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Respiratory resistive impedance in obstructive patients: linear regression analysis *vs* viscoelastic modelling

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Respiratory resistive impedance in obstructive patients: linear regression analysis vs *viscoelastic modelling. A.M. Lorino, F. Zerah, C. Mariette, A. Harf, H. Lorino. ©ERS Journals Ltd 1997.*

ABSTRACT: The aim of this study was to test the ability of a simple two segment model to describe the frequency dependence of resistive impedance in obstructive patients, and to investigate the significance of parameters derived from this model.

The study was performed in 38 patients, in the basal state and after inhalation of 200 µg salbutamol. Impedance data measured over 4–32 Hz were fitted by a general four parameter viscoelastic model describing gas redistribution, and completed by an inertial component. This model yielded Newtonian resistance (R_{min}) and maximal resistance ($R_{max} = R_{min}$ plus delayed resistance due to gas redistribution). Resistive impedance data were also submitted to linear regression analysis over the 4–16 and 17–32 Hz frequency ranges, which, respectively, yielded resistive impedance extrapolated at 0 Hz (R_0) and resistive impedance estimated at 32 Hz (R_{32}). R_0 and R_{32} were compared to R_{max} and R_{min}, respectively. The airway response to salbutamol inhalation was assessed by the percentage changes in these parameters (R_0%, R_{32}%, R_{max}%, and R_{min}%, respectively).

Significant linear correlations ($p<0.0001$) were found between R_0 and R_{max}, R_{32} and R_{min}, and R_0% and R_{max}%. Furthermore, the linear regression lines of R_0 *vs* R_{max}, and R_0% *vs* R_{max}%, were not significantly different from the identity line.

These results demonstrate that resistive impedance extrapolated at zero frequency is equivalent to maximal resistive impedance, and can be proposed as an index, not only of the level of airway obstruction, but also of its reversibility.
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The standard forced oscillation technique (FOT) is a convenient method for measuring respiratory resistance without the need for patient co-operation. In normal subjects, the resistive respiratory impedance derived from this technique, appears to be a linear function of frequency over the usual range (4–32 Hz). Resistive impedance can, therefore, be characterized by two parameters, namely its intercept with the ordinate axis, which represents respiratory resistance extrapolated at zero frequency (R_0), and its slope (S) which is then close to zero [1–7]. By contrast, in patients with airway obstruction or in subjects shown to be hyperreactive on bronchial challenge, resistive impedance displays a marked negative frequency dependence up to about 16 Hz, and at least two straight line segments are then necessary to approximate it by linear functions of frequency. Consequently, the estimation of R_0 by linear regression analysis of resistive impedance *vs* frequency can only be made on a reduced frequency range, such as 4–16 Hz [8]. Whereas the parameters of such multisegment models are easy to calculate, their physiological interpretation may seem questionable.

The frequency dependence of respiratory resistive impedance over 4–32 Hz is usually interpreted in terms of series or parallel gas redistribution and described by the corresponding Mead or Otis models [9, 10]. Whereas the parameters derived from these two compartment viscoelastic models have the advantage of being mechanically interpretable, they have the disadvantage of needing iterative least square methods to be determined.

The aim of this study was, therefore, to test the ability of a two segment model to assess respiratory resistance, and its changes in response to the bronchodilating effects of a β_2-adrenergic agonist, in obstructive patients. To test this ability we compared the parameters derived from the two segment model with those derived from the viscoelastic models.

Materials and methods

Respiratory impedance measurement

Respiratory impedance was measured by the forced noise technique [5, 11, 12]. The forced pseudorandom noise used in this study was composed of 29 harmonics (4–32 Hz) of the fundamental (1 Hz), with enhanced amplitudes at the lower frequencies, to limit the influence of spontaneous breathing. The phases were calculated in order to minimize the peak-to-peak amplitude

