Single-breath method for assessing the viscoelastic properties of the respiratory system


ABSTRACT: In order to explain the time dependency of resistance and elastance of the respiratory system, a linear viscoelastic model (Maxwell body) has been proposed. In this model the maximal viscoelastic pressure (P_visc,max) developed within the tissues of the lung and chest wall at the end of a constant-flow (V') inflation of a given time (t) is given by: P_visc,max = R2V'(1 - e^(-t/τ2)), where R2 and τ2 are, respectively, the resistance and time constant of the Maxwell body. After rapid airway occlusion at tI, tracheal pressure (P_tr) decays according to the following function: P_tr(t) = P_visc(t) + P_visc,max e^(-t/τ2)P_occ, where tocc is time after occlusion and P_visc,max is static recoil pressure of the respiratory system. By fitting P_tr after occlusion to this equation, τ2 and P_visc,max are obtained. Using these values, together with the V' and τ1 pertaining to the constant-flow inflation preceding the occlusion, R2 can be calculated from the former equation. Thus, from a single breath, the constants τ2, R2 and E2 (R2/τ2) can be obtained.

This method was used in 10 normal anesthetized, paralyzed, mechanically ventilated subjects and six patients with acute lung injury. The results were reproducible in repeated tests and similar to those obtained from the same subjects and patients with the time-consuming isoflow, multiple-breath method described previously. Eur Respir J 1998; 12: 1191–1196.

In 1955, Mount [1] proposed a linear viscoelastic model in order to explain the time dependency of the resistance and elastance observed in normal rat lungs. In this model, the viscoelastic properties can be characterized by two parameters, the theoretical maximal viscoelastic resistance (R2) and elastance (E2). A third useful variable, the time constant (τ2) can also be obtained as R2/E2 [2]. Using the technique of rapid airway occlusion (RAO) during constant-flow inflation, it has been possible to determine the values of these viscoelastic constants for the lung, chest wall and total respiratory system in normal mechanically ventilated humans [3–5] and experimental animals [2, 6] based on either one of the following functions:

\[ P_{visc}(t) = R2V'(1 - e^{-t/\tau2}) \]  

\[ R_{visc}(t) = \frac{P_{visc}(t)}{V'} = R2 \left(1 - e^{-t/\tau2}\right) \]  

where \( P_{visc} \) is viscoelastic pressure within the lung and chest wall and \( P_{visc}(t) \) in Equation 1 represents the viscoelastic pressure dissipation within the lung, chest wall or both during constant-flow (V’) inflation started from the relaxed volume of the respiratory system, and t is any given time during lung inflation. Equation 2, where \( R_{visc} \) is viscoelastic resistance, is obtained by dividing both sides of Equation 1 by V’ [3]. This analysis, however, is time consuming and technically complex because it requires either a series of isovolume inflations with different inspiratory flows, or multiple isoflow inflations of different volumes [3, 6]. As a result, the above analysis has been used only in a limited number of studies on normal subjects [3–5] and patients [7–9].

In the present investigation, a single-breath method to assess the viscoelastic constants of the respiratory system is described and results obtained in normal anesthetized paralyzed subjects and in patients with acute lung injury (ALI) are provided. These data are compared with those obtained on the same subjects and patients using the method of multiple isoflow inflations of different volumes.

Theory

Figure 1 shows a representative record of tracheal pressure (P_tr) obtained in a normal anesthetized paralyzed subject during constant-flow inflation with RAO performed at an inspiratory (inflation) time (tI) of 0.9 s. End-inspiratory airway occlusion is characterized by a rapid initial drop in P_tr (P_tr,max - P1) where P_tr,max is maximal P_tr and P1 is the pressure that P_tr,max falls to) followed by a slow decay to an apparent plateau pressure. The latter reflects the static end-inspiratory elastic recoil pressure of the respiratory system (P_visc,max) whilst P_tr,max - P1 represents the interruptor pressure, which mostly reflects flow-dependent pressure dissipations within the airways, although there is also a
small component due to the Newtonian resistance of the chest wall [10, 11]. By contrast, the difference between \( P_1 \) and \( P_{rs,st} \) reflects \( P_{visc} \). At the time of occlusion (i.e. \( t \)), \( P_{visc} \) is maximal and henceforth will be labelled \( P_{visc,max} \). From Equation 1, \( P_{visc,max} \) is given by
\[
P_{visc,max} = R_2 V(1 - e^{-\frac{t_{occ}}{\tau_2}})
\]  
(3)

According to the viscoelastic model of MONT [1], \( P_{visc} \) during the end-inspiratory occlusion, should decay according to the following function:
\[
P_{visc}(t) = P_{visc,max} e^{-\frac{t}{\tau_2}}
\]  
(4)

where \( t_{occ} \) is time after RAO. The time course of \( P_t \) during the end-inspiratory occlusion is obtained by adding \( P_{rs,st} \) to both sides of Equation 4:
\[
P_{rs}(t) = P_{visc}(t) + P_{rs,st} = P_{visc,max} e^{-\frac{t}{\tau_2}} + P_{rs,st}
\]  
(5)

where, at \( t=0, P_t = P_{visc,max} + P_{rs,st} = P_{1} \) (fig. 1).

