to date", "Asthma-like Syndrome and Asthma-COPD Overlap Syndrome", "Early diagnosis of asthma in children", "Methacholine test versus Mannitol test: what is more benefit to asthma patient?", and so on.

Of all above, I wish that this thesis is the first step of standardizing and expanding lung function tests in Vietnamese population, especially the

Plethysmography technique, together with spirometry, FOT, and bronchoprovocation tests in Vietnamese population, particularly in children.

9. SUMMARY OF CONCLUSION

This thesis would provide some outcomes as follow:

To the first aim:

- There is no difference between sRaw among Caucasian and Asiatic young adults when measuring at their native country.
- Standing height is the best predictor of lung volume.
- Ethnicity may be an independent factor of lung volumes due to two reasons: larger lung size and stronger respiratory muscle in Caucasians than Asians, but it is not a predictor of sRaw.

To the second aim:

- This is the first study to provide lung function reference data of Vietnamese healthy young adults including Raw, sRaw, lung volumes and capacities those are measured by Plethysmography.
- The Plethysmography technique was by that validated in the north of Viet Nam.

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11. LIST OF PUBLICATIONS

The thesis's scientific products are the following papers:

I. **Specific airway resistance in healthy young Vietnamese and Caucasian adults.** Thanh LE TUAN, MD[O], Ngoc Minh NGUYEN, MSc[O]; Bruno DEMOULIN, RT[1]; Claude BONABEL, RT[2], Phi Lin NGUYEN THI-LAMBERT, MD, PhD[3]; Iulia IOAN, MD[2]; Cyril SCHWEITZER, MD, PhD[1]; H.T.T. NGUYEN, MD, PhD[O]; Silvia VARECHOVA, MD, PhD[1]; François MARCHAL, MD, MSc[12]. Respir Physiol Neurobiol. 2015 Mar 18.

II. **Specific airway resistance in Children: Panting or Tidal Breathing?** Laurianne Courtier, MD, Silvia Varechova, MD, PhD, Bruno Demoulin, RT, Claude Bonabel, RT, Clotilde Romanamat, **Thanh LE TUAN**, MD, Iulia Ioan, MD, Cyril Schweitzer, MD, and François Marchal, MD. Pediatr Pulmonol. 2014 Mar;49(3):245-51

III. **Flow dependence of Specific airway resistance and diagnostic of asthma in children.** Laurianne Coutier, MD, Iulia Ioan, MD, Ayria Sadegheghbali, Cla ude Bonabel, RT,1Bruno Demoulin, RT, **Thanh LE TUAN,** MD, Fr ançois Marchal, MD, MSc,Cyril Schweitzer, MD, PhD, and Silvia Varech-ova, MD, PhD, Pediatr Pulmonol. 2014;9999:1–6.

APPENDIX

Respiratory Physiology & Neurobiology 211 (2015) 17–21

PAPER I

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

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

Specific airway resistance in healthy young Vietnamese and Caucasian adults

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article info

Article history:
Received 13 November 2014
Received in revised form 25 February 2015
Accepted 2 March 2015
Available online 19 March 2015

Keywords:
Ethnicity
Airway resistance
Functional residual capacity
Specific airway resistance
Plethysmography

abstract

In healthy Vietnamese children the respiratory resistance has been suggested to be similar at 110 cm height but larger at 130 cm when compared with data in Caucasians from the literature, suggesting smaller airways in older Vietnamese children (Vu et al., 2008). The hypothesis tested here is whether the difference in airway resistance remains consistent throughout growth, and if it is larger in adult Vietnamese than in Caucasians. Airway resistance and Functional Residual Capacity were measured in healthy young Caucasian and Vietnamese adults in their respective native country using identical equipment and protocols. Ninety five subjects in Vietnam (60 males) and 101 in France (41 males) were recruited. Airway resistance was significantly larger in Vietnamese than in Caucasians and in females than in males, consistent with difference in body dimensions. Specific airway resistance however was not different by ethnicity or gender. The findings do not support the hypothesis that airway size at adult age – once normalized for lung volume – differs between Vietnamese and Caucasians.

1. Introduction

A better identification of asthma prevalence around the world following the ISAAC studies has indicated a similar incidence of paediatric asthma in Vietnam compared to European countries, in contrast to other developing countries that show comparatively low prevalence (Nga et al., 2003). To optimize the care of asthmatic children in Hanoi, collaborative studies have been undertaken to better characterize lung function in this population (Vu et al., 2008, 2010). Close assessment of the respiratory resistance relationship to body height of healthy Vietnamese children suggests differences with previous values reported in the literature in Caucasians. While the respiratory resistance appeared similar in both groups at 110 cm body height, a larger apparent difference at 130 cm suggested smaller airways in older Vietnamese children (Vu et al., 2008). It was reasoned that, should such a difference in airway calibre be consistent and significant later throughout growth, young healthy Caucasian and Vietnamese adults should demonstrate a similar trend. This hypothesis prompted us to characterize airway mechanics in healthy young Caucasian and Vietnamese adults, in a comparable manner. The repeated observation that lung function differs between Caucasian and Asian subjects (Ip et al., 2000a,b; Quanjer et al., 2012; Strippoli et al., 2013; Yang et al., 1991) further encouraged the study.

Body plethysmography is a unique methodology to assess airway calibre in relation to lung volume. Because the technique is based on measuring a relatively small amount of gas compressed or expanded in the lung, significant metrological care is required, and equipment standardization is mandatory.

The aim of this study was to compare airway resistance measured by plethysmography between healthy young Vietnamese and Caucasian adults. The study was conducted at the lung function laboratory in Hanoi Medical University, in Vietnam (HMU) using a body plethysmograph identical to that used in the lung function department, children's hospital in Nancy, France. The null hypothesis was that airway calibre would be similar in Vietnamese subjects compared with Caucasians. The main end points were the airway resistance and the specific airway resistance.

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ttp://dx.doi.org/10.1016/j.resp.2015.03.002
1569-9048/

2. Materials and methods

2.1. Subjects

Healthy young adults aged 18–30 years were recruited among students from HMU and from the Faculté de Médecine, Université Lorraine, France. Subjects were included on the basis of a history negative for hospital admittance or medical consultation for asthma and past year asthma related symptoms, tobacco smoking, and past month respiratory tract infection. They were otherwise free of chronic respiratory or systemic disease. Physical respiratory and cardiac examinations were normal. Body weight, standing, and sitting height were measured. The protocol was approved by ethical committees from both institutions, and informed consent was obtained from all subjects.

2.2. Equipment and study set up

Two Jaeger MedGraphics 1085 plethysmographs were customized in the department of physiology, Faculté de Médecine, Université Lorraine, France. Body boxes were equipped with similar transducers, electronics, filtering, acquisition procedures, and mathematical handling that have been described previously (Peslin et al., 1987). Briefly, the acquisition frequency was 100 Hz. The time drift in the box volume change was corrected, but no attempt was made to eliminate the looping in the X–Y display vs flow.

One plethysmograph was set in the lung function department, Hôpital d'Enfants, CHU de Nancy France (HELFD) and the other shipped to the department of physiology, HMU. In both locations, ambient temperature and relative humidity were respectively about 25 °C and 60%, the conditions in HMU being maintained in a climate room.

Body boxes were serviced on site by the research engineer (BD) that developed them. A calibration check was performed by this operator on initiating the study, by compressing the gas of a 2.92 L container connected to a 4.3 hPa s/L resistor. The measurements of the mock thoracic gas volume (TGV) and airway resistance (Raw) expressed as percentage of the corresponding nominal value were respectively 105% and 93% in HELFD and 104% and 95% in HMU. The latter body box was subjected to a mid-study on site visit, and remote on demand technical assistance was available via an internet connection. Daily quality control procedures included adjusting the gain of the pressure transducer against a water manometer, calibrating the pneumotachograph by the integral method and the plethysmograph signal using the built-in 50 mL reciprocating pump.

The first author of this report (TL) spent a 2 year fellowship in the department of physiology, Faculté de Médecine, Université Lorraine and in HELFD where he was trained with the measuring equipment and technique, before returning to HMU and completing the Vietnamese side of the study.

2.3. Measurements

The subject was coached with the relevant respiratory manoeuvres and placed in the plethysmograph. After about 1 min to achieve temperature equilibration, the subject was connected to the breathing apparatus of the plethysmograph through a bacterial filter (PALL filter pro-tec PF 30 SG, USA). During a quiet breathing period, the end-expiratory position was determined and the subject was then asked to pant at around 2 Hz, to continue the efforts during closure of the shutter and finally to perform a full inspiration followed by a full expiration. Specific airway resistance (sRaw), thoracic gas volume (TGV) and vital capacity were thus obtained consecutively, in the same order. The sRaw and TGV acquisitions each lasted 2 s, and the signals were digitized at 100 Hz. The plethysmograph volume signal vs flow or airway pressure relationships were examined visually immediately after the acquisition. Those manoeuvres showing obvious signal distortion – mostly suggestive of glottis closure or swallowing – were excluded. The drift-corrected plethysmograph signal (Peslin et al., 1987) was subjected to linear regression versus V′ to compute sRaw, or vs airway pressure to compute TGV. The goodness of fit of each regression line was characterized by a correlation coefficient, usually better than 0.80 for sRaw and 0.97 for TGV. The latter was finally adjusted for the volume difference from the end expiratory position during occlusion so as to determine FRC which was used to compute the airway resistance (Raw).