of the excitation signal. The forced signal, generated by a digital-to-analogue converter, excited, through a power amplifier, two 60W loudspeakers attached to a 12 L rigid chamber. The peak-to-peak amplitude of the resulting flow ranged 0.2–0.5 $L \cdot s^{-1}$, so as to limit the amplitude of the resulting pressure oscillations to 2 cmH_2O peak-to-peak. The forced volume excitation was applied at the mouth of the subject, who was wearing a noseclip and with cheeks supported. Mouth pressure was measured using a differential pressure transducer (Sensym SCX 01D (Sunnyvale, CA, USA), ±70 cmH_2O), and mouth flow, with a screen pneumotachograph (Jaeger Lilly (Würzburg, Germany), internal resistance: 0.35 $cmH_2O \cdot s \cdot L^{-1}$) connected to a similar pressure transducer. Pressure and flow signals were low-pass filtered (Butterworth (Kemo, Beckenham, UK), 8th order, cut-off frequency =32 Hz), and sampled at 128 Hz for 16 s. The data were then high-pass filtered (3rd order, cut-off frequency=3.5 Hz) to eliminate the low harmonics of the breathing noise.

A Fast Fourier Transform (FFT) algorithm was applied to adjacent 4 s periods. Impedance data were calculated from the auto- and cross-spectra obtained by averaging the spectra of three consecutive 16 s manoeuvres. Impedance data corresponding to a coherence value higher than 0.9 were retained for analysis [13].

Impedance data modelling

Two types of model were successively used to fit impedance data.

Two segment model. This model was applied to resistive impedance data only. Resistive impedance was submitted to linear regression analysis over the 4–16 and 17–32 Hz frequency range. The resistive impedance extrapolated at 0 Hz was derived from the first linear regression analysis, and the resistive impedance estimated at 32 Hz ($R32$) was derived from the second linear regression analysis.

Viscoelastic model. Real and imaginary respiratory impedance data were fitted by Equations (A3) and (A4) (see Appendix), using an iterative least square method [2], which yielded the five parameters: maximal resistive impedance ($R\text{max}$), Newtonian resistance ($R\text{min}$), pressure time constant in response to a flow input (τ), central airway inertance ($I\text{caw}$), and elastance ($E\text{st}$).

For each model, the quality of the fit for resistive impedance data was assessed by calculating the mean relative distance (RD) between measured and fitted resistive impedance data, according to the following equation derived from the one proposed by OOSTVEEN *et al*. [14] for complex impedance data:

$$RD = \frac{100}{n} \sum_{i=1}^{n} \frac{| R\omega,m,i - R\omega,f,i |}{R\omega,m,i} \qquad (1)$$

where n is the number of data points, and Rω the resistive impedance measured (index m) or fitted (index f).

Table 1. – Patients characteristics (n=38)

Age yrs	Height cm	Weight kg	Smoking pack-yrs	FEV_1 % pred	ΔFEV_1 %
66±17	164±91	66±17	21±23	63±18	19±18

Values are presented as mean±SD. FEV_1: forced expiratory volume in one second; ΔFEV_1: reversibility of salbutamol, calculated as the ratio of the difference ($FEV_{1,salbutamol}$ - $FEV_{1,baseline}$) to $FEV_{1,baseline}$.

Patients

The study was performed in a group of 38 randomly selected obstructive patients (21 males and 17 females) who underwent ventilatory tests in the lung function laboratory. This group included 18 asthmatics and 20 patients with chronic obstructive pulmonary diseases (COPD), whose characteristics are presented in table 1. In these patients, who had increased respiratory resistance in the basal state, a bronchial inhalational challenge was performed with 200 µg of salbutamol, a β_2-adrenergic agonist (Ventoline, Glaxo Laboratory, France). Respiratory resistance was assessed in the basal state and after salbutamol inhalation by parameters derived from both types of model, namely $R0$, $R32$, $R\text{max}$ and $R\text{min}$. The two differences ΔR ($\Delta R = R\text{max} - R\text{min}$), and δR ($\delta R = R0 - R32$) were also calculated. The respiratory response to salbutamol was assessed by the changes in these parameters expressed as a percentage of their respective basal values ($R0\%$, $R32\%$, $R\text{max}\%$, $R\text{min}\%$). The influence of salbutamol inhalation on the τ, $E\text{st}$, and $I\text{caw}$ parameters was also investigated.

Data analysis

Statistical analysis was performed using Student's paired t-test and linear regression analysis. A p-value of less than 0.05 was considered to be statistically significant.

Results

The fit of resistive impedance data by both models is illustrated in figure 1. The mean relative distance between the resistive impedance and its model was slightly, but significantly, higher with the viscoelastic model than with the two segment resistive model, both in the basal state (3.0±0.7 *vs* 2.8±0.6%; p<0.02), and after salbutamol inhalation (3.5±0.9 *vs* 3.1±0.7%; p<0.001). For each model, the mean relative distance increased significantly after salbutamol inhalation (p<0.02).