By fitting the experimental time course of the decay in \( P_t \) during end-inspiratory occlusion to Equation 5, the values of \( P_{visc,max} \), \( \tau_2 \) and \( P_{rs,st} \) can be derived. Using the values of \( P_{visc,max} \) and \( \tau_2 \), together with those of \( V \) and \( t \) pertaining to the corresponding constant-flow lung inflation, the value of \( R_2 \) can be computed from Equation 3. Next, \( E_2 \) is obtained by \( E_2 = R_2/\tau_2 \). Thus, during a single constant-flow inflation followed by an end-inspiratory pause with occluded airway (single-breath method), the viscoelastic constants of the respiratory system can be obtained.

Materials and methods

Ten subjects (seven males) undergoing general anaesthesia (premedication: diazepam, 7.5 mg per os; anaesthesia: propofol, 2 mg·kg⁻¹·i.v.; muscle paralysis: succinylcholine, 1 mg·kg⁻¹·i.v.; maintenance: continuous infusion of propofol, 8–12 mg·kg⁻¹·h⁻¹, and vecuronium, 0.15 mg·kg⁻¹·h⁻¹) for minor lower abdominal or limb surgery were studied before skin incision. None had a history or clinical evidence of cardiopulmonary disease. Their mean (±SD) age, weight and height were 29±8 yrs, 71±13 kg and 175±8 cm, respectively. In all subjects the vital capacity and forced expiratory volume in one second (FEV1) were within ±10% of the predicted values [12].

Six patients with ALI (arterial oxygen tension (\( P_{a,O2} \))/inspiratory oxygen fraction (\( F_{I,O2} \)) <300 mmHg and bilateral infiltrates on the chest radiograph) [13], who were admitted to the intensive care unit, were also studied. In all of them the measurements were performed after haemodynamic stabilization had been achieved for 1 day. The patients were sedated (propofol, 4 mg·kg⁻¹·h⁻¹) and paralysed (vecuronium 0.15 mg·kg⁻¹·h⁻¹). The anthropometric characteristics of the ALI patients are provided in table 1.

None had a history or clinical evidence of either chronic lung disease, cardiogenic pulmonary oedema or active cardiac disease. The patients were studied at zero end-expiratory airway pressure (ZEEP). All subjects, in supine position, were intubated with a Rush cuffed endotracheal tube (7.5–8.0 mm i.d.) and ventilated with constant-inflation, flow-controlled ventilation by means of a Servo Ventilator 900C (Siemens-Elema AB, Solna, Sweden). RAOs were performed using a solenoid valve (Airmatic SV; Airmatic-Allied, Wilmington, OH, USA) placed next to the oral end of the endotracheal tube. The solenoid valve has a closing time of 11 ms (as measured at the Electronics Laboratory, Dept of Energetics, Faculty of Engineering, Trieste, Italy, with an accelerometer (Bruel & Kjær 4332; Bruel & Kjær Italiana, Milan, Italy) and a current probe (AC-DC Fluke Y8100; Fluke Corporation, Everett, WA, USA) connected to a rapid recorder (Hioki 8830; Hioki E.E. Corporation, Nagano, Japan)). Flow was measured with a heated Jäger Baby pneumotachograph (Würzburg, Germany) with a ±3 L·s⁻¹ linearity range. The pneumotachograph was inserted between the endotracheal tube and the solenoid valve, and was connected to a Validyne MP-45 pressure transducer (±2 cmH2O, Northridge, CA, USA) and to a carrier amplifier (13–4615–35; Gould, Cleveland, OH, USA). Tracheal pressure was measured, via a polyethylene catheter protruding 2–3 cm beyond the tracheal end of the endotracheal tube with a piezoresistive differential pressure transducer (Microswitch 142PC05D; Honeywell, Scarborough, Ontario, Canada). The tracheal catheter (1.5 mm i.d.) had six side holes at its distal end and an occluded tip. The system used to measure \( P_t \) had no appreciable phase shift and its response was flat up to 20 Hz. The overall dead space of the measuring equipment (excluding the endotracheal tube) was 35 mL. The

