Separation of airway and tissue properties by transfer respiratory impedance and thoracic gas volume in reversible airway obstruction


ABSTRACT: The aim of this study was to establish the ability to estimate separate airway and tissue properties from transfer respiratory impedance \(Z_{rs,tr}\) data in the presence of airway obstruction.

\(Z_{rs,tr}\), thoracic gas volume (TGV) and airway resistance \(R_{aw,pleth}\) were measured in the presence of obstruction and after use of a bronchodilator (BD) in 13 normal or asymptomatic asthmatic adults and 28 children with symptomatic asthma. An analytical approach was used to solve the equations of a simplified variant of DuBois’ model, including airway resistance \(R_{aw}\) and inertance \(I_{aw}\), tissue compliance \(C_t\) and resistance \(R_t\) and pulmonary gas compliance \(C_g\).

The equations of the model could not be reliably solved in four children before BD. Mean \(R_{aw,pleth}\) was not different from mean \(R_{aw}^*\) in adults before (mean±SEM) \(3.4±0.5\) vs \(3.1±0.3\) hPa·s·L\(^{-1}\)) or after BD \((1.4±0.2\) vs \(1.8±0.2\) hPa·s·L\(^{-1}\)), or in children after BD \((2.9±0.3\) vs \(3.2±0.2\) hPa·s·L\(^{-1}\), respectively). In children before BD, \(R_{aw}^*\) was significantly underestimated compared with \(R_{aw,pleth}\) \((3.8±0.4\) vs \(5.4±0.6\) hPa·s·L\(^{-1}\)). Overall, a significant positive correlation was found between the difference \([R_{aw,pleth} - R_{aw}^*]\) and \(R_{aw,pleth}\) \((r=0.82)\). In adults, BD induced a decrease in \(R_{aw}^*\) and \(R_t\), an increase in \(C_t\), and no change in \(I_{aw}\). In children after BD, there was no significant change in \(R_{aw}^*\) or \(C_t\) whilst \(R_t\) decreased and \(I_{aw}\) increased.

Taking \(R_{aw,pleth}\) as the gold standard, it is concluded that coherent estimation of parameters of DuBois’ model may be obtained from combined \(Z_{rs,tr}\) and TGV measurements in normal subjects and moderately obstructed adults, but not in children with significant airway obstruction. This seems to be due to the systematic under-estimation of \(R_{aw}^*\).

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Respiratory input impedance \(Z_{rs,in}\) measured by the forced oscillation technique is becoming increasingly popular in lung function testing, and provides a convenient, noninvasive estimation of respiratory system resistive and reactive properties. Another interesting approach is to obtain the transfer impedance of the respiratory system \(Z_{rs,tr}\) by varying pressure at the chest wall and measuring flow at the mouth. The advantage of this technique is twofold. Firstly, pressure variations in the pneumotachograph are small and the accuracy of flow measurement at high frequency does not critically depend on the symmetry of the flow channel. This is particularly important when large resistances are to be measured [1], which is the case of children with airway obstruction. Secondly, \(Z_{rs,tr}\) is significantly influenced by pulmonary gas compressibility \(C_g\) described in DuBois’ model [2].

The parameters of airway and tissue impedance were estimated from \(Z_{rs,tr}\) in normal adult humans, using \(C_g\) value provided by thoracic gas volume (TGV) measurement [3]. With comparative measurements of \(Z_{rs,in}\) and \(Z_{rs,tr}\) it was found that the second, but not the first, approach could provide a correct estimation of airway and tissue parameters [4]. It was also shown in healthy dogs and humans that the spectrum of excitation frequency should include the antiresonance peak for optimal parameter estimation [4, 5]. The sensitivity functions of the model are highly dependent on the relative values of these parameters [5, 6], which are subjected to substantial between-species variation, and, within a given species, to the effect of growth and respiratory disease. An important practical limitation to the use of high frequency is the parallel arrangement of upper airway wall and pneumotachograph, which is responsible for an error in the measurement of flow that increases with increasing frequency. Moreover in a recent study, we found that coherent estimation of airway and tissue parameters was possible below 40 Hz in infants, in the absence of overt airway obstruction [7].

An important and practical indication to the adequate description of the mechanical properties of the respiratory system by DuBois’ model is the demonstration...
that the parameters are correctly estimated when one compartment (e.g. airway impedance) is changed. The aim of this study was, thus, to compare airway resistance estimated after DuBois' model with that measured by plethysmography in patients with airway obstruction and after reversal by use of a bronchodilator.