As illustrated in figure 2, in the basal state, a highly significant correlation was found between $R0$ and $R\text{max}$, and the linear relationship of $R0$ *vs* $R\text{max}$ was not significantly different from the identity line. Significant correlations were also found between $R32$ and $R\text{min}$ on the one hand (fig. 3), and between δR and ΔR on the other (r=0.97; p<0.0001). However, $R\text{min}$ was found to be lower than $R32$ (p<0.001), and ΔR, higher than δR (p<0.001).

Salbutamol inhalation significantly reduced $R\text{max}$, $R0$, $R32$, ΔR and δR, but did not affect $R\text{min}$ (table 2). Significant correlations were still observed between $R0$ and

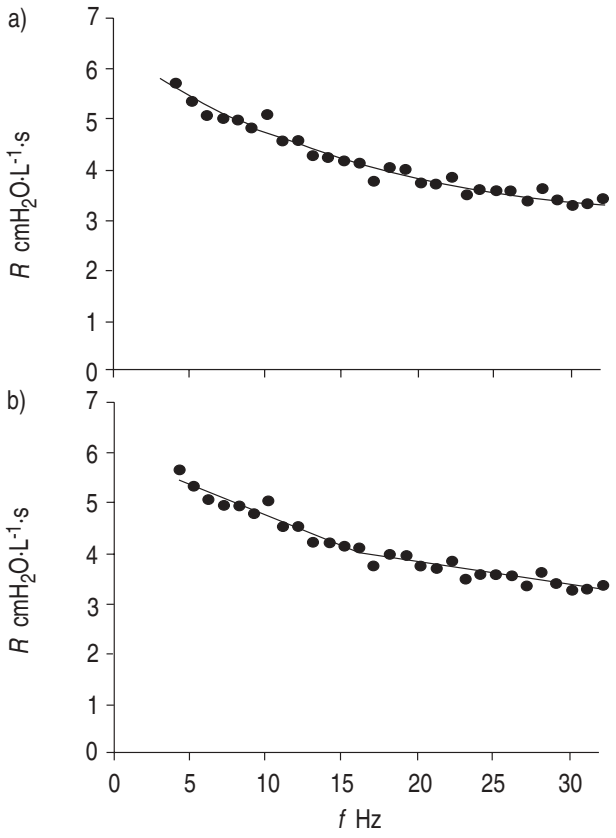

Fig. 1. – Typical data of resistive impedance (R) plotted as a function of frequency (f). The circles show the values measured. The solid lines show the fit of: a) the viscoelastic model; and b) the two segment model.

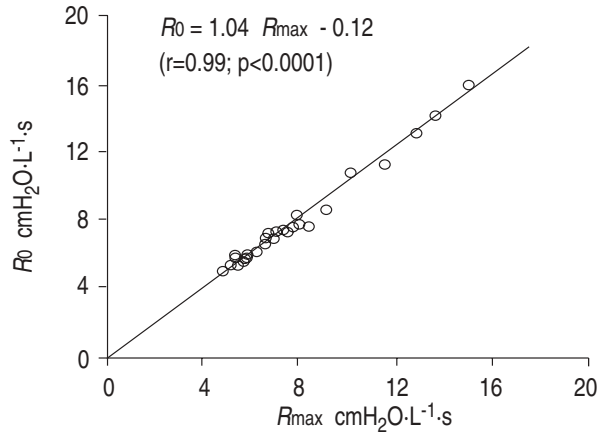

Fig. 2. – Resistive impedance extrapolated at 0 Hz by the two segment model (R_0), plotted in relation to maximal resistive impedance derived from the viscoelastic model (R_{max}). The circles present the data from individual patients; the straight line is the regression line.