<table>
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<th>Characteristic and diagnosis of patients with acute lung injury</th>
<th>( P_{a,O2}/F_{I,O2} ) mmHg</th>
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<tbody>
<tr>
<td>Sex</td>
<td>Height cm</td>
</tr>
<tr>
<td>-----</td>
<td>------------</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
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<td>2</td>
<td>M</td>
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<td>5</td>
<td>F</td>
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<td>6</td>
<td>M</td>
</tr>
</tbody>
</table>

M: male; F: female; \( P_{a,O2} \): arterial oxygen tension; \( F_{I,O2} \): inspiratory oxygen fraction. (1 mmHg=0.133 kPa.)

![Figure 1](image_url)
Resistance offered by this equipment was 8 cmH$_2$O·L$^{-1}$·s$^{-1}$ at a V of 1 L·s$^{-1}$. Flow and P$_T$ signals were fed through a 12-bit analogue-to-digital converter (Data Translation DT-2801A; Data Translation, Marlboro, MD, USA) into an IBM-compatible computer. Sampling frequency was established at 200 Hz. Volume was obtained by numerical integration of the flow signal. All data were analysed using ANADAT data analysis software (RHT-InfoData, Montreal, Quebec, Canada). Great care was taken to avoid leaks around the tracheal cuff and in the equipment. In all patients, the electrocardiogram and arterial blood pressure were monitored continuously, along with peripheral oxygen saturation and end-tidal carbon dioxide tension (Ohmeda 5250 RGM; Louisville, CO, USA). An anaesthetist who was not involved in the experiment was present to provide patient care.

Experimental procedure and data analysis: baseline conditions

Normal subjects were ventilated on ZEEP (F$_{1o2}$ = 0.4) with a V of 0.5±0.01 L·s$^{-1}$, a t of 0.9±0.08 s and a respiratory frequency (f) of 15–16 breaths·min$^{-1}$, except for subject No. 9. This patient weighed 100 kg and had a body weight that was 24.6 kg (33%) above the desirable weight for his height. This patient, No. 9, was overweight and was not involved in the experiment. All data obtained from each individual or their next of kin.

Multiple-breath method

The iso-flow occlusion method was used, as previously described in detail [3, 4]. Under the same baseline conditions, four-second end-inspiratory occlusions were performed at four or five different inflation volumes by intermittently changing t while keeping the basal inflation V constant. The corresponding occluded inflation volumes ranged from 0.3–1.25 L. These tests were repeated three times. At each occlusion volume, the values of P$_{visc}$ were obtained and, together with the corresponding values of V and t, were fitted to Equation 2 to obtain R$^2$ and t. The investigation was approved by the local Ethics Committee and informed consent was obtained from each individual or their next of kin.

Results

Table 2 depicts the values of R$_{int}$ of the respiratory system (R$_{int}$, P$_{visc}$, E$_{rs, st}$ and E$_{rs, dyn}$ obtained with the first single-breath test (SB1) and the average of three repeated single-breath tests (SB3) in the normal subjects and ALI patients. There was no significant difference obtained between the SB1 and SB3 results. With SB1, the mean (±s) intranormal subject and intra-ALI patient coefficients of variation of R$_{int}$, P$_{visc}$, E$_{rs, st}$ and E$_{rs, dyn}$ were 24±12%; 6±6%; 2±1% and 2±2%, and 31±19%; 16±8.7%; 7.2±5.6% and 5.2±4%, respectively. In all subjects, the data closely fitted Equation 2, the correlation coefficients (r) being highly significant (p<0.001). The values of r ranged from 0.883–0.990 in the normal subjects and 0.871–0.981 in ALI patients. The values of t, R$_2$ and E$_2$ obtained with SB1 and SB3 in the normal subjects and ALI patients are given in table 3. There was no significant difference between the SB1 and SB3 results. With SB1, the mean (±s) intranormal subject and intra-ALI patient coefficients of variation of t, R$_2$ and E$_2$ were 10±8%, 7±5% and 8±9%.
and 14.4±10%, 15.6±12.9% and 15.5±6.3%, respectively. Table 3 also depicts the mean values of \( \tau_2, R_2, \) and \( E_2 \) obtained with the multiple breath method. The mean differences (±SD) of \( \tau_2, R_2, \) and \( E_2 \) in normal subjects were -0.09±0.42 s, -0.19±0.66 cmH\(_2\)O·L\(^{-1}\) and 0.27±0.66 cmH\(_2\)O·L\(^{-1}\)·s\(^{-1}\), respectively. The mean differences (±SD) of \( \tau_2, R_2, \) and \( E_2 \) in ALI patients were -0.11±0.24 s, -1.13±1.10 cmH\(_2\)O·L\(^{-1}\)·s\(^{-1}\), and 1.56±0.86 cmH\(_2\)O·L\(^{-1}\)·s\(^{-1}\), respectively. No lack of agreement could be detected between the two methods for all variables in normal subjects and in ALI patients.

