

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 ± 1 L/sec and ± 0.5 L/sec. sRaw was not different between asthmatics (0.87 ± 0.20 kPa.s) and controls (0.80 ± 0.25 kPa.s) when computed full scale, while it was significantly larger in asthmatics than controls within ± 1 L/sec (0.77 ± 0.16 kPa.s vs 0.65 ± 0.15 kPa.s, $P < 0.004$) or ± 0.5 L/sec (0.77 ± 0.21 kPa.s vs 0.61 ± 0.17 kPa.s, $P < 0.002$). On the other hand, the within subject coefficient of variation was significantly larger when sRaw was computed within ± 1 L/sec ($13.7 \pm 7.2\%$) or ± 0.5 L/sec ($28.3 \pm 18.1\%$) than full scale ($11.0 \pm 6.7\%$), 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. ©2014 Wiley Periodicals, Inc.

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

Funding source: Ministère de la Santé et de la Recherche Médicale; Number: EA 3450.

INTRODUCTION

Body plethysmography is a unique technique to assess lung volume compression/decompression (ΔV_{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

approaches⁶, namely because temperature equilibration in the airway is not instantaneous².

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 ± 0.5 L/sec or ± 1 L/sec in adults^{1,13} or ± 0.5 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 $\Delta V_{\text{plet}} - V'$ 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 (Hôpital d'Enfants, Vandoeuvre-lès-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 (Comité 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 ΔV_{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 ± 2 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 ΔV_{plet} and V' were digitized at 100 Hz. The $\Delta V_{\text{plet}} - V'$ relationship was examined visually X-Y immediately after the acquisition and those maneuvers showing obvious signal distortion—mostly ΔV_{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. ΔV_{plet} was drift-corrected¹⁷ 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 ± 1 L/sec interval (sRaw₁) and those outside the ± 0.5 L/sec interval (sRaw_{0.5}). A typical $\Delta V - V'$ 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.

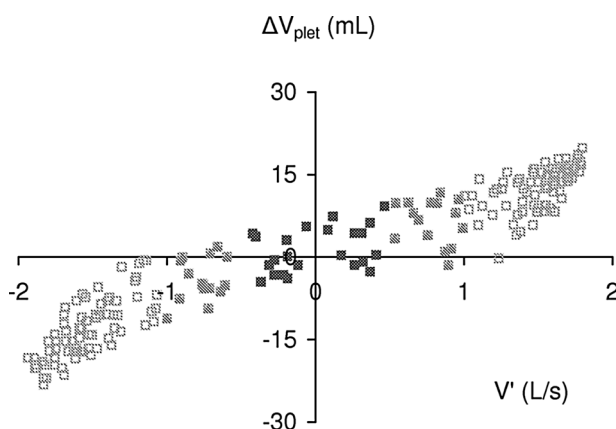


Fig. 1. Plethysmographic signal (ΔV_{plet}) and airflow (V') obtained with a single measurement during panting. The S shaped relationship is typical of non linear behavior. The slope is the specific airway resistance. Slope estimates are obtained within three flow intervals: using all data point—that is, in the full scale flow—within ± 0.5 L/sec and ± 1 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 children¹⁹ 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 -2 L/sec to $+2$ L/sec. In the characteristic plot of ΔV_{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, $s\text{Raw}_{0.5}$ or $s\text{Raw}_1$ were significantly lower than $s\text{Raw}_{\text{fs}}$ in controls (*P* < 0.0001) as well as asthmatics (*P* < 0.002, Fig. 3). There was no significant difference between $s\text{Raw}_1$ and $s\text{Raw}_{0.5}$. $s\text{Raw}_{\text{fs}}$ was not different between groups (Fig. 3). In contrast, either $s\text{Raw}_1$ or $s\text{Raw}_{0.5}$ was significantly larger in subjects with asthma than controls (respectively, *P* < 0.004 and *P* < 0.002). The Bland–Altman plots showed $(s\text{Raw}_{\text{fs}} - \text{Raw}_{0.5})$ or $(s\text{Raw}_{\text{fs}} - \text{Raw}_{0.5})$ were predominantly positive in both groups, with a trend for $(s\text{Raw}_{\text{fs}} - \text{Raw}_1)$ 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 ΔV_{plet} and V' , and the full scale gave a larger value than either ± 1 L/sec or 0.5 L/sec (*P* < 0.0001). There also was a difference between ± 1 L/sec and ± 0.5 L/sec (*P* < 0.0001), and the latter was significantly larger in asthmatic subjects than controls (*P* = 0.01). In addition, the within subject—between series coefficient of variation full scale was smaller than within ± 1 L/sec in asthmatics (*P* < 0.04) or ± 0.5 L/sec in both groups (*P* < 0.0001). The coefficient of variation was also significantly lower for ± 1 L/sec than for ± 0.5 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
<i>n</i> (M/F)	25 (13/12)	40 (22/18)
Age (year)	9.1 ± 1.2	8.7 ± 1.2
range	7–11	6.5–10.5
Height		
cm	135 ± 9	132 ± 8
Z score	0.34 ± 1.04	0.17 ± 0.84
Weight		
kg	31 ± 7	28 ± 5
Z score	0.16 ± 0.97	0.04 ± 0.90
FEV1		
L	2.04 ± 0.37	1.81 ± 0.31^1
Z score ²	0.87 ± 0.74	0.41 ± 0.92^1