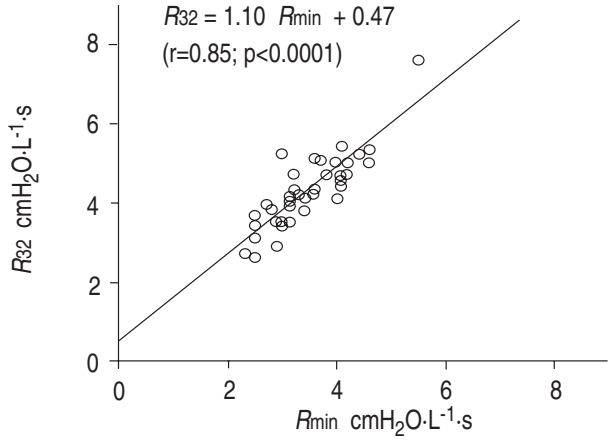

Fig. 3. – Resistive impedance estimated at 32 Hz by the two segment model (R_{32}), plotted in relation to resistance derived from the viscoelastic model (R_{min}). The circles present data from individual patients; the straight line is the regression line.

R_{max} (r=0.99; p<0.0001), R_{min} and R_{32} (r=0.68; p<0.0001) and ΔR and δR (r=0.90; p<0.0001). The respiratory response to salbutamol was also characterized by a significant decrease in τ (0.008±0.006 *vs* 0.014±0.004 s; p<0.0001) and E_{st} (44±18 *vs* 55±19 $cmH_2O \cdot L^{-1}$; p< 0.001), and by unchanged I_{caw} values (0.014±0.003 *vs* 0.014±0.002 $cmH_2O \cdot L^{-1} \cdot s^2$).

As illustrated by figure 4, the assessments of the bronchodilating effect of salbutamol by R_0% and R_{max}% were highly correlated, and the linear relationship of R_0% to R_{max}% was not significantly different from the identity line. By contrast, no correlation was found between R_{min}% and R_{32}%.

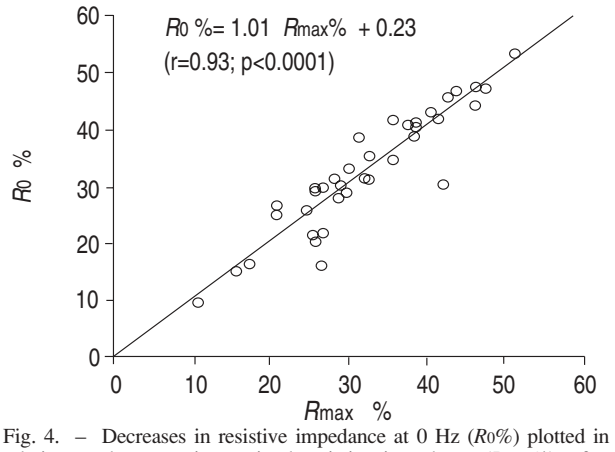

Fig. 4. – Decreases in resistive impedance at 0 Hz (R_0%) plotted in relation to decreases in maximal resistive impedance (R_{max}%), after inhalation of 200 µg salbutamol. R_0% and R_{max}% are expressed as a percentage of the R_0 and R_{max} basal values, respectively. The circles present data from individual patients; the straight line is the regression line.

Table 2. – Respiratory resistance values derived from resistive impedance

	R_{max} $cmH_2O \cdot L^{-1} \cdot s$	R_{min} $cmH_2O \cdot L^{-1} \cdot s$	R_0 $cmH_2O \cdot L^{-1} \cdot s$	R_{32} $cmH_2O \cdot L^{-1} \cdot s$	ΔR $cmH_2O \cdot L^{-1} \cdot s$	δR $cmH_2O \cdot L^{-1} \cdot s$
Basal state	7.3±2.4	3.5±0.7	7.4±2.5	4.3±1.0^{+}	3.8±2.0$^{\#}$	3.1±2.0
Salbutamol	4.9±1.7†	3.3±0.8	5.0±1.9†	3.8±0.9$^{\dagger +}$	1.6±1.5$^{\dagger \#}$	1.2±1.4†

R_{max} and R_{min}: maximal resistive impedance and Newtonian resistance, respectively, derived from the viscoelastic model; R_0 and R_{32}: resistive impedances at 0 and 32 Hz, respectively, derived from the two-segment model; ΔR: R_{max} - R_{min}; δR: R_0 - R_{32}. †: significantly lower (p<0.0001) than the corresponding basal value; $^{+}$: significantly higher (p<0.0001) than R_{min} in the same condition; $^{\#}$: significantly higher (p<0.0001) than δR in the same condition.