At least three technically acceptable acquisitions were retained. All recordings were stored on disk for later systematic check by the research engineer. From the FRC and vital capacity, total lung capacity and residual volume were computed. For clarity, this part of the data has been omitted from the current paper. Mean values of sRaw, Raw, and FRC were calculated and tabulated for each individual.

2.4. Statistical analysis

Data were summarized in Excel files and statistical analysis was performed using SAS statistical software 9.3, SAS Institute Inc., NC, USA.

2.4.1. Bivariate analyses

Gender distribution was examined using the Chi square test, and difference between group means was determined using the Wilcoxon test. Relationships between Raw or sRaw and age, body weight, standing, and sitting height were analysed using Pearson's correlation coefficients.

2.4.2. Multivariate analyses

Variables significant at the 0.05 level were subsequently used in multiple linear regression analysis of the factors associated with Raw or sRaw.

3. Results

Ninety five subjects in HMU (60 males, 35 females) and 101 in HELFD (41 males, 60 females) fulfiled inclusion criteria. The sex ratio was significantly different, with a larger proportion of males being recruited in Hanoi ($p = 0.002$) and the data are therefore presented while stratified for gender. Biometrical characteristics are summarized in Table 1. Weight, standing or sitting height, TGV and FRC were significantly lower in Vietnamese than Caucasians and in females than in males ($p < 0.0001$). The gender-related difference was similar in both ethnic groups. FRC was found significantly lower than TGV ($p < 0.0001$) in both Vietnamese (2.86 ± 0.74 L vs 3.36 ± 0.76 L) and Caucasians (3.26 ± 0.75 L vs 3.54 ± 0.74 L) and the difference was larger in Vietnamese ($p < 0.01$).

The panting frequency was found slightly but significantly larger in the Vietnamese than Caucasians ($p = 0.008$) and in females than in males ($p < 0.05$, Table 1). Raw was also significantly larger in the Vietnamese ($p = 0.0003$) and in females ($p < 0.0001$), with comparable effects of gender in both ethnic groups (Table 1). Significant correlations were disclosed between Raw and standing or sitting height, weight, FRC but not with age or panting frequency. The multiple linear regression analysis indicated that FRC was in fact the only parameter significantly and independently related to Raw. The relationship between Raw and FRC presented in Fig. 1 indeed indicates that the data points for Vietnamese or French males and females were roughly distributed along the same hyperbola.

As expected from prior relationships, sRaw was not found to be different between males and females nor between Vietnamese

Table 1
Biometrics and lung function stratified for gender and ethnicity.

n	Vietnamese		French		p (V vs F)
	Male	Female	Male	Female	
	60	35	41	60	
Age (year)	20.8 ± 1.65	20.7 ± 2.0	21.2 ± 2.1	21.4 ± 2.1	0.07
Standing height (cm)	168.3 ± 4.1	154.7 ± 5.6*	176.1 ± 5.3	164.4 ± 5.3*	<0.0001
Sitting height (cm)	88.3 ± 4.0	83.8 ± 4.0*	92.5 ± 3.0	87.6 ± 3.0*	<0.0001
Body weight (kg)	61.0 ± 8.4	49.1 ± 5.1*	70.0 ± 8.3	57.6 ± 8.7*	<0.0001
FRC (L)	3.2 ± 0.7	2.31 ± 0.56*	3.74 ± 0.76	2.93 ± 0.54*	<0.0001
Panting frequency (Hz)	3.3 ± 0.9	3.1 ± 0.7**	3.0 ± 0.8	2.7 ± 0.7**	0.0008
Raw (hPa s/L)	1.75 ± 0.65	2.53 ± 1.40*	1.47 ± .58	1.95 ± .56*	0.0003
sRaw (hPa s)	5.19 ± 1.86	5.38 ± 2.03	5.10 ± 1.90	5.41 ± 1.65	0.84

vs male
* $p < 0.0001$.
** $p < 0.05$.

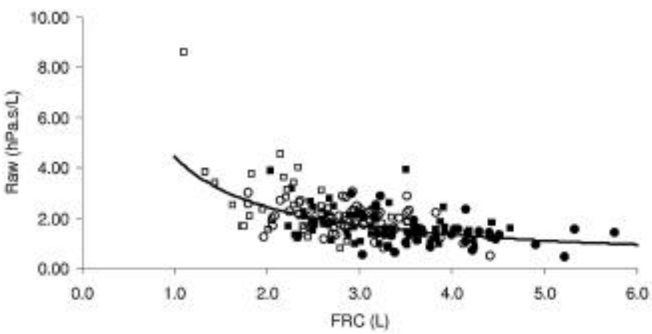

Fig. 1. Relationship between airway resistance (Raw) and functional residual capacity (FRC) in healthy young adult males (closed symbols) and females (open symbols) from Hanoi, Vietnam (squares) and Nancy, France (circles). Note distribution along a single hyperbola, in keeping with lack of gender or ethnic related difference in specific airway resistance.

and Caucasians (Table 1), and was independent of almost all relevant variables, except FRC, which was found to show significant relationship ($p = 0.04$).

4. Discussion

To the best of our knowledge, this is the first comparison of airway resistance in young Asian and Caucasian adults measured in their native countries using identical plethysmographic equipments. The major findings were that Raw was found to relate to FRC similarly in both laboratories, and that sRaw was independent of both gender and ethnicity. The current results do not support the hypothesis that the putative difference in respiratory resistance – body height relationship that was suggested earlier between Vietnamese and Caucasian children (Vu et al., 2008) extends into adult age – once resistance is normalized for lung volume.

The hyperbolic relationship between airway resistance and lung volume has been characterized using multiple data points at different volumes in some healthy individuals (Briscoe and Dubois, 1958). In the current report, a unique relationship may also be demonstrated from single measurements at FRC in a number of subjects with different ethnical backgrounds. sRaw averages about 5.3 hPa s, and, in contrast to Raw, does not significantly depend on standing or sitting height, gender or ethnicity. Interestingly, the fact that comparable measurements were obtained in each ethnical group in its own native country indicates that environmental factors do not significantly impact on the airway resistance – lung volume relationship in young adults.

The airway size – lung volume relationship is determined by the tethering of the intra-parenchymatous airways by lung tissue, and generally expresses the interaction between elastic lung recoil and airway distensibility. Measurements during growth have demonstrated lung compliance to be linearly related to FRC in children beyond 4 years of age, with a slope – i.e., the specific lung compliance – approximating 0.04–0.06 hPa^{-1} (Polgar, 1971). In young adults the elastic recoil of the lung was found to be similar in Asian and Caucasian subjects, not surprisingly since the specific lung compliance was shown to be rather constant among mammals of different species (Chan et al., 1995). As a result, the recoil exerted by the lung tissue pull on the airway wall should be similar in both ethnic groups. Airway, bronchial and/or tracheal distensibility have been studied in healthy young adults using different methodological approaches (Brown et al., 2007; Hoffstein et al., 1987; Kelly et al., 2012; Noble et al., 2010), but we are aware of little data on ethnicity – dependence of this mechanical property. Comparative measurements in asthmatics and controls demonstrated that airway smooth muscle tone and airway wall remodelling were major determinants for the increased airway wall stiffness in asthma (Brown et al., 2007; Kelly et al., 2012). Unless difference in airway smooth muscle mechanical properties exists between healthy Caucasian and Asian subjects, airway distensibility is unlikely to vary with ethnicity. Interestingly, while reviewing lung function data of healthy young adults enrolled in a study of the respiratory effects of ambient ozone concentration, no difference in sRaw was reported between Caucasian Americans and African Americans, in contrast with differences observed in lung volume and expiratory flows (McDonnell and Seal, 1991).

While the Raw–FRC relationship was found comparable in young Caucasian and Asian adults of both genders, the multiple regression analysis disclosed a weak but significant positive relationship between sRaw and FRC. When analysing the coupling between lung size and airway size, Mead used the ratio of the upstream airway conductance to vital capacity during forced expiration. The theoretical analysis showed the ratio – that has the dimension of a specific airway conductance – could be predicted to decrease slightly with vital capacity if turbulent flow was accounted for (Mead, 1980). We are aware that the specific airway conductance in that study was defined with respect to vital capacity, so that transposition to the current data – where sRaw is related to the volume at which it is measured – should be made with caution (Mead, 1980). Nevertheless, it is interesting that the current positive association between sRaw and FRC may relate to rheological conditions, especially as turbulent flow is majored during panting.