Data are mean $\pm$ SD.

¹*P* < 0.05.

²From Stanojevic et al.²⁰

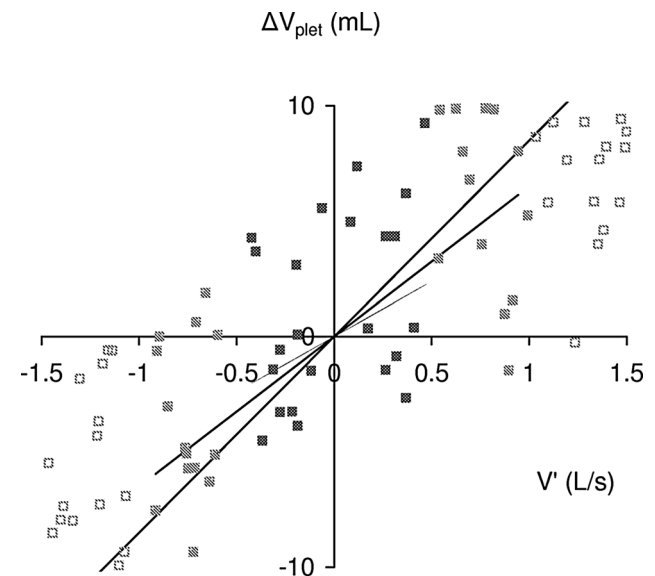


Fig. 2. Same data as in Figure 1. The slope of the $\Delta V_{\text{plet}}-V'$ relationship (specific airway resistance) decreases when flow range for computation is narrowed. Y-axis scale has been enlarged and symbols lightened for better readability.

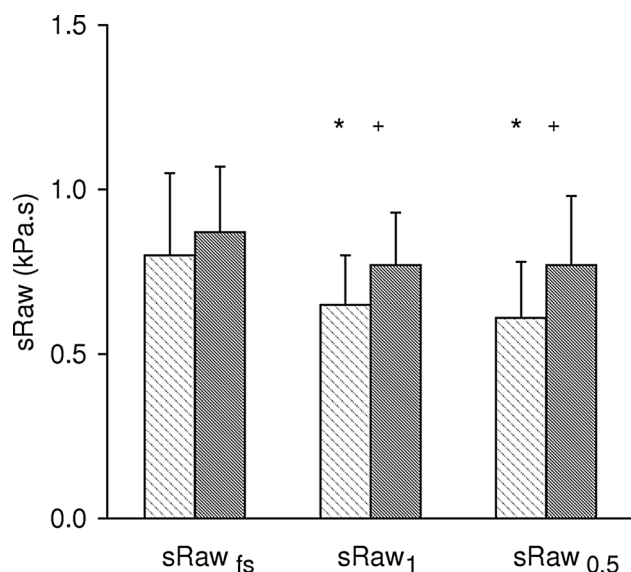


Fig. 3. Different estimates of specific airway resistance (sRaw) are provided within 3 panting flow intervals: full scale (sRaw_{fs}), ± 1 L/sec (sRaw₁) ± 0.5 L/sec (sRaw_{0.5}). sRaw₁ or sRaw_{0.5} are significantly lower than sRaw_{fs} ($P < 0.0001$). In addition a significant difference between patients (dark bars) and controls (light bars) is disclosed with sRaw_{0.5} ($*P < 0.002$) or sRaw₁ ($*P < 0.004$) but not sRaw_{fs}.