Discussion

The FOT is increasingly used to assess respiratory resistance in spontaneously breathing patients in the basal state and in the course of bronchial challenges. Consequently, more attention is generally devoted to resistive impedance than to reactance.

In normal subjects, resistive impedance ($R\omega$) can be fairly well described over 4–32 Hz by a linear frequency-dependent model characterized by its intercept with the ordinate axis and its slope, which is generally close to zero [1–7]. By contrast, in obstructive patients, $R\omega$ exhibits a negative frequency-dependence, which mostly occurs below 16 Hz, and is better described by two regression lines [8]. However, although the two-segment model allows description of the frequency dependence of $R\omega$ [8], it is not completely satisfactory, because it does not afford any physiological interpretation of this frequency dependence.

It is now commonly admitted that the negative frequency dependence of $R\omega$ observed over 4–32 Hz in obstructive patients results mainly from intrapulmonary gas redistribution due either to pulmonary inhomogeneities [10], or to airway compliance [9]. It has been shown that the corresponding models obey similar equations and respond similarly to forced sinusoidal excitations [15]. Therefore, as the relevance of the choice of either model remains difficult to prove, no *a priori* assumption was made in the present study regarding the origin of gas redistribution.

No attempt was made to correct impedance data for the upper airway shunt. Indeed, besides the fact that correction for this shunt makes the FOT less applicable in routine tests, it has been reported that: 1) correction for the upper airway shunt by subtracting the impedance measured during a Valsalva manoeuvre was not satisfactory, since the manoeuvre itself modified the upper airway shunt [16]; 2) the head generator reduced the influence of the upper airway shunt but did not suppress it altogether [16]; 3) on comparison of the standard and head generators in COPD patients there was no evidence of a significant difference in $R0$, despite a more marked slope with the standard than with the head generator [17].

Furthermore, no attempt was made, in this study, to complete the Otis or Mead models by a tissue viscoelastic component. Indeed, over 4–32 Hz, this tissue component behaves like a simple elastance included in Est, and is therefore unlikely to influence resistive impedance (*cf.* Appendix). This is of major physiological interest because, in such conditions, the $R\text{max}$ may be assumed to represent only Newtonian resistance plus delayed resistance originating from gas redistribution. Consequently, $R\text{max}$ reflects mainly airflow resistance and may be expected to be a good index of airway obstruction.

As the two segment model describes resistive impedance only, the mean relative distance (RD) between measured and fitted data was calculated solely from resistive impedance. The low values of RD obtained with both models in the basal state as well as after salbutamol inhalation illustrate the good quality of the fits. RD was found to be smaller with the two segment model, probably due to the respective parameter number of the two models. After salbutamol inhalation RD was found to be significantly increased for both models, whereas the absolute distance remained unchanged, which probably reflects the decrease in resistive impedance (*cf.* Equation (1)).

$R0$ was compared to $R\text{max}$, which corresponds to resistive impedance at zero frequency (*cf.* Equation (A3)). Although resistive impedance at higher frequencies has often been used for the assessment of airway response to bronchial challenges [18–21], it has been shown that, both in the basal state and in the course of induced bronchoconstriction, plethysmographic airway resistance correlated better with resistive impedance extrapolated at 1 Hz than with mean impedance determined at higher frequencies [22]. $R32$, which represents resistive impedance estimated at the highest frequency, was compared to $R\text{min}$ which corresponds to resistive impedance at infinite frequency (*cf.* Equation (A3)).

The strong linear correlations found between $R\text{max}$ and $R0$ in the basal state, combined with the fact that the regression line of $R0$ *vs* $R\text{max}$ was not significantly different from the identity line, show that $R0$ and $R\text{max}$ are identical estimates of resistive impedance at zero frequency. Thus, $R0$ appears to be equivalent to $R\text{max}$, *i.e.* to airway and tissue Newtonian resistance plus the delayed airway resistance resulting from gas redistribution. This latter resistance characterizes the frequency dependence of resistive impedance, which has been shown to be more pronounced in patients with severe airway obstruction [11, 12, 22]. Thus, extrapolation of resistive impedance at zero frequency by a simple linear fitting might provide an index of the degree of airway obstruction. Comparable observations have been reported by PIMMEL *et al.* [22], who found that resistive impedance extrapolated at 1 Hz was highly correlated with plethysmographic airway resistance.