In early infancy the rapid increase in lung volume with ongoing postnatal alveolar multiplication, contrasts with the slower development of the more mature bronchial tree and results in an increase in sRaw (Doershuk et al., 1974; Stocks, 1977). Furthermore, the lung volume-corrected maximal mid expiratory flow has been observed to decrease from 8 to 12 years of age, a further indication that the airway calibre would continue to grow at a slower rate than lung volume (Hibbert et al., 1984). The multiethnic analysis of spirometry across the world indicates larger FVC and FEV1 in Caucasians than in any other ethnicities, in contrast with the FEV1/FVC ratio that is lower than in south-east Asians (Quanjer et al., 2012). While sRaw is recognized to reflect the more central airway calibre in normal subjects, FEV1/FVC depends to a large extent on the pattern of dynamic compression of the airways. Taken together, the fact that sRaw is similar but FEV1/FVC larger in Vietnamese than Caucasians would indicate a larger lung volume corrected airway size upstream to the choke point in the former population.

In our previous study (Vu et al., 2008), the respiratory resistance measured using the forced oscillation technique at 8 Hz encompassed some properties not strictly related to airway size, such as the mechanical characteristics of lung and chest wall tissues or the parallel impedance of the airway wall. Of the two reference populations on whom this comparison of respiratory resistance was based, one consisted of a majority of Caucasians, but also small numbers of African-Americans, Asians, and some other ethnical backgrounds (Ducharme et al., 1998). The second comprised exclusively of Caucasians (personal communication from the author, Hall et al., 2007). It is unclear from other papers whether Rrs measurement eventually detects ethnic specificity of airway properties in children. From bi-centre studies, a difference has been identified between Australian and Mexican (Shackleton et al., 2013) – but not Italian (Calogero et al., 2010) – preschool children, while a significant difference was shown when comparing Australian and Italian children over the age range of 3–13 years (Calogero et al., 2013). The interrupter resistance on the other hand failed to identify differences among East-London Afro-Caribbean, Bangladeshi, and Caucasian children aged 2–10 years (McKenzie et al., 2002). The relationship between FEV1 and body height exhibited a lower slope in Chinese compared with Caucasian 10 year old children (Yang et al., 1991). However, similar FEV1 or FEV1/FVC trends from early childhood to old age have been described among ethnic groups, including south-east Asians and Caucasians (Quanjer et al., 2012). It is therefore doubtful that the occasional report of within-centre difference in Rrs relates to ethnic specificity of airway dimensions.

The current study has some methodological limitations. The data could not be blinded during the assessment of quality control, because an open access to measuring set ups was important for maintenance, particularly in Ha Noi. We believe however the potential bias was minimal since the engineer's input was limited to double-checking of individual flow – volume tracings prior to final validation. The panting frequency was observed to be significantly higher in Vietnamese than Caucasians, accounting for a larger difference between FRC and TGV in the former. The volume correction required to obtain FRC and calculate the corresponding Raw was thus slightly larger in Vietnamese. The difference was however unlikely to have significantly biased the results since, in a given individual, sRaw has been described to be constant from residual volume to total lung capacity (Briscoe and Dubois, 1958). In addition, the multiple regression analysis indicated that breathing frequency was not a significant input variable to sRaw or Raw.

It is concluded that the specific airway resistance offers similar characteristics in healthy Asian and Caucasian young adults while measured in their native countries. Further studies, based on the current study set up, are needed to elucidate whether airway mechanical properties distal to the choke point are different between Vietnamese and Caucasian subjects.

Acknowledgement

The authors gratefully thank the Hoa Trang Fleur Blanche Association for logistic assistance and financial support, and the students from Hanoi Medical University, Hanoi, Vietnam and from the Faculté de Médecine, Université Lorraine, Nancy, France for their contribution to the study. The authors also thank Prof Graham Hall for helpful discussion and Prof Sam Bayat for careful edition of the manuscript. Grant EA 3450 from Ministère de la Santé et de la Recherche Médicale.

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Paper II

Pediatric Pulmonology

Flow Dependence of Specific Airway Resistance and Diagnostic of Asthma in Children

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Summary. Panting majors turbulent flow and contribution of larger airways to the measurement of specific airway resistance (sRaw). The hypothesis was tested that the difference between asthmatic and healthy children is enhanced by narrowing the flow interval to compute sRaw. sRaw was measured during panting in 40 asthmatic and 25 healthy children and computed using all data points (full scale flow) and limited to the flow intervals Æ1L/sec and Æ0.5 L/sec. sRaw was not different between asthmatics (0.87 Æ0.20 kPa.s) and controls (0.80 Æ0.25 kPa.s) when computed full scale, while it was significantly larger in asthmatics than controls within Æ1L/sec (0.77 Æ0.16 kPa.s vs 0.65 Æ0.15 kPa.s, $P < 0.004$) or Æ0.5 L/sec (0.77 Æ0.21 kPa.s vs 0.61 Æ0.17 kPa.s, $P < 0.002$). On the other hand, the within subject coefficient of variation was significantly larger when sRaw was computed within Æ1L/sec (13.7 Æ7.2%) or Æ0.5 L/sec (28.3 Æ18.1%) than full scale (11.0 Æ6.7%), respectively $P < 0.002$ and $P < 0.0001$. It is concluded that narrowing the flow interval to compute sRaw is associated with better discrimination between asthma and health in children, although the short term variability of sRaw is increased. Pediatr Pulmonol. 2014;9999:1–6. ß2014 Wiley Periodicals, Inc.

Key words: asthma; thermal effect; turbulent airflow; laminar airflow; healthy; panting; tidal breathing; plethysmography.

Funding source: Ministe`re de la Sante et de la Recherche Medicale; Number: EA 3450.

INTRODUCTION

Body plethysmography is a unique technique to assess lung volume compression/decompression (DV_{plet}) related to alveolar pressure and alveolar gas compressibility, thereby allowing the measurement of the specific airway resistance (sRaw). A relatively large volume contraction/ expansion also originates from change in gas temperature and humidity in the airway during breathing that may be responsible for serious error in this measurement.[1,2] The so-called thermo-hygrometric artifact may be minimized in three ways. Conditioning the respired gas to airway temperature and humidity has been the gold standard because relevant physical differences between inspiration and expiration are properly cancelled.[3] The procedure however required a cumbersome apparatus where the theoretical risk of bacterial growth had disqualified the use during routine clinical sessions.

The electronic compensation is based on the assumption that the thermal artifact is entirely in phase with tidal volume.[4] It has become popular in pediatrics, because measurements are allowed during tidal breathing, thus with minimal subject cooperation.[5] Comparing electronic compensation and physical gas conditioning however has indicated significant differences between the two

approaches[6], namely because temperature equilibration in the airway is not instantaneous[2].

Panting has been shown most reliable and practical a way to minimize the thermal artifact, typically when frequency is 2 Hz or more.[2,7] In addition, the glottis is maintained open throughout the breathing cycle, thus the caliber difference between inspiration and expiration is minimized.[8] Significant discrepancies between tidal

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Conflict of interest: None

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Received 14 February 2014; Revised 7 July 2014; Accepted 31 July 2014.

DOI 10.1002/ppul.23127. Published online in Wiley Online Library (wileyonlinelibrary.com).

breathing with electronic compensation versus panting in adult subjects further suggested inadequacies of the former procedure.[9] Similar comparison in children aged 6 or more showed significant increase by the electronic compensation, and the method-related difference in sRaw exceeded that observed between asthma and health.[10]

A significant drawback relates to airway rheology during panting. Higher air velocity and turbulent flow (V′) should imply more contribution of larger airways to the measured sRaw,[11] compared to tidal breathing. To minimize the effect, it has been proposed to compute sRaw within a limited V′ range,[12] such as Æ0.5 L/sec or Æ1 L/sec in adults[1,13] or Æ0.5 L/sec in children,[14] or within 50% of the peak to peak V′ amplitude in infants.[15] As a result, the sRaw difference between asthma and health related to intrathoracic airways mechanics would possibly be enhanced. To the best of our knowledge, it has not been studied whether the diagnostic value of sRaw measured during panting in children may be improved by narrowing the V′ range for computation.

The aim of the study was to analyze the DV_{plet} À V′ relationship within different V′ intervals in healthy and asthmatic children. The hypothesis was tested that lowering amplitude of V′ would enhance contribution of intrathoracic airways to sRaw, and therefore the difference between subjects with asthma and controls.

MATERIAL AND METHODS

Subjects

School children with stable asthma and healthy children were recruited. All were free of respiratory symptoms at time of the study. Asthmatics were recruited among children attending the pediatric pulmonology clinics and referred to the lab for lung function testing (Ho^pital d'Enfants, Vandoeuvre-le`s-Nancy, France). Asthma was identified by the past year medical history positive for one or more of the followings: wheeze at rest; cough, dyspnoea, or wheeze on exertion; beneficial use of anti-asthma medications. Inhaled steroids and antileukotriene medications were documented and bronchodilators discontinued >12 hr prior to the study. Age-matched healthy children, free of respiratory tract infection, recruited from local primary schools served as control. Written informed consent had been obtained from the children and their parents at the time of lung function testing. The study was approved by the Ethics Committee (Comit e de Protection des Personnes de Lorraine) and registered with the ClinicalTrials.gov registry (002822–31).