Figure 2a depicts the relationships between the average values of \( R_{\text{visc}} \) and \( \tau \) obtained with the multiple-breath method in the 10 normal subjects and six ALI patients, together with those predicted according to Equation 2, using the individual values of the viscoelastic constants obtained with the single-breath method (both SB1 and SB3). Figure 2b depicts the corresponding changes in elastance of the respiratory system (\( \Delta E_{\text{rs}} \)). The latter relationship was obtained according to the following equation [4]:

\[
\Delta E_{\text{rs}} = P_{\text{visc, max}} \cdot V = R_2 \cdot \frac{V}{1 - e^{-\tau/V}} (6)
\]

where \( V \) is inflation volume. Equation 6 is obtained by dividing both sides of Equation 3 by \( V \). Also shown on the right ordinate of fig. 2b is the ratio \( E_{\text{rs,dyn}} / E_{\text{rs,stat}} \) in the normal subjects and in ALI patients, where \( E_{\text{rs,dyn}} \) is the sum of \( \Delta E_{\text{rs}} \) and \( E_{\text{rs,stat}} \). In these computations, the average values of \( E_{\text{rs,stat}} \) found with the single-breath method in the 10 normal subjects (18.8 cmH\(_2\)O·L\(^{-1}\)) and in the six ALI patients (22.75 cmH\(_2\)O·L\(^{-1}\)) were used.

**Discussion**

Viscoelastic constants of the respiratory system

The standard mechanics variables were obtained during single-breath RAO manoeuvres performed at baseline lung inflation volume (fig. 1) [3–5]. The present investigation shows that the viscoelastic constants obtained with the multiple-breath method can also be derived from the same manoeuvre. This method is reproducible and does not require many repeated occlusion tests, as is the case for the isoflow and isovolume multiple-breath methods previously used [3–5]. Furthermore, this analysis is based on Equations 3 and 5, which are independent of \( R_{\text{visc, stat}} \) and \( E_{\text{visc, stat}} \). Accordingly, the values of the viscoelastic constants obtained with the single-breath method are not affected by the volume dependence of \( E_{\text{visc, stat}} \) or the volume and flow dependence of \( R_{\text{visc, stat}} \) [3]. As with the multiple-breath method, the viscoelastic constants may be obtained from measurements of pressure at the airway opening instead of \( P_r \) [3]. The values of the viscoelastic constants obtained with the single-breath method were not significantly different from those obtained with the isoflow multiple-breath method. Using the isoflow multiple-breath method, D'Angelo et al. [3] determined the viscoelastic constants of the total respiratory system in 16 normal young subjects under similar experimental conditions to those of the present study. Their values of \( \tau_2, R_2, \) and \( E_2 \) amounted to 0.96±0.2 s, 4.60±0.81 cmH\(_2\)O·L\(^{-1}\)·s\(^{-1}\) and 5.10±1.57 cmH\(_2\)O·L\(^{-1}\), respectively, and are not significantly different from those obtained in the present study with the multiple-breath method. Using a modified multiple-breath method, Joisson et al. [18] determined the viscoelastic constants of the respiratory system in six normal, anaesthetized paralysed subjects, which also do not differ significantly from the present results.

As in normal subjects, in ALI patients the viscoelastic constants could be obtained by the single-breath method and the values were not significantly different from those obtained by the multiple breath method. In patients and animal models of lung disease, \( \tau_2, R_2, \) and \( E_2 \) represent not only viscoelasticity, but also the mechanical inhomogeneities of the lung. In this line, the values found in the present ALI patients should be regarded as encompassing viscoelasticity and/or mechanical inhomogeneities of the respiratory system. In ALI patients the values of \( R_2, \) and \( E_2 \) were significantly higher than in normal subjects while \( \tau_2 \) was not significantly different. This suggest that most

**Table 3.** – Viscoelastic time constant (\( \tau_2 \)), resistance (\( R_2 \)), and elastance (\( E_2 \)) of the respiratory system in normal subjects (n=10) and in patients with acute lung injury (ALI) (n=6)