**Material and methods**

**Subjects**

Forty one subjects were studied: 13 adults aged 22–55 yrs (mean±SEM 33±3 yrs) and 28 children aged 10–19 yrs (13±1 yrs). Nine adults were normal subjects, members of the laboratory staff, and four were former asthmatics without history of asthma attack in the past year, and receiving no medication. The 28 children were all asthmatics, and their baseline forced expiratory volume in one second (FEV1) was <70% predicted in 10, and >70% pred in 18. The study was approved by the Regional Committee on Human Subjects Experimentation.

**Protocol**

*Airway challenge.* Eight normal adults, and 12 asthmatic children with FEV1 >70% pred were challenged with methacholine. Methacholine chloride (Pharmacie centrale des Hôpitaux de Paris) was administered in cumulative doses, from 100 to 1,200 µg, with metered-dose inhaler and spacer device. The six other children with FEV1 >70% pred were challenged with allergenic extracts of house dust mites (Alyostal, Stallergenes, Pasteur), from a solution of 0.5–12 IR, using a Wright nebulizer [8].

*Reversibility of airway obstruction.* Salbutamol (300 µg) was given to one normal adult, to four adults with history of asthma and to the 10 children with baseline FEV1 <70% pred. Bronchodual (150 µg fenoterol and 60 µg ipratropium bromide) was given to all subjects after provocation. Both bronchodilators were administered with metered-dose inhaler and spacer device.

FEV1 was first measured to detect the presence of airway obstruction. In the presence of obstruction, the measurements of Zrs,tr, TGV and airway resistance (Raw,pleth) were performed and repeated after use of the bronchodilator. Without evidence of airway obstruction, methacholine was administered, until 15% decrease in FEV1 was observed, or the maximum dose was attained. The measurements of Zrs,tr, TGV and Raw,pleth were then obtained, and repeated, as above, after use of the bronchodilator.

**Measurements**

FEV1 was measured using a spirometer (Spiromatic, Gauthier, France). The subjects were trained to perform a forced vital capacity (FVC) manoeuvre, and the best (largest peak flow and largest FVC) of three reproducible curves was retained.

Thoracic gas volume (TGV) and airway resistance (Raw,pleth) were measured in a pressure type 890 L body plethysmograph (Siregnost 91S, Siemens, Erlangen, Germany). The subject was trained to make respiratory efforts at about 1–2 Hz for 3–5 s. TGV was measured from the box volume-airway pressure relationship obtained during airway occlusion at end-expiration. Both signals were analogue-to-digital (A/D) converted, and the linear correlation between pressure and volume was calculated by the least square method, after correction for the drift of the box volume signal [9]. Raw,pleth was measured at about the same breathing frequency, whilst the subject was panting through a dead space. The relationship between box pressure and airflow was calculated using similar algorithms.

The set-up for Zrs,tr measurement is described in figure 1a. The subject was enclosed in a wooden chamber up to his neck. Pressure was varied around the chest by

![Fig. 1.](image-url)
two 45 W loudspeakers connected to the chamber and driven by a pseudorandom signal containing all harmonics of 2 Hz from 6 to 32 Hz, generated by a microcomputer at 512 Hz, D/A converted and amplified. Airway flow was measured with a Fleisch No. 2 pneumotachograph connected to a differential pressure transducer (Honeywell ±35 cmH2O), and the pressure at the chest was measured with an identical transducer, matched to the first within 1% of amplitude and 2° of phase up to 32 Hz. The common mode rejection ratio of the flow channel was 60 dB at 32 Hz. The pneumotachograph was calibrated by the integral method, and the pressure channel with a precision fluid-mанometer. The accuracy of the apparatus was checked daily with a physical analogue, and the whole calibration procedure was repeated whenever the results were found to deviate by more than 5% from the expected value.

Pressure and flow were A/D converted at 128 Hz, for a 16 s data acquisition period. The fast Fourier transforms of pressure and flow were calculated using seven data blocks of 4 s with 50% overlapping. Respiratory resistance (Rs) and reactance (Xs) were then computed from the in-phase and out-of-phase components of pressure and flow, together with the coherence function between these signals (γ2), an index of signal-to-noise ratio. Data with γ2 lower than 0.95 were not retained for analysis. At least three data acquisition periods were averaged.