Measurements and Analysis

Forced spirometry and the procedure for measuring sRaw have been described previously.[10,16] A Jaeger MedGraphics 1085 barometric body box reequipped with transducers, electronics and informatics was used. Calibration of V′ by the integral method and of DV_{plet} using a built-in 50 ml reciprocating pump was performed daily. The body box was subjected to regular biological calibration check by measuring members of the staff. The child was connected to the breathing apparatus of the plethysmograph through a bacterial filter (PALL filter pro-tec PF 30 SG), the resistance of which (0.007 kPa.s/L) is linear within Æ2 L/sec. The child was coached to pant at frequencies ! 2 Hz. An acquisition lasted 2 sec—usually yielding 4–6 breaths—during which time DV_{plet} and V′ were digitized at 100 Hz. The DV_{plet} À V′ relationship was examined visually X-Y immediately after the acquisition and those maneuvers showing obvious signal distortion—mostly DV_{plet} swings without corresponding change in V′ suggestive of glottis closure or swallowing were excluded. The selected recordings were stored on disk for later analysis. DV_{plet} was drift-corrected[17] and subjected to linear regression versus V′, where the slope is sRaw. A triplicate estimate of sRaw was obtained from the 3–6 breaths pooled for each measurement. The calculation was first performed including all data points, that is, using the full scale range of flow ($sRaw_{fs}$). The procedure was then repeated twice, while excluding those data lying outside the Æ1 L/sec interval ($sRaw_1$) and those outside the Æ0.5 L/sec interval ($sRaw_{0.5}$). A typical DVÀV′ relationship is illustrated in Figure 1. The goodness of fit of each regression line was characterized by the correlation coefficient. Two to four technically acceptable acquisitions were usually performed in each subject. The measurements were averaged for each individual and a coefficient of variation computed within the relevant flow interval.

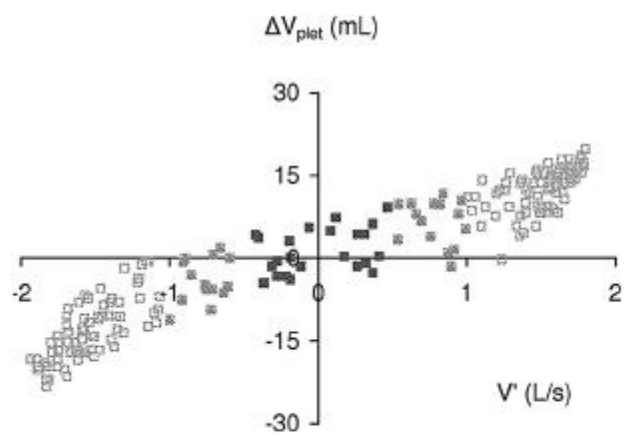

Fig. 1. Plethysmographic signal (DV_{plet}) and airflow (V′) obtained with a single measurement during panting. The S shaped relationship is typical of non linear behavior. The slope is the specific airway resistance. Slope estimates are obtained within three flow intervals: using all data point—that is, in the full scale flow—within Æ0.5 L/sec and Æ1 L/sec. The different symbols help identifying relevant intervals.

Data Analysis

Data were expressed as mean and standard deviation. Comparisons between asthma and control were performed using analysis of variance and t tests as required. A statistically significant difference was retained at a P-value less than 0.05.

Modeling

Rohrer's two-coefficient model describes the non linear resistive pressure—V' curve. The coefficients are shape descriptive but have also been used to quantify to some extent the "zero flow" (K1) and the flow dependent (K2) resistance.[11,18] The model was used here to test the impact of different flows on airway resistance, in the presence of mild bronchial obstruction. Sets of values for K1 and K2/K1 were derived from data in children[19] and the degree of airway obstruction thought to occur in our asthmatic children was simulated by increasing K1.

RESULTS

The study included records from 40 asthmatic and 25 healthy children aged 6.5–11. All but 10 healthy controls have been included in a recently published study.[10] The characteristics of the population are reported in Table 1. There was no significant difference in growth characteristics, but FEV1 and corresponding Z score were significantly lower in asthmatics compared with controls (P < 0.05).

The average full scale flow during panting in these children ranged À2 L/sec to þ2 L/sec. In the characteristic plot of DV $_{plet}$ versus V' presented in Figure 1, the S shaped relationship suggests nonlinearities showing at the extreme of inspiratory and expiratory flows. It may be expected from the shape of the curve that limiting flow range for computation would be associated with a decrease in slope—that is, a decrease in sRaw, as suggested in Figure 2. Indeed, $sRaw_{0.5}$ or $sRaw_1$ were significantly lower than $sRaw_{fs}$ in controls (P < 0.0001) as well as asthmatics (P < 0.002, Fig. 3). There was no significant difference between $sRaw_1$ and $sRaw_{0.5}$. $sRaw_{fs}$ was not different between groups (Fig. 3). In contrast, either $sRaw_1$ or $sRaw_{0.5}$ was significantly larger in subjects with asthma than controls (respectively, P < 0.004 and P < 0.002). The Bland–Altman plots showed ($sRaw_{fs}$À $Raw_{0.5}$) or ($sRaw_{fs}$À $Raw_{0.5}$) were predominantly positive in both groups, with a trend for ($sRaw_{fs}$À Raw_1) to increase with sRaw (Fig. 4).

Quality control criteria are described in Table 2. Lowering the V' range to compute sRaw was associated with a decrease in the correlation coefficient between DV $_{plet}$ and V', and the full scale gave a larger value than either Æ1 L/sec or 0.5 L/sec (P < 0.0001). There also was a difference between Æ1 L/sec and Æ0.5 L/sec (P < 0.0001), and the latter was significantly larger in asthmatic subjects than controls (P ¼ 0.01). In addition, the within subject—between series coefficient of variation full scale was smaller than within Æ1 L/sec in asthmatics (P < 0.04) or Æ0.5 L/sec in both groups (P < 0.0001). The coefficient of variation was also significantly lower for Æ1 L/sec than for Æ0.5 L/sec (P < 0.0001). There was no difference between subjects with asthma and controls.

Figure 5 represents the difference in airway resistance between asthma and health predicted from Rohrer's 2-coefficient model in the flow range 0–2 L/sec. It may be seen that when K1 is increased in asthmatics, the

TABLE 1— Characteristics of the Children

	Control	Asthma
n (M/F)	25 (13/12)	40 (22/18)
Age (year)	9.1 Æ 1.2	8.7 Æ 1.2
range	7–11	6.5–10.5
Height		
cm	135 Æ 9	132 Æ 8
Z score	0.34 þ 1.04	0.17 þ 0.84
Weight		
kg	31 Æ 7	28 Æ 5
Z score	0.16 þ 0.97	0.04 þ 0.90
FEV1		
L	2.04 Æ 0.37	1.81 Æ 0.31[1]
Z score[2]	0.87 Æ 0.74	0.41 Æ 0.92[1]

Data are mean Æ SD.
[1]P < 0.05.
[2]From Stanojevic et al.[20]

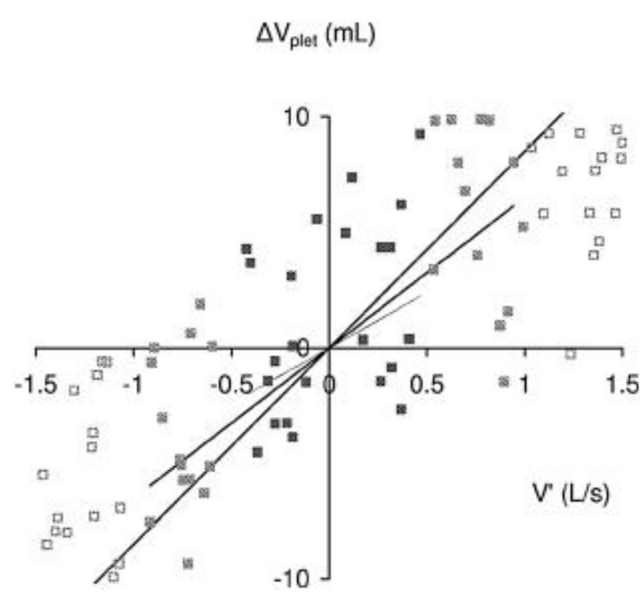

Fig. 2. Same data as in Figure 1. The slope of the DV $_{plet}$–V' relationship (specific airway resistance) decreases when flow range for computation is narrowed. Y-axis scale has been enlarged and symbols lightened for better readability.