The significant correlation observed between $R\text{min}$ and $R32$ (fig. 3), combined with the observation that $R\text{min}$ was significantly lower than $R32$ (table 2), shows that, in most of our patients, the frequency dependence of resistive impedance persisted above 32 Hz, *i.e.* the frequency range of our forced oscillations was not sufficiently wide to allow resistive impedance to reach its first relative minimum value.

The strong linear correlation found between ΔR and δR illustrates the fact that, over 4–32 Hz, the frequency dependence of resistive impedance (δR) is all the more marked as the delayed airway resistance (ΔR) is high, *i.e.* as gas redistribution is large [23, 24]. However, it cannot be excluded that our ΔR and δR parameters might have been similarly affected by the upper airway shunt.

In obstructive patients, inhaled salbutamol is known to dilate the airways, thus reducing intrapulmonary gas redistribution and lowering the frequency dependence of resistive impedance [11, 12, 20]. In the present study, these effects are clearly illustrated by the significant decreases observed in $R\text{max}$, $R0$, $R32$, ΔR and δR (table 2). No effect of salbutamol was detected on $R\text{min}$, which may be explained as follows. $R\text{min}$ reflects Newtonian tissue resistance plus Newtonian airway resistance, *i.e.* airflow resistance in the airways down to the point where gas redistribution occurs. Newtonian tissue resistance is unlikely to be affected by 200 µg of inhaled salbutamol, since the alveolar penetration of the aerosol is weak, and this route of administration results, at therapeutic doses,

in very low plasma concentrations. Newtonian airway resistance represents, in obstructive lungs, the resistance in the upper and central airways in which obstruction is absent, and consequently salbutamol is ineffective. Another explanation might be that the effect of salbutamol on R_{min} could have been masked by the upper airway artefact, but, in that case, it is likely that no salbutamol-induced change in R_{32} would have been observed. However, in this study R_{32} was found to decrease.

As regards the other parameters, both E_{st} and τ were lowered by salbutamol inhalation. Respiratory compliance, the inverse of E_{st}, accounts for tissue and airway distensibility, and for gas compressibility. Changes in compliance mainly reflect events occurring in the peripheral airways. The decrease in E_{st} probably reflects the improvement in lung distensibility associated with peripheral airway dilatation. The decrease in τ illustrates the tendency for the obstructive lung to behave like a more homogeneous lung after salbutamol inhalation (*cf.* Appendix). No significant change was observed in I_{caw} after salbutamol inhalation, probably because most of I_{caw} originates from the airways located above the carena, and therefore unaffected by obstruction.

The significant correlation found between the percentage changes in R_{max} and R_0 induced by salbutamol inhalation, with a linear regression line of $R_0\%$ *vs* $R_{max}\%$ not significantly different from the identity line (fig. 4), proves that these two parameters provide similar assessments of bronchodilatation. Thus, $R_0\%$ appears to be equivalent to $R_{max}\%$, which mainly reflects the changes in the non-Newtonian airway resistance originating from gas redistribution. Consequently, $R_0\%$ might be proposed as an index of reversibility of airway obstruction. This index has already proved to be as efficient as plethysmographic airway resistance in assessing bronchial sensitivity and reactivity to inhaled carbachol [25]. By contrast, VAN NOORD *et al*. [20] found that resistive impedance (R_6) was less sensitive than plethysmographic airway resistance for assessing salbutamol-induced bronchodilatation. This lesser sensitivity may be due to the fact that, at 6 Hz resistive impedance no longer accounts for total airway resistance, and that the difference between R_0 and R_6 is all the greater as airway obstruction is severe.

In conclusion, this study shows that a simple linear regression analysis of resistive impedance data allows the determination of a parameter characterizing bronchial obstruction. Indeed, resistive impedance extrapolated at zero frequency, R_0, appears to be equivalent to maximal resistive impedance which has a physiological meaning and mainly reflects total airway resistance. R_0 might, therefore, be proposed as an index, not only of the level of airway obstruction, but also of its reversibility.