Data analysis

Third order model. This model features tissue (Zt) and airway impedances (Zaw) separated by the impedance of the alveolar gas (Zg), as described in figure 1b. For a pressure input at the chest, flow measurement at the mouth, and parallel arrangement between airway and pulmonary gas, Zrs, tr may be written:

\[ Z_{rs, tr} = Z_t + Z_{aw} + Z_{aw} \cdot Z_d/Z_g \] (1)

Each impedance is characterized by one or more resistive, inertive and/or elastic elements, and Zaw, Zt and Zg may, thus, be written:

\[ Z_{aw} = R_{aw} + j\omega_1 \cdot \omega \] (2)

\[ Z_g = -jC_g \cdot \omega \] (3)

\[ Z_t = R_t - jC_t \cdot \omega \] (4)

where Raw and Iaw are airway resistance and inertance, Rt and Ct are tissue resistance and compliance, and Cg is the gas compressibility or compliance, ω is angular frequency (2πf), and j=√-1 is the unit of imaginary numbers. Note also that the model is simplified by neglecting tissue inertance, which has been shown not to significantly affect the frequency response of Zrs, tr up to 30 Hz [3].

Determination of the coefficients of Zrs, tr. Zrs, tr is characterized by a decrease of the resistance with frequency, which may become negative at high frequencies, and an increase of the reactance, which is negative below and positive above resonant frequency. When solving for the real and imaginary part of Equation (1), using the five elements described in Equations (2) to (4), it may be shown that both resistance and reactance may be written as functions of angular frequency:

\[ R_{is} = m_1 - m_3 \cdot \omega^2 \] (5)

\[ X_{is} = -m_0/\omega + m_2/\omega \] (6)

where the coefficients m0 to m3 have the following meaning:

\[ m_0 = 1/C_t \] (7)

\[ m_1 = R_t + R_{aw} (1 + C_g/C_t) \] (8)

\[ m_2 = I_{aw} (1 + C_g/C_t) + R_{aw} \cdot R_t \cdot C_g \] (9)

\[ m_3 = I_{aw} \cdot R_t \cdot C_g \] (10)

m0 to m3 were calculated by least square regression analysis of Rs and of Xs vs ω2 using Equations (5) and (6). The goodness of fit of the data to the model was evaluated by the residual term (χ) between observed and predicted impedance:

\[ \chi^2 = \sqrt{\left( \sum (R_{is,o} - R_{is,m})^2 + (X_{is,o} - X_{is,m})^2 \right)/(2n-a)} \] (11)

where Rs,o, Xs,o, Rs,m, Xs,m are the observed and model resistance and reactance, respectively, and n and a the number of frequencies and coefficients, respectively.

The relative distance (d) was then obtained by dividing χ by the average impedance modulus. Cg was calculated from TGV measurement as:

\[ C_g = [(TGV + V/2)/(P_0 - PH_{1} O)] \] (12)

where P0 is barometric pressure, PH_{1} O alveolar water vapour pressure and V/2 roughly accounts for the average contribution of tidal volume to gas compressibility in spontaneously breathing subjects.

Knowing Cg, the other coefficients may be obtained by solving Equations (7) to (10) for Rt, which yields the following third degree equation:

\[ R_t^3 - m_1 R_t^2 + (K m_2 C_g - m_3 K^2 C_g^2)/2 = 0 \] (13)

where K=1 + m0 Cg. The other coefficients may then be easily computed from Equations (8) to (10). A practical problem is that, in some instances, Equation (13) may have three real roots, so that the analysis provides three sets of coefficients. This was the case in four out of a total of 82 determinations. As discussed later on, this happens when airway resistance is increased. One of the solutions then provides an unrealistically high value for Rt and low value for Iaw, and may readily be excluded. The two other solutions, however, are usually realistic, and there is little ground on which to make a choice between them. We therefore discarded the corresponding measurements (see Discussion).
Statistics

Analysis of variance for repeated measures and least square linear regression were used as necessary. The agreement between Raw,pleth and the value of airway resistance obtained derived from model (Raw*) was also assessed by plotting the difference [Raw,pleth-Raw*] with the reference measurement (i.e. Raw,pleth), as suggested by BLAND and ALTMAN [10]. The normalized residuals of respiratory resistance and reactance were compared to zero using one group t-test. Statistical significance was considered at p-values less than 0.05. Data are expressed as mean±SEM, unless otherwise indicated.