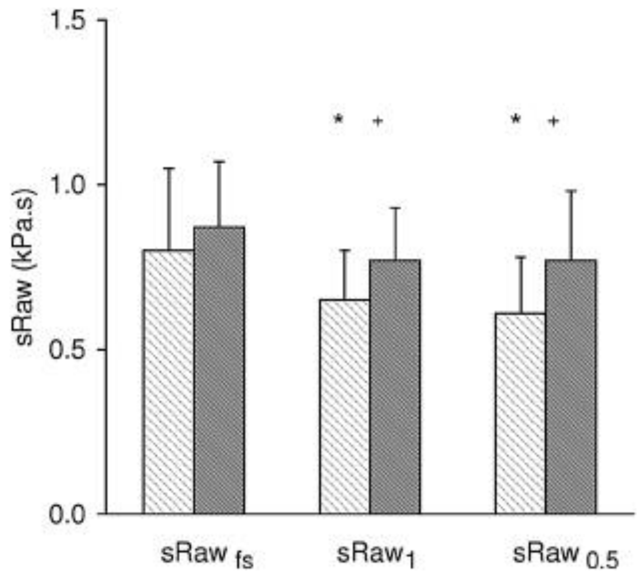

Fig. 3. Different estimates of specific airway resistance (sRaw) are provided within 3 panting flow intervals: full scale ($sRaw_{fs}$), Æ1 L/sec ($sRaw_1$) Æ0.5 L/sec ($sRaw_{0.5}$). $sRaw_1$ or $sRaw_{0.5}$ are significantly lower than $sRaw_{fs}$ (þ$P < 0.0001$). In addition a significant difference between patients (dark bars) and controls (light bars) is disclosed with $sRaw_{0.5}$ (*$P < 0.002$) or $sRaw_1$ (*$P < 0.004$) but not $sRaw_{fs}$.

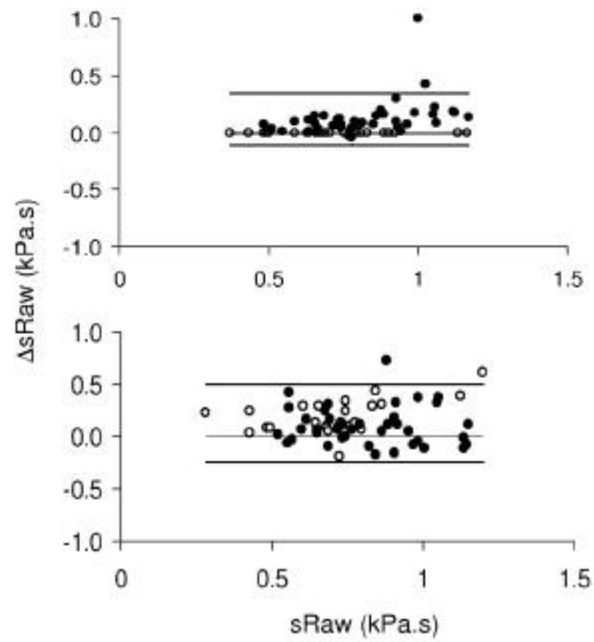

Fig. 4. Bland and Altman plots showing difference between 2 estimates of sRaw (DsRaw) against their mean. (A) sRaw computed within full scale flow and within 1 L/sec; (B) sRaw computed within full scale flow and within 0.5 L/sec. Note the generally positive difference and a trend for larger difference when sRaw increases in panel A. Open circles: control; closed circles: asthma. The 95% confidence interval is indicated.

difference with controls becomes more apparent when flow amplitude is decreased.

DISCUSSION

In this paper we demonstrate that airflow significantly impacts on sRaw measured during panting with the major finding that significant difference between asthma and control may not be detected unless sRaw is computed within a narrower airflow interval.

The breathing pattern in this study is clearly different from that recommended for preschool children where the expected lack of cooperation incites measuring during tidal breathing, and therefore at much lower frequency.[5] In the current school age group, the 2–3 Hz range—adopted based on prior validation in adult subjects[7]—was found to be easily reproduced. Larger flows during panting are associated with more turbulence and non linearities as illustrated in Figure 1. The transition from turbulent to laminar profile is predicted by Reynolds number that depends—for a given fluid—on the product of its velocity by the airway diameter. Therefore larger airways—which are known to be major determinants of the total airway resistance in healthy subjects[20,21]—are mostly impacted by turbulent flow,[11] and their contribution is expected to increase further during panting compared to tidal breathing. It should be noted that the bacterial filter contributes to the sRaw expressed here, as it may not be corrected for unless airway resistance has been properly calculated. However, the filter contribution to the current findings should be negligible as the device showed little non linearity in the relevant flow interval and the nominal resistance was small considering the airway resistance range expected in children (see methods).

The velocity profile tends to become laminar toward smaller airways as Reynolds number decreases, with critical value estimated around 2000.[18] In healthy adults hyperventilating 3 L/sec—a range close to that achieved in the current study—Reynolds number has been estimated to decrease from ca 16000 at the glottis—a value where the profile is turbulent—down to around 1900 in small (4 mm) bronchi,[11] where flow is mostly laminar.[20] Some degree of bronchoconstriction in children with stable asthma is thus expected to increase that component of sRaw. According to Figure 5, computing sRaw in a limited range of airflow is associated with larger group difference because the part of the airway tree where bronchoconstriction takes place contributes more to the measurement. Therefore a better discrimination between healthy children and those with asthma is expected by narrowing the flow range available to the computation.

A drawback with the procedure described here is indicated by apparently poorer quality control when flow range is decreased. Narrowing the range of the least square regression is expected to decrease the covariance between DV_{plet} and V' relative to the signals individual variance. As a result, the correlation coefficient is

TABLE 2— Quality Control Criteria

		Control	Asthma
n	Flow interval	25	40
Correlation coefficient	Full scale	0.90 Æ 0.03[1]	0.89 Æ 0.04[1]
	Æ1 L/sec	0.71 Æ 0.08	0.75 Æ 0.10
	Æ0.5 L/sec	0.44 Æ 0.09[2]	0.51 Æ 0.12[2,3]
Coefficient of variation (%)#	Full scale	11.7 (9.8)[1]	9.8 (5.9)[1,4]
	Æ1 L/sec	12.9 (11.6)	12.3 (10.4)
	Æ0.5 L/sec	28.8 (22.9)[2]	23.9 (24.3)[2]

Data are mean Æ SD except coefficient of variation showing median (interquartile range).
[1]P < 0.0001: versus 0.5 L/sec or 1 L/sec.
[2]P < 0.0001: versus 1 L/sec.
[3]P < 0.01 control versus asthma.
[4]P < 0.04 versus 1 L/sec.

decreased. This may express firstly the relative increase in random noise in the breathing signals. More importantly, some residual looping between DV$_{plet}$ and V' may be observed during panting, although significantly reduced compared with tidal breathing.[10] There may be several explanations for this. The airway—instrumental dead space thermal time constant has been shown substantially variable among healthy adult subjects[2,7] and the efficiency of panting in suppressing the loop may vary accordingly, because it depends on the ratio of the thermal time constant to the period of the breath. There is no reason to believe that this may not be the case in children as well, where objective measurements of these thermal characteristics are lacking. Furthermore, thermal and hygrometric exchanges between the respired gas and the airway mucosa may not be strictly symmetrical in inspiration and expiration, a condition that is also

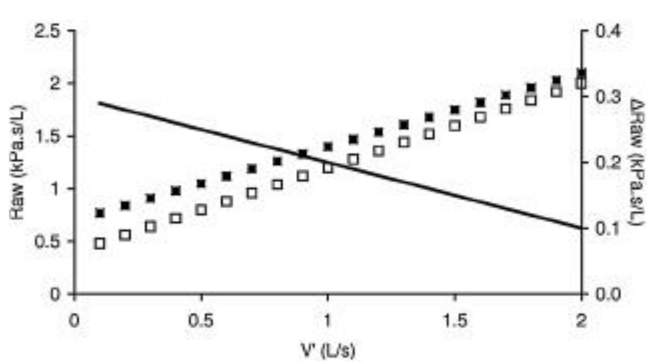

Fig. 5. Airway resistance (Raw) is computed using Roher's model-coefficients K1 and K2 to simulate the contribution of upper and lower airways when flow (V') ranges from 0–2 L/sec. Raw for control and asthma are open and closed squares, respectively. The line is the Raw difference between asthma and control (DRaw) that decreases when the amplitude of flow is increased. Raw is given by K1 þ K2.V'. K1 and K1/K2 are respectively 4 hPa.s/L and 0.5 L in control, and 7 hPa.s/L and 1 L in asthma.

expected to induce some phase shift between DV$_{plet}$ and V'.[2] The role of respiratory exchange ratio fluctuations during panting should be negligible in practice.[1] Airway inertance is larger in children than in adults[22] and could therefore contribute more significantly to the phase shift observed between DV$_{plet}$ and V' at higher frequencies. To test the hypothesis, a typical airway inertance of 0.004 kPa.s^2/L was simulated at 3 Hz using previously reported equations.[2] When sRaw was 0.6 kPa.s, airway inertance was found to induce a DV$_{plet}$À V' phase shift less than 108, that would correspond to a correlation coefficient better than 0.99,[17] thus larger than usually observed here. The role of inertance is therefore unlikely. Nevertheless, it should be noted that some factors may have opposite effects on the sign of the phase between DV$_{plet}$ and V'. For instance, the thermal effect has a large component in phase with volume, while the airway inertial reactance is in phase with volume acceleration. Whatever the mechanisms accounting for this increased variability of sRaw when computed within a smaller flow interval, the clinical impact in the day to day practice may be questioned. It obviously does not appear to impede the diagnostic of asthma. On the other hand, the larger variability could be associated with a lower repeatability of sRaw, and therefore a decreased sensitivity in identifying a positive response to bronchodilator.