Appendix

Description of the respiratory system mechanical behaviour over 4–32 Hz

Over 4–32 Hz, the frequency dependence of resistive impedance observed in obstructive patients may be attributed to parallel or series gas redistribution, originating from pulmonary inhomogeneities [10] and central airway compliance [9], respectively. It has been shown that the corresponding Otis and Mead models obey similar equations of motion [15]. A single equation of motion may even be proposed, for both models, expressed as a function of their lumped parameters. If $P(t)$ is the applied pressure, $V(t)$, the corresponding volume deformation, $P'(t)$ and $V'(t)$ the first time derivatives of $P(t)$ and $V(t)$, and $V''(t)$ and $V'''(t)$ the second and the third time derivatives of $V(t)$, respectively, the general equation of motion can indeed be expressed as:

$$P(t) + \tau P'(t) = E_{st} V(t) + (\tau E_{st} + R_{max}) V'(t) + (\tau R_{min} + I_{caw}) V''(t) + \tau I_{caw} V'''(t) \quad (A1)$$

where τ is the pressure time constant in response to a flow input, R_{min} is resistance at infinite frequency, *i.e.* instantaneous or Newtonian resistance, I_{caw} is central airway inertance, and E_{st} and R_{max} are elastance and resistance at zero frequency, as derived from respiratory impedance, respectively.

One may observe that, when $\tau \rightarrow 0$, Equation (A1) reduces to:

$$P(t) = E_{st} V(t) + R_{max} V'(t) + I_{caw} V''(t)$$

which is the equation of motion of a one compartment model. When the respiratory system is oscillated at the frequency f ($f = 2\pi/\omega$) with a sinusoidal flow in-put, and when the steady state is achieved, respiratory impedance ($Z\omega = R\omega + j X\omega$, $j^2 = -1$) can be derived from a particular solution of Equation (A1) [15].

Resistive impedance ($R\omega$) can then be expressed as:

$$R\omega = R_{min} + \frac{R_{max} - R_{min}}{1 + \tau^2\omega^2} \quad (A3)$$

Equation (A3) shows that resistive impedance is a decreasing function of frequency which varies from R_{max} ($f = 0$) to R_{min} ($f \rightarrow \infty$).

Similarly, reactance ($X\omega$) can be expressed as:

$$X\omega = I_{caw} \cdot \omega - \frac{1}{\omega} \cdot E\omega \quad (A4)$$

where respiratory elastance is given by:

$$E\omega = E_{st} + \frac{R_{max} - R_{min}}{\tau} \cdot \frac{\tau^2\omega^2}{1 + \tau^2\omega^2} \quad (A5)$$

Equation (A5) shows that respiratory elastance is an increasing function of frequency, which varies from:

$$E_{st} \ (f = 0), \text{ to } \{E_{st} + (R_{max} - R_{min}) / \tau\} \ (f \rightarrow \infty)$$

It is worth noting that the mechanical interpretation of τ, E_{st}, R_{max} and R_{min} depends both on the model considered [15] and the frequency of the forced flow inputs.

The R_{max} derived from resistive impedance measured over 4–32 Hz, does not equal the total respiratory resistance actually measured at zero frequency, *i.e.* during an end-inspiratory pause following a constant flow inflation R_{max} represents respiratory resistance to the exclusion of the delayed resistance due, to the tissue viscoelastic properties, *i.e.* airway and tissue Newtonian resistance (R_{min}) plus delayed resistance ($\Delta R = R_{max} - R_{min}$) due to gas redistribution, if present. Indeed, the tissue viscoelastic component, which is described in the Mount model by the series association of the non-Newtonian resistance

(Rt) and of the tissue elastance Et, is characterized by a time constant $\tau t = R t/E t$, which has been estimated to be about 0.4, 1.3, and 2.6 s [26–28]. The value of this time constant makes it possible to predict that the percentage of Rt which contributes to resistive impedance is less than 1% over 4–32 Hz. Thus, Rt does not contribute to resistive impedance, and hence to its extrapolation at 0 Hz. Consequently, the present Rmax resistance does not take into account the delayed resistance (Rt), which means that, above 4 Hz, the tissue viscoelastic component (Rt, Et) behaves as a simple elastance Et included in Est.

The Est elastance derived from respiratory reactance measured over 4–32 Hz, does not equal the static elastance actually measured at zero frequency, *i.e*. during an end-inspiratory pause following a constant flow inflation. Est takes into account not only respiratory static elastance, but also gas elastance plus elastance of the tissue viscoelastic component (Et), as mentioned previously.

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