Results

Evaluation of the reversibility of airway obstruction

The mean data on FEV1 and TGV presented in table 1 are for adults and children. In both groups, bronchodilation is associated with a significant increase in FEV1, but the decrease in TGV observed in both groups is significant only in children, probably because of the larger sample size. In both groups, we also found a significant decrease in Raw,pleth, as shown in table 2.

Frequency response of Zrs,tr

An example of frequency response of Zrs,tr in an asymptomatic asthmatic before and after bronchodilator is illustrated in figure 2. It can be seen that the fitting of the model curve to the data is satisfactory in both cases. In this example, Raw* (airway resistance extracted from the model) is 4.0 hPa·s·L\(^{-1}\) before and 1.9 hPa·s·L\(^{-1}\) after salbutamol, and both values compare well with Raw,pleth (3.8 hPa·s·L\(^{-1}\) before and 1.8 hPa·s·L\(^{-1}\) after salbutamol). Zrs,tr: transfer respiratory impedance; Raw,pleth: plethysmographic airway resistance.

Table 1. – FEV1 and TGV before and after bronchodilation (BD)

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th></th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV1</td>
<td>TGV</td>
<td>FEV1</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>PreBD</td>
<td>2.1±0.2</td>
<td>1.92±0.11</td>
<td>3.3±0.2</td>
</tr>
<tr>
<td>PostBD</td>
<td>2.5±0.2*</td>
<td>1.77±0.10*</td>
<td>3.7±0.3*</td>
</tr>
</tbody>
</table>

Values are presented as mean±SEM. FEV1: forced expiratory volume in one second; TGV: thoracic gas volume. *: p<0.001 vs preBD.

Table 2. – Plethysmographic airway resistance (Raw,pleth), and model estimated airway resistance (Raw*), airway iner-tance (Iaw), tissue resistance (Rt) and compliance (Ct), and distance to the model (d) before and after bronchodilation (BD)

<table>
<thead>
<tr>
<th></th>
<th>Raw,pleth</th>
<th>Raw*</th>
<th>Iaw</th>
<th>Rt</th>
<th>Ct</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hPa·s·L(^{-1})</td>
<td>hPa·s·L(^{-1})</td>
<td>Pa·s(^{-1})·L(^{-1})</td>
<td>hPa·s·L(^{-1})</td>
<td>mL·hPa(^{-1})</td>
<td>%</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreBD</td>
<td>5.4±0.6</td>
<td>3.8±0.4(^{\oplus})</td>
<td>1.8±0.2</td>
<td>4.4±0.9</td>
<td>22.5±2.8</td>
<td>4.7±0.2</td>
</tr>
<tr>
<td>PostBD</td>
<td>2.9±0.3(^{\circ})</td>
<td>3.2±0.2</td>
<td>2.7±0.1(^{\circ})</td>
<td>1.4±0.1(^{\circ})</td>
<td>24.1±1.8</td>
<td>5.0±0.2</td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreBD</td>
<td>3.4±0.5</td>
<td>3.1±0.3</td>
<td>1.8±0.2</td>
<td>1.9±0.3</td>
<td>27.5±2.2</td>
<td>4.7±0.3</td>
</tr>
<tr>
<td>PostBD</td>
<td>1.4±0.2(^{\circ})</td>
<td>1.8±0.2(^{\circ})</td>
<td>2.0±0.1</td>
<td>1.3±0.1(^{\circ})</td>
<td>31.9±2.5(^{\circ})</td>
<td>5.4±0.4</td>
</tr>
</tbody>
</table>

Values are presented as mean±SEM. \(^{\oplus}\): p<0.05 vs Raw,pleth; \(^{\circ}\): p<0.005 vs preBD; \(^{*}\): p<0.05 vs preBD. d: distance to the model (calculated from equation 11).
5% at 4 Hz, decreases to -5% at 16 Hz, and then increases again to about 3% at 32 Hz. The error on reactance shows almost opposite changes: negative at 4 Hz, it increases to about 5% at 18 Hz, and decreases from 22 to 32 Hz. Adults and children show a similar pattern, and there is no systematic difference between obstruction and bronchodilation.