It is interesting that at lower range of flow, the correlation coefficient is larger in asthmatics compared to controls. The observation is explained by the fact that within a given V' interval, DV$_{plet}$ is larger in asthmatics, thereby increasing the signals covariance in this group. Associated with the lower correlation coefficient, larger within-subject coefficients of variation were observed with smaller flow amplitude, also expected to result from the less well defined DV$_{plet}$–V' relationship. This effect was similarly observed in asthmatics and controls.

It is concluded that setting thresholds to narrow the flow range to compute sRaw may help improve diagnostic value in children. Larger airways—where air velocity profile is mostly turbulent—should contribute less to the measurement, and the role of smaller airways—that determine the difference between asthmatics and controls—should be enhanced. The drawback relates to the decreased coefficient of variation associated with narrowing the flow interval. A provisory recommendation on sRaw measurement during panting is to compute within À1 to þ1 L/sec. From the current data, this interval represents a good compromise that allows differentiating asthma from health, yet with minimal effect on variability. The suggestion however would not hold for tidal breathing measurements where flow is low and the major issue is the thermo-hygrometric component in DV$_{plet}$. Altogether, the optimal V' range for sRaw computation and practical consequences of increased variability have to be assessed. Panting should similarly eliminate the thermo-hygrometric artifact from sRaw measurements and therefore benefit the diagnostic of asthma in younger children. Further studies are needed to determine their ability to perform the necessary maneuver. Different computation algorithms may also be useful with smaller amplitude of flow during panting. For instance, it may be advantageous to compute within a relative—for example, mid flow range, rather than absolute flow interval.

ACKNOWLEDGMENTS

The authors thank the children that contributed to the study, their families and the teachers from “Ecole de Brabois” and gratefully acknowledge the technical assistance of Sylvie Meline, Francine Cael, Marie-Jeanne Arnoux, Marianne Mougin, Myriam Chamagne, and Dominique Binot-Saintot.

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Paper III

Pediatric Pulmonology

Specific Airway Resistance in Children: Panting or Tidal Breathing?

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Summary. Background: The measurement of specific airway resistance during tidal breathing ($sRaw_{tb}$) has gained popularity in children, but methodological concerns have been raised regarding the electronic compensation for the thermal artifact. The panting method ($sRaw_p$) is efficient in minimizing the latter, but may be associated with a change in end expiratory lung volume if the effort is not properly balanced. The aim of the study was to compare $sRaw_{tb}$ with $sRaw_p$ in children. Methods: Fifty-five children aged 6.5–11.5 years were studied. $sRaw_{tb}$ was measured in a commercial plethysmograph. $sRaw_p$ was measured with a home made equipment that allowed breath by breath analysis ($sRaw_{p1}$) as well as with the commercial body box ($sRaw_{p2}$). Results: $sRaw_{tb}$ was significantly larger than either $sRaw_{p1}$ or $sRaw_{p2}$ ($P < 0.0001$). The mean (95% CI) difference $sRaw_{p1}$ À $sRaw_{tb}$ was À0.374 (À0.835 to 0.088) kPa s. The difference between $sRaw_{p1}$ and $sRaw_{p2}$ was significant ($P < 0.005$) but not clinically relevant, and mean (95% CI) difference $sRaw_{p1}$ À $sRaw_{p2}$ was 0.115 (À0.094 to 0.324) kPa s. The breath by breath analysis showed small but significant increase in $sRaw_{p1}$ throughout the maneuver ($P < 0.001$), whatever the pattern of end expiratory level. Conclusion: Tidal breathing is associated with an overestimation of sRaw compared with panting in children. Although the latter results in small increase throughout the panting maneuver, $sRaw_p$ is probably more trustful than $sRaw_{tb}$. Pediatr Pulmonol. ß 2013 Wiley Periodicals, Inc.

Key words: body plethysmography; thermal artifact; asthma; healthy; child.

Funding source: Ministe`re de la Sante et de la Recherche Medicale, Number: EA 3450

INTRODUCTION

The specific airway resistance (sRaw) measured during tidal breathing ($sRaw_{tb}$) has become a popular outcome variable for identifying airway obstruction and reversibility in pediatrics because little cooperation is required.[1–9] The volume change measured by the plethysmograph (DV_{plet}) related to sRaw may be rather small compared to that resulting from the change in gas temperature and humidity along the airways. Gas cooling and condensation in expiration, warming and humidifying in inspiration is proportional to tidal volume and the so-called "thermal artifact" results in significant looping of the DV_{plet}–airflow (V') relationship.

The artifact is optimally corrected if the respired gas is at body temperature and pressure, saturated with water vapor (BTPS conditions).[10] The required apparatus however is cumbersome, has the theoretical drawback of favoring bacterial growth and has thus been eliminated from modern plethysmographs. Instead, an "electronic" BTPS compensation has been proposed to flatten the DV_{plet}–V' loop based on the assumption that the thermal component of DV_{plet} is entirely in phase with tidal volume.[11] Softwares that now equip most commercially

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Conflict of interest: None.

Presented at European Respiratory Society meetings: Amsterdam, September 2011; Vienna, September 2012.

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Received 26 September 2012; Accepted 28 April 2013.

DOI 10.1002/ppul.22829
Published online in Wiley Online Library (wileyonlinelibrary.com).

available plethysmographs have been implemented with the procedure.[2,12–14] Changes in gas temperature and humidity in the airways are not instantaneous but slightly out of phase with volume, hence the thermal artifact has a component in phase with V'.[15,16] In other words, the thermal component of DV_{plet} contributes to the apparent sRaw which—if not taken into account by the electronic correction—may result in significant error. Difficulties with this method of correction have been reported in routine clinical measurements in infants and children.[13,14,17,18] Measuring sRaw during panting ($sRaw_p$) is a valuable alternative, because the DV_{plet}–V' relationship is analyzed in such a time domain that dynamics of thermal exchanges should have minimal impact.[16] In addition, the mechanical component of DV_{plet} is magnified by the comparatively larger amplitude of V'. Therefore, under routine clinical conditions, $sRaw_p$ appears a sound and easy reference method, provided the subject is able to breathe at sufficiently high and regular frequency. Ideally, a stable end expiratory level (EEL) should be ensured throughout the maneuver. It is our experience however that this may not be the case in children where, frequently, EEL tends to increase during panting. It is not known to what extent this may affect the computation of $sRaw_p$. Altogether we are aware of little data comparing $sRaw_{tb}$ and $sRaw_p$ in children.

The aim of this study was to compare $sRaw_p$ and $sRaw_{tb}$ in children in a clinical setting and to test the potential effect of EEL instability, with the null hypothesis that $sRaw_p$ should vary little within an acquisition and provide estimates that compare well with $sRaw_{tb}$ after proper electronic compensation.

MATERIALS AND METHODS

Subjects

School children with stable asthma were recruited from the local pediatric pulmonology clinic (Hoˆpital d'enfants, CHU de Nancy, Vandoeuvre, France) and included on the basis of lack of recent acute exacerbation and the current finding of a normal FEV1.[19] Healthy children were recruited from a neighboring primary school. All subjects were free of respiratory symptoms at time of the study. Written informed consent was obtained from the child and his/her parents. The study was approved by the Ethics Committee (Comit ede Protection des Personnes de Lorraine) and registered with the ClinicalTrials.gov registry (NCT-002822-31).

Measurement

Forced spirometry was performed as previously described.[20] A commercial plethysmograph (Vmax 29C, Sensormedics, Viasys Healthcare) was used to measure $sRaw_{tb}$ with the electronic BTPS compensation using the appropriate protocol. The acquisition of DV_{plet} and V' was made while the subject was breathing quietly and consisted in a series of 6–8 breaths. From these, an automated procedure selected and displayed 4.

An estimate of $sRaw_p$ ($sRaw_{p1}$) was measured in a Jaeger MedGraphics 1085 body box which had been reequipped with transducers, electronics, filtering, acquisition procedures and mathematical handling that have been previously described and validated.[21,22] The barometric plethysmograph has an 8–10 sec mechanical time constant. The daily quality control procedure includes adjusting the gain of the pressure transducer against a water manometer, calibrating the pneumotachograph by the integral method and the plethysmograph signal using the built-in 50 ml reciprocating pump. In addition the equipment is regularly checked by measurements obtained in a few staff members. The pediatric measurement was performed as follows. The child was first coached to pant at a frequency >2 Hz for 2 sec. The V' signal was electrically zeroed prior to each 2 sec acquisition ($sRaw_{p1}$). The DV_{plet}–V' relationship was examined visually X–Y immediately after the acquisition. Those maneuvers showing obvious signal distortion—mostly DV_{plet} swing without corresponding change in V' suggestive of glottis closure or swallowing—were excluded. The selected digitized DV_{plet} and V' were subjected to linear regression while a validated correction procedure was applied to eliminate the time drift from DV_{plet}.[21] The slope of the line is sRaw and the corresponding correlation coefficient may be used as an index of measurement quality control. Pilot trials indicated that setting the correlation coefficient to a minimal value of 0.80 to accept, would best attest of the quality of the DV_{plet}–V' curve while accounting for the expected residual looping—that was apparent during most maneuvers. Thus the DV_{plet}–V' curve selection was based on both visual detection of gross artifacts and mathematical criterion. In a given subject, 2–4 technically acceptable acquisitions were obtained, from which a mean was computed. In addition, the software offered easy access to raw signals for off line breath by breath analysis. Each acquisition was thus tracked for a definite pattern of change in EEL: ascending, descending, or stable.