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 subjects⁷—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

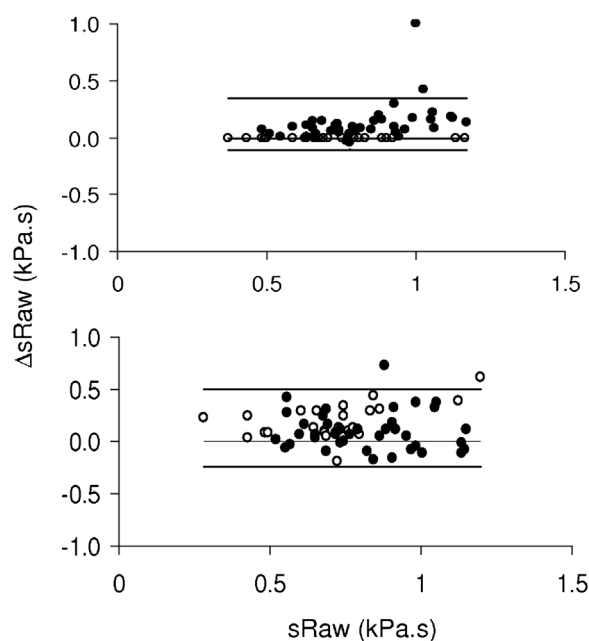


Fig. 4. Bland and Altman plots showing difference between 2 estimates of sRaw (Δ sRaw) against their mean. (A) sRaw computed within full scale flow and within 1 L/sec; (B) sRaw computed within full scale flow and within 0.5 L/sec. Note the generally positive difference and a trend for larger difference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

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 ΔV_{plet} and V' relative to the signals individual variance. As a result, the correlation coefficient is

TABLE 2—Quality Control Criteria

n	Flow interval	Control	Asthma
		25	40
Correlation coefficient	Full scale	0.90 ± 0.03 ¹	0.89 ± 0.04 ¹
	±1 L/sec	0.71 ± 0.08	0.75 ± 0.10
	±0.5 L/sec	0.44 ± 0.09 ²	0.51 ± 0.12 ^{2,3}
Coefficient of variation (%)#	Full scale	11.7 (9.8) ¹	9.8 (5.9) ^{1,4}
	±1 L/sec	12.9 (11.6)	12.3 (10.4)
	±0.5 L/sec	28.8 (22.9) ²	23.9 (24.3) ²

Data are mean ± 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 ΔV_{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

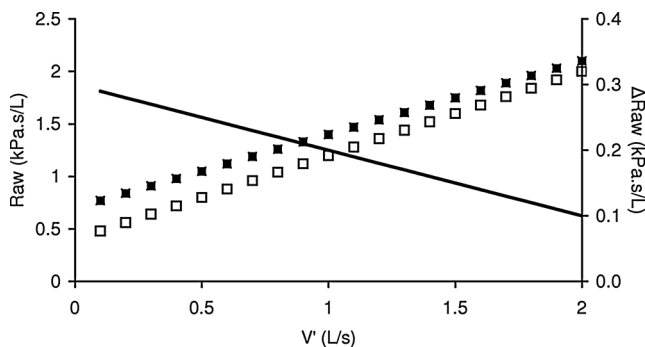


Fig. 5. Airway resistance (R_{aw}) is computed using Rohrer's model-coefficients K_1 and K_2 to simulate the contribution of upper and lower airways when flow (V') ranges from 0–2 L/sec. R_{aw} for control and asthma are open and closed squares, respectively. The line is the R_{aw} difference between asthma and control (ΔR_{aw}) that decreases when the amplitude of flow is increased. R_{aw} is given by $K_1 + K_2 \cdot V'$. K_1 and K_1/K_2 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 ΔV_{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 adults²² and could therefore contribute more significantly to the phase shift observed between ΔV_{plet} and V' at higher frequencies. To test the hypothesis, a typical airway inertance of 0.004 kPa.s²/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 $\Delta V_{\text{plet}}-V'$ phase shift less than 10°, 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 ΔV_{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, ΔV_{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 $\Delta V_{\text{plet}}-V'$ 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 −1 to +1 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 ΔV_{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 Méline, Francine Cael, Marie-Jeanne Arnoux, Marianne Mougin, Myriam Chamagne, and Dominique Binot-Saintot.

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