**Coefficients of DuBois’ model**

The coefficients obtained by solving Equations (7) to (10), using $C_b$ calculated from the TGV value, are listed in Table 2. Adults show significant reduction in the estimated airway resistance ($R_{aw}^*$) and much less but still significant reduction in tissue resistance, with no change in $Iaw$. Tissue compliance is also found to increase after bronchodilation. In the children, the findings are markedly different. $R_{aw}^*$ and $C_i$ are, surprisingly, not changed by use of a bronchodilator but airway inertance increases, whilst tissue resistance decreases significantly after bronchodilation.

**Correspondence between $R_{aw,pleth}$ and $R_{aw}^*$**

The agreement between the two estimates of airway resistance was also variable. In adults, $R_{aw}^*$ was not significantly different from $R_{aw,pleth}$, both before and after bronchodilators. In children before bronchodi- lation, $R_{aw}^*$ was significantly lower than $R_{aw,pleth}$, but the difference was cancelled after bronchodilation (Table 2). The correlation observed between the two estimates of $R_{aw}$ was variable in adults and children. $R_{aw}^*$ and $R_{aw,pleth}$ were significantly correlated in adults ($r=0.62$) as well as in children after bronchodilation ($r=0.52$), but not in children with airway obstruction. Interestingly, plotting the difference [$R_{aw,pleth} - R_{aw}^*$] against $R_{aw,pleth}$ disclosed a strong positive relationship ($r=0.82$). Larger $R_{aw,pleth}$ was associated with larger difference between $R_{aw,pleth}$ and $R_{aw}^*$, i.e. there was a significant underestimation of $R_{aw}^*$ in the presence of severe airway obstruction (Fig. 4).

There was a significant correlation between the percentage change in $R_{aw,pleth}$ and in ml induced by bronchodilation ($r=0.57$; $p<0.005$), as reported in Figure 5. In contrast, there was no significant correlation between $\Delta R_{aw,pleth}$ and $\Delta R_{aw}^*$. In adults, $\Delta R_{aw}^*$ (-39.3±5.7%) was smaller than $\Delta R_{aw,pleth}$ (-53.6±5.3%) but the difference did not reach statistical significance ($p=0.06$). In children, $\Delta R_{aw,pleth}$ (-41.8±3.7%) was significantly different from $\Delta R_{aw}^*$ (20.9±2.7%; $p<0.05$) which showed very large dispersion, as a result of the underestimation of $R_{aw}^*$ in subjects with severe obstruction (Fig. 4).
Discussion

This study suggests that DuBois’ model may be applied to the respiratory system of asthmatic children after bronchodilation, normal adults or adults with incipient or moderate airway obstruction. In contrast, the coefficients of DuBois’ model cannot be reliably estimated in asthmatic children with more severe obstruction.

In adults, the mean value of $R_{aw,pleth}$ and $R_{aw}^*$ were not statistically different either before or after bronchodilation, and neither was the average drop in airway resistance, which indicates that the parameter estimation is able to describe the effect of bronchodilation in this study group. However, the model may not be realistic enough for accurate quantitation of individual responses. Also, the differences in measuring conditions may account for some discrepancies between changes in these two estimates of $R_{aw}$. $R_{aw}^*$ and $R_{aw,pleth}$ cannot be measured simultaneously and are, therefore, subjected to the spontaneous variation resulting from lung volume history and bronchodilation in the present study group. However, the identity line is shown. $R_{aw,pleth}$: plethysmographic airway resistance.

No change in airway inertance was found after bronchodilator in the adult group, and this confirms our previous finding for respiratory inertance obtained with the head generator technique [8]. This is not surprising, since $I_{aw}$ is mainly related to the dimensions of the trachea, which contributes little to the bronchomotor response.

More interestingly, we found that tissue impedance parameters contributed to the response to bronchodilation, with a significant increase in respiratory compliance and decrease in tissue resistance. The interpretation of respiratory impedance data may be complicated by the viscoelastic properties of the chest wall, which explain marked negative frequency dependence [16]. However, it may reasonably be assumed that the bronchodilator affects only the lung. The mechanical properties of lung tissues may be modelled by a viscoelastic compartment with two parameters: a tissue viscosity that accounts for the negative frequency dependence of lung resistance, and an effective elastance [17]. The Newtonian component to lung tissue resistance suggested by measurements of pulmonary impedance in adult humans [18] has not been supported by further studies in open-chest dogs and isolated dog lungs [19]. The increase in lung tissue viscosity and elastance by methacholine or histamine has been demonstrated in a number of studies both of lung [20–22] and respiratory impedance [23, 24]. These changes are best measured at low frequency, because of the strong frequency dependence of lung tissue viscosity and elastance below a few Hz, and they are thought to be related to the lung tissue response associated with bronchoconstriction. Thus, the changes in $R_t$ and $C_t$ observed after bronchodilation in the present study may well express reversal of lung parenchymal constriction. An alternative - or complementary - explanation for these changes may be the reduced effect of airway wall compliance, and/or the more homogeneous distribution of ventilation within the lung, although the regional inhomogeneity of mechanical time constants may be difficult to detect from model analysis [25].