With the commercial equipment sRaw was also measured while the child was asked to pant at similar frequency ($sRaw_{p2}$), an acquisition consisting in a series of 6–8 breaths. Of these, an automated procedure selected and displayed 4.

Ambient temperature throughout the study averaged 258C and relative humidity 60%.

Protocol

The child was first familiarized with the more patient friendly commercial equipment and measurements of

TABLE 1— Characteristics of the Children

	Control	Asthma
n (M/F)	15 (8/7)	40 (22/18)
Age (year)	8.5 (6.5–10.5)	8.6 (6.3–11.0)
Height (cm)	134 (115–152)	132 (116–148)
Weight (kg)	29 (17–41)	28 (17–39)
FEV1 (%pred)Ã	106 (82–130)	101 (77–125)

Data are mean (95% CI).

Ã From Knudson et al.[19]

sRaw$_{tb}$ were obtained. This was followed by the measurement of sRaw$_{p2}$. Finally, measurement of sRaw$_{p1}$ was obtained from the custom made equipment. Each acquisition of sRaw was completed with measurement of thoracic gas volume and total lung capacity, not reported here for the sake of clarity.

Data Analysis

Data were expressed as mean and 95% confidence interval limits. Comparisons were performed using an analysis of variance for repeated measurements. A methodological difficulty arose when examining the effect of EEL because several trends could be observed on repeated measurements in a given subject. Therefore the statistics were performed on the number of acquisitions—rather than subjects—within each pattern of EEL. To make sure that any possible bias due to some pattern of distribution among subjects was avoided, the effect was analyzed further by using only the first acquisition from each subject, so that the degree of freedom now depended on the number of subjects rather than measurements. The effect of breathing frequency was assessed by comparing sRaw$_{tb}$ to sRaw$_{p1}$ and sRaw$_{p2}$. The body boxes were tested by comparing sRaw$_{p1}$ and sRaw$_{p2}$. Agreements between estimates of sRaw (sRaw$_{tb}$ vs. sRaw$_{p1}$ or sRaw$_{p2}$, sRaw$_{p1}$ vs. sRaw$_{p2}$) were examined using Bland and Altman scatter plot.[23] A statistically significant difference was retained at a P value less than 0.05.

RESULTS

Forty asthmatic and 15 healthy children aged 6.5–11.5 years were recruited. The characteristics of the study population are reported in Table 1. There was no significant difference in growth characteristics or FEV1 between groups.

Panting Versus Tidal Breathing

There was a highly significantly larger sRaw$_{tb}$ compared with sRaw$_{p1}$ in both children with asthma and controls ($P < 0.0001$), while both groups showed similar breathing or panting frequencies (Table 2). Taking the panting condition as reference, there was a significant overestimation of sRaw by the tidal breathing method ($P < 0.0001$) and the difference sRaw$_{p1}$ À sRaw$_{tb}$ was À0.374 (À0.835 to 0.088) kPa s. The findings are illustrated by the Bland and Altman plot in Figure 1A that also shows larger scatter at higher values. The trend is similar for sRaw$_{p2}$ À sRaw$_{tb}$: À0.479 (À0.884 to 0.075) kPa s, $P < 0.0001$ (Fig. 1B).

sRaw$_{p1}$ and EEL During Panting

Twenty-six series of 4 breaths were collected from controls and 71 from children with asthma, altogether 97 that could classify from their EEL pattern in 55 subjects. The pattern of change in EEL was found ascending in 43, descending in 28 and stable in 26. Altogether, the ascending pattern represented about 44% of the series. There was a small but significant increase in sRaw$_{p1}$ from breath 1 to 4 ($P < 0.001$), occurring regardless of the observed pattern of EEL and not different between children with asthma and controls. The data—pooled from both groups for clarity—are presented in Table 3A. It may be seen that sRaw from breath 3 to 4 was significantly larger than breath 1 with all 3 patterns. Findings were similar when reanalyzing the data using only the first acquisition from each subject (Table 3B).

Equipment

sRaw during panting was duplicated in the two plethysmographs in six healthy controls and 38 asthmatics (sRaw$_{p1}$, sRaw$_{p2}$). The panting frequency was

TABLE 2— sRaw During Panting and Tidal Breathing

	Control (n ¼ 15)		Asthma (n ¼ 40)	
	Tidal breathing	Panting	Tidal breathing	Panting
Frequency (Hz)	0.4 (0.2–0.7)	3.3 (1.9–4.7)	0.5 (0.3–0.8)	3.3 (2.0–4.6)
sRaw (kPa s)	1.08 (0.60–1.56)Ã	0.67 (0.25–1.10)	1.07 (0.66–1.47)Ã	0.70 (0.37–1.04)

Data are mean (95% CI).

Ã P 0.0001 versus panting.

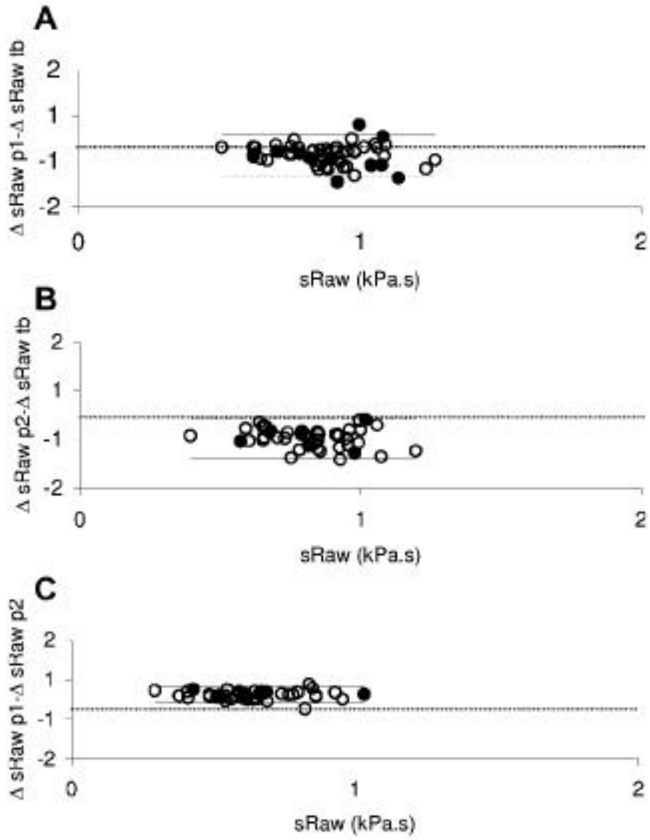

Fig. 1. Bland and Altman diagrams plot the difference between two estimates of specific airway resistance (sRaw) against their corresponding mean. (A) sRaw measured during panting in a custom made plethysmograph (sRawp1) and during tidal breathing in a commercial equipment (sRawtb). (B) sRaw measured during panting in a commercial equipment (sRawp2) and sRawtb. (C) sRawp1 and sRawp2. (A and B) Note large scatter between sRawtb and either estimate of sRawp, with sRawtb being generally larger than sRawp. (C) In contrast, note comparatively smaller difference between sRawp1 and sRawp2. Closed circles: controls; open circles: patients.

similar for both measurements and $sRaw_{p2}$ observed to be significantly lower than $sRaw_{p1}$ ($P < 0.005$, Table 4). The Bland and Altman diagram for $sRaw_{p1}$ and $sRaw_{p2}$ (Fig. 1C) indicated the average magnitude of the difference was rather small compared with that observed between either $sRaw_{p1}$ or $sRaw_{p2}$ and $sRaw_{tb}$ (Fig. 1A and B).