In children with marked airway obstruction, $R_{aw}^*$ was significantly underestimated compared with $R_{aw,pleth}$. Also, the clear change induced by BD on $R_{aw,pleth}$ did not show on $R_{aw}^*$, in contrast to the significant correlation between changes in $R_{aw,pleth}$ and in $m_1$ - which
represents mostly the total respiratory resistance at zero frequency (Equation (8)) - showing reasonably good agreement between plethysmographic and transfer impedance methods in evaluating the magnitude of the response to bronchodilatation. This, together with the strong correlation shown in figure 4, indicates that the discordance between $R_{aw}^*$ and $R_{aw,pleth}$ in the obstructive children reflects the failure to extract the accurate value of airway resistance from the model, provided there is no major flaw in estimating $C_g$. It has previously been shown that the accurate separation of airway and tissue impedances in normal adults was also dependent on accuracy of $C_g$ determination [4]. The determination of TGV, on which was based the calculation of $R_{aw}^*$, may be subjected to error in the presence of significant airway obstruction, and this may lead to inaccurate determination of airway and tissue impedance. In order to evaluate the possible contribution of erroneous estimation of TGV, we recalculated airway and tissue parameters using $C_g$, respectively, 25 and 50% higher and lower than that measured, in two children with airway obstruction (table 3). It may be seen that the effect of 25% variations in $C_g$ is generally small, except for $I_{aw}$ in subject No. 2. Fifty percent variations in $C_g$ are associated with more significant errors, but such under- or overestimation of $C_g$ are unlikely to be encountered in the population described here.

Finally, the possibility of deriving airways and tissue properties from $Z_{rs, tr}$ data has been demonstrated mainly in healthy adults [3, 4]. When studying patients with airway obstruction, Yng et al. [26] observed unrealistic values of $I_{aw}$ and, occasionally, of $R_t$. Although this could be explained to some extent by airway wall shunting, we wondered if the analysis was reliable during airway obstruction, even if the model was adequate. To answer the question, we numerically generated impedance data corresponding to known sets of coefficients (Equations (1) to (4)) at the frequencies used in the patients. We analysed them in the same way as the experimental data, both with and without added noise. Without noise, we observed that, as mentioned in the Methods section, the analysis could provide three different solutions. This was seen to be systematically the case when $R_{aw}$ or $C_g$ were large, or when $I_{aw}$, $R_t$ or $C_t$ were low. For reasonable values of $I_{aw}$ (2 Pa.s²·L⁻¹), $R_{aw}$ (2 hPa.s·L⁻¹), $C_t$ (20 mL·hPa⁻¹) and $C_g$ (2 mL·hPa⁻¹) in children, a triple solution was always seen when $R_{aw}$ exceeded 6.3 hPa.s·L⁻¹.

Table 3. – Effect of using different gas compressibilities ($C_g$s) on airway and tissue parameter estimation in two children with airway obstruction

<table>
<thead>
<tr>
<th>$C_g$</th>
<th>$R_{aw}$ hPa.s·L⁻¹</th>
<th>$I_{aw}$ Pa.s²·L⁻¹</th>
<th>$R_t$ hPa.s·L⁻¹</th>
<th>$C_t$ mL·hPa⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>-50%</td>
<td>5.8</td>
<td>3.4</td>
<td>3.0</td>
<td>23</td>
</tr>
<tr>
<td>-25%</td>
<td>6.3</td>
<td>2.9</td>
<td>2.2</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>6.6</td>
<td>2.7</td>
<td>1.9</td>
<td>23</td>
</tr>
<tr>
<td>+25%</td>
<td>6.6</td>
<td>2.3</td>
<td>1.7</td>
<td>23</td>
</tr>
<tr>
<td>+50%</td>
<td>3.0</td>
<td>0.6</td>
<td>5.6</td>
<td>23</td>
</tr>
</tbody>
</table>

For abbreviations see heading to table 2.

Table 4. – Example of multiple solutions to noise-free transfer impedance data

<table>
<thead>
<tr>
<th>Solution</th>
<th>$R_{aw}$ hPa.s·L⁻¹</th>
<th>$I_{aw}$ Pa.s²·L⁻¹</th>
<th>$R_t$ hPa.s·L⁻¹</th>
<th>$C_t$ mL·hPa⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution 1</td>
<td>3.4</td>
<td>0.56</td>
<td>7.1</td>
<td>20.0</td>
</tr>
<tr>
<td>Solution 2</td>
<td>8.0</td>
<td>2.00</td>
<td>2.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Solution 3</td>
<td>8.3</td>
<td>2.35</td>
<td>1.7</td>
<td>20.0</td>
</tr>
</tbody>
</table>

For abbreviations see heading to table 2.

An example is shown in table 4. In this example, the second solution corresponds to the values used for computing $Z_{rs, tr}$. Whilst the first solution may be discarded as unrealistic, there is no way to choose between the two others. In our study, all four determinations with three solutions were observed during obstruction and in three determinations, $R_{aw,pleth}$ was above 6 hPa.s·L⁻¹, which is in agreement with the numerical simulation. As mentioned before, the corresponding data were discarded. When adding a random noise with a reasonable amplitude (±5% of the mean impedance modulus) to the real and imaginary parts of the generated impedance data, a triple solution was not always found when $R_{aw}$ was above the noise-free resistance threshold. For instance, with $R_{aw}$=8 hPa.s·L⁻¹ and the other coefficients as above, it was only the case in about 50% of the instances. More interestingly, in the other 50%, the unique solution was frequently unrealistic with, seemingly, most of $R_{aw}$ shifted to $R_t$, and a low $I_{aw}$. In that example, with 1,000 trials, $R_{aw}$ averaged 3.24±0.26 hPa.s·L⁻¹, $R_t$ 7.30±0.36 hPa.s·L⁻¹ and $I_{aw}$ 0.587±0.014 Pa.s²·L⁻¹. As shown in figure 6a, the larger the actual $R_{aw}$, the more it is underestimated, so that the computed $R_{aw}$ may decrease when the actual one increases. The results of these computer simulations (fig. 6) are in close agreement with the clinical data in children. This phenomenon may, thus, explain the underestimation of $R_{aw}^*$, the large $R_t$ and low $I_{aw}$ found in our asthmatic children before bronchodilatation.

Figure 6b also shows that the noise-related variability of $R_{aw}^*$ depends very much upon the degree of airway obstruction. The confidence interval (1.64 sd), expressed as a percentage of the mean, increases from about 5 to 56% when $R_{aw}$ increases from 4 to 7 hPa.s·L⁻¹; it decreases afterwards, so that, for $R_{aw}$=10 hPa.s·L⁻¹, $R_{aw}^*$ is strongly underestimated, but with little variability. For the same level of noise on the impedance
data, the confidence intervals of $I_{aw}$ and $R_t$ vary similarly with the degree of airway obstruction (fig. 6b), being largest when $I_{aw}$ is close to 7 hPa·s·L$^{-1}$. In contrast, the noise-related variability of $C_t$, which is obtained directly from the parameter $m_0$ (Equation (7)), increases monotonously with the degree of obstruction; this increase may, in part, be due to that of the impedance modulus, of which the amplitude of the noise was kept a fixed percentage. One should stress that the confidence intervals of $R_{aw}$, $I_{aw}$ and $R_t$ shown in figure 6b only pertain to the situation where the solution to Equation (13) is unique. Much larger differences may occur between multiple solutions, as shown in table 4.

We conclude that the analysis of transfer respiratory impedance in terms of airways and tissue properties, according to this simplified variant of DuBois’ model is unreliable in children with airways resistance above about 6 hPa·s·L$^{-1}$. Computer simulation suggests that this threshold would increase to 10 hPa·s·L$^{-1}$ if airways inertaance was raised to about 5 Pa·s$^2$·L$^{-1}$. This could easily be achieved by placing an additional inertaance at the airway opening. On the other hand, the use of a larger frequency spectrum to include the antiresonant peak should theoretically improve the parameter estimation in the moderately obstructed subjects [4]. However, both solutions have the potential drawback of increasing the errors related to the shunt impedance of upper airway walls. Further work is needed to assess these possibilities.

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