DISCUSSION

Body plethysmography is the only non-invasive method to obtain airway resistance, a valuable tool to studying airway physiology and pathophysiology during growth and development. Airway resistance is computed from sRaw, identified as the slope of the DV_{plet}–V′ relationship. DV_{plet}—the product of alveolar pressure by thoracic gas volume divided by barometric pressure—may be very small in children. For instance, with a thoracic gas volume of 1 L and a change in alveolar pressure of 0.6 kPa, the amplitude of DV_{plet} related to sRaw would be only 6 ml. Furthermore, when measured during tidal breathing, this component of DV_{plet} must be extracted from a signal that is contaminated by the thermal artifact. It is therefore not surprising that metrological difficulties have repeatedly been reported with $sRaw_{tb}$ in infants[17,18] and children.[13,14]

Thermal and water exchanges between respired gas and airways—instrumental dead space may not be instantaneous and this very fact determines a frequency dependence of sRaw.[16] While measured in adults breathing unconditioned air, sRaw has been shown to increase markedly from a value that may be negative at 0.5 Hz to a positive plateau at 2–3 Hz.[16] Findings were similar in a commercial plethysmograph equipped with an electronic BTPS compensation.[12] On the other hand, sRaw measured in children during tidal breathing was found significantly larger with electronic compensation compared with "physical" BTPS conditioning.[2] Both studies used the same type of plethysmograph but different versions of the software[2,12] with presumably

TABLE 3—sRaw (kPa s) Breath by Breath During Panting

		Breath #			
EEL	n	1	2	3	4
A[a]					
Ascending	43	0.74 (0.32–1.17)	0.77 (0.33–1.21)	0.82 (0.37–1.26)[Ã]	0.85 (0.41–1.31)[Ã]
Stable	26	0.78 (0.24–1.32)	0.81 (0.39–1.23)	0.83 (0.35–1.31)[Þ]	0.86 (0.42–1.30)[Ã]
Descending	28	0.77 (0.21–1.33)	0.82 (0.30–1.34)	0.86 (0.38–1.34)[Ã]	0.87 (0.35–1.39)[Ã]
B[b]					
Ascending	28	0.73 (0.31–1.15)	0.74 (0.35–1.13)	0.80 (0.36–1.24)[Ã]	0.85 (0.37–1.32)[Ã]
Stable	11	0.82 (0.28–1.37)	0.81 (0.28–1.34)	0.83 (0.34–1.33)[Þ]	0.88 (0.41–1.36)[Ã]
Descending	14	0.76 (0.31–1.20)	0.80 (0.30–1.30)	0.81 (0.39–1.23)[Ã]	0.82 (0.32–1.33)[Ã]

[a]Data are mean and 95% CI; EEL, end expiratory level; n, number of measurements; [Þ]P 0.05, [Ã]P 0.001, breath 3–4 versus 1.
[b]n: Number of subjects; [Þ]P 0.05, [Ã]P 0.002, breath 3–4 versus 1.

TABLE 4— sRaw During Panting in Two Plethysmographs

	Control 6	6	Asthma 38	38
n	Plet$_1$	Plet$_2$	Plet$_1$	Plet$_2$
Frequency (Hz)	3.2 (2.1–4.3)	3.1 (2.2–4.1)	3.3 (2.1–4.6)	3.2 (1.9–4.6)
sRaw (kPa s)	0.72 (0.31–1.13)	0.58 (0.14–1.02)[Ã]	0.70 (0.36–1.03)	0.58 (0.25–0.92)[Ã]

Data are mean (95% CI).

Plet$_1$, custom equipped body box; Plet$_2$, commercial plethysmograph.

[Ã] P 0.005 versus Plet$_1$.

different BTPS compensation algorithms. In fact, a study comparing plethysmographs of the same brand equipping six centers in a given group of children, disclosed large discrepancies, partly explained by different internal settings.[14] Significant inter-center variability of sRaw$_{tb}$ obtained with electronic BTPS compensation in the same type of plethysmograph was reported by a different group.[13]

A better understanding of the airway thermal and hygrometric dynamics has been provided by the frequency response of the DV_{plet}–V′ relationship in healthy adult subjects.[16,24] A thermal time constant was estimated assuming a 1st order system where the thermal properties of airways and instrumental dead space were combined and linearity assumed. Mechanical and thermal events were supposed to be independent of each other and fluctuations of the respiratory exchange ratio during breathing as well as asymmetry of the thermal dynamics between inspiration and expiration neglected.[16] Various correction algorithms have further been proposed.[25] To the best of our knowledge, there has been no such approach in children because the required procedure appears hardly feasible due to age, at least on a routine basis. It is doubtful that a single algorithm could be successfully applied to subjects with different airway size, let alone different measuring conditions and equipments. Whatever the algorithm used to achieve the electronic compensation with our commercial equipment, sRaw$_{tb}$ was much larger than either sRaw$_{p1}$ or sRaw$_{p2}$. Since in our protocol the child was first familiarized with the easier tidal breathing method and more friendly commercial equipment, a bias could have resulted from this systematic order of measurements. In fact, we have verified that the order of Raw$_{tb}$ À sRaw$_p$ measurements did not significantly alter the difference illustrated in Figure 1A and B (data not shown for clarity). The observation is not at variance with the overestimation of sRaw by the electronic compensation compared with the "physical" BTPS conditioning reported in children by Klug and Bisgaard.[2]

Tidal breathing and panting impose different conditions of rheology and upper airway opening. Panting has been shown to be associated with an increased diameter of the glottis[26] that—compared with tidal breathing—would minimize the contribution of the extrathoracic airways to sRaw. On the other hand, the higher flows being generated during panting should magnify the flow dependent component of the resistance, thus increasing sRaw$_p$. This was indeed thought to explain the slight positive frequency dependence of (physically) BTPS conditioned sRaw.[16] The effect was small however compared with that of breathing unconditioned air.[16] Furthermore, the difference between electronic- and "physical" BTPS conditioning of sRaw has been shown to occur independent of breathing frequency in children.[2] In addition, the difference in amplitude of instantaneous flow would not account for the observation here that sRaw$_{tb}$ was larger than sRaw$_p$.

The panting method has long been recommended as an easy and accurate procedure to minimize the thermal artifact in sRaw measurement as it was thought to maintain the thermal front within the airways—instrumental dead space.[27] Also, it allows studying the DV_{plet}–V′ relationship in a time domain where the thermal time constant should have minimal impact.[16] In the current context, the issue is whether children may be able to achieve the proper maneuver. In a number of instances, the child was found to have difficulties in maintaining a stable EEL. This was presumably attributable to an imbalance between expiratory and inspiratory efforts. A comparatively less powerful expiration could be suspected in about 40% maneuvers, accounting for the progressive increase in EEL. A possible drawback would be anticipated with significant departure from linearity of the specific airway conductance–lung volume relationship. The explanation does not hold however because the increase in sRaw was similarly observed with all EEL patterns and notably in the case of stability (Table 4). Therefore the changing EEL per se has little impact on the breath by breath sRaw. Altogether, significantly larger sRaw was found for the last 2 breaths of panting compared with the first one (Table 3). Given the importance of thermal dynamics, the progressive increase in sRaw could be suspected to relate to an increase in temperature and humidity in the instrumental dead space while panting was initiated. Altogether, the variation of sRaw throughout the measurement averaged about 12%, that is, much less than the ca 40% difference between $sRaw_{tb}$ and $sRaw_{p1}$. The panting technique has in fact been successfully applied to large populations of children aged 5 or 6 and older.[28,29] To the best of our knowledge, it is not known whether $sRaw_p$ may be measured in even younger children. The issue is important because sRaw has been developed primarily for preschool children, and, in a longitudinal study, the different steps require identical techniques and protocols. Extending the measurement of sRawp into younger age would thus have significant advantages to the interpretation of longitudinal measurements, given the large difference reported here between panting and tidal breathing. Of interest is the report of longitudinal studies in $sRaw_p$ from age 5 on.[29]

The body box related difference ($sRaw_{p1}$ À $sRaw_{p2}$) was also statistically significant, in keeping with previous multi center studies that reported between center differences due to methods of analysis[13] or internal settings.[14] The overall difference observed here however was only about 18%, therefore much less than that observed between $sRaw_{tb}$ and either estimate of $sRaw_p$. This is best shown on the Bland–Altman diagram in Figure 1 where ($sRaw_{p1}$ À $sRaw_{tb}$) is negative and exhibits larger scatter toward larger sRaw, while ($sRaw_{p1}$ À $sRaw_{p2}$) is positive, of smaller amplitude and homogeneous over the range of values.

Altogether, the current study indicates significantly larger estimates by $sRaw_{tb}$ with electronic compensation, compared with $sRaw_p$. The findings extend the reported sRaw difference between electronic compensation—and "physical" BTPS conditioning in children.[2] The frequency dependence of $sRaw_{tb}$ when breathing unconditioned air could thus be a confounding factor whenever the child's clinical condition is associated with an altered rate of breathing. To our knowledge, the putative error has not been estimated. Little difference was detectable between asthmatic subjects with normal lung function and controls, in keeping with previous reports,[30] but in both groups, sRaw was similarly dependent on breathing frequency. A drawback with the panting method is the maneuver understanding and feasibility by a young child. The current study suggests however that even improperly balanced panting efforts may provide more trustful results than tidal breathing. Because the main advantage of sRaw is for measuring preschool children, an important further step is to test the feasibility of the panting method at younger age. A substantial advantage of such achievement would be to unify measurement protocols from early childhood into adulthood.

ACKNOWLEDGMENTS

The authors thank the children that contributed to the study and their families, and gratefully acknowledge the technical assistance of Sylvie Meline, Franc¸oise Bebon, Marie Jeanne Arnoux, Marianne Mougin and Francine Cael.

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