<table>
<thead>
<tr>
<th>Normal subjects</th>
<th>ALI patients</th>
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<tbody>
<tr>
<td>( \tau_2 ) s</td>
<td>( R_2 ) cmH(_2)O·L(^{-1})·s(^{-1})</td>
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<tr>
<td>SB1</td>
<td>1.13±0.17</td>
</tr>
<tr>
<td>SB3</td>
<td>1.17±0.19</td>
</tr>
<tr>
<td>MB</td>
<td>1.08±0.37</td>
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<tr>
<td>( \tau_2 ) s</td>
<td>( R_2 ) cmH(_2)O·L(^{-1})·s(^{-1})</td>
</tr>
<tr>
<td>SB1</td>
<td>1.31±0.51</td>
</tr>
<tr>
<td>SB3</td>
<td>1.29±0.39</td>
</tr>
<tr>
<td>MB</td>
<td>1.40±0.50</td>
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Values are presented as means±SD: SB1: first single-breath test; SB3: average of three single-breath tests; MB: multiple-breath method.
of the increase in $R_2$, and $E_2$ in ALI patients was due mainly to a reduction in lung volume. Indeed, according to the "baby lung" concept of GATTINONI et al. [19], in ALI patients the aerated parts of the lung should be normal (as reflected by the unchanged $T_2$), while the increase in $R_2$, and $E_2$ should simply reflect reduced lung volume.

This analysis, which was based on a linear viscoelastic model, should not be regarded as a complete and perfect representation of respiratory mechanics. More complex nonlinear viscoelastic [20] and viscoplastoelastic models [21] have been used to explain the volume and time dependency of energy dissipation within the respiratory system. Nevertheless, the linear viscoelastic model has been shown to provide an accurate description of the time dependency of resistance and elastance over the lung volume range used in the present study [3–5]. In fact, the present results show that the $\eta$ dependency of resistance and elastance of the total respiratory system as well as the viscoelastic constants of the respiratory system can be predicted with reasonable accuracy from the values of viscoelastic constants obtained with the single-breath method, as shown in figure 2. This is especially true for the range of $\eta$ commonly used during mechanical ventilation (up to 2 s). Thus, with the single-breath method, not only can the values of $R_{ss}$ and $E_{rs,dyn}$ during baseline ventilation be obtained, but the $\eta$ dependency of these variables can also be provided (fig. 2).

$R_{s,int}$ and $E_{s,int}$

In the present investigation $R_{s,int}$ amounted to 1.49±0.81 cmH$_2$O·L$^{-1}$·s$^{-1}$ with SB1 and 1.56±0.86 cmH$_2$O·L$^{-1}$·s$^{-1}$ with SB3. These values were significantly lower (p<0.02) than those found in 16 normal young subjects by D’ANGELO et al. [3]. These authors, however, did not obtain $R_{s,int}$ directly from measurements of $P_{tr}$, as in the present study. Instead, they derived $R_{s,int}$ indirectly by correcting the drop in airway opening pressure after end-inspiratory occlusion for the resistive pressure drop due to the endotracheal tube, which was measured in vitro. This indirect method, however, is not accurate [22]. Indeed, in a subsequent study based on $P_{tr}$ measurements in 12 normal subjects, D’ANGELO et al. [11] found values of $R_{s,int}$ similar to those of the present study (1.54±0.46 cmH$_2$O·L$^{-1}$·s$^{-1}$). In the present study, the mean intrasubject coefficient of variation of $R_{s,int}$ was relatively high, amounting to 24±12%. This reflects the fact that in some of the subjects at inflation flow of 0.5 L·s$^{-1}$, the values of $P_{max}$ - $P_{t}$ were relatively low in relation to the cardiac artefacts in $P_{tr}$. In such instances, accurate assessment of $R_{s,int}$ requires ensemble averaging of several end-inspiratory occlusion records [11]. The present values of $E_{s,st}$ were similar to those found in two previous studies on normal young subjects under similar experimental conditions [4, 11], but significantly higher than those found by D’ANGELO et al. [3]. The reason for this discrepancy is not clear.

The single-breath method was also successfully applied to ALI patients who were selected according to the North American-European Consensus Conference [13]. The definition of ALI encompasses a wide range of severity of sickness, which is reflected in the marked interindividual variation in respiratory mechanics values in the ALI patients (tables 2 and 3).

Conclusions

The results show that with the single-breath method it is possible to derive not only the standard mechanics data but also the inflation time-dependence of the viscoelastic resistance and the dynamic elastance of the respiratory system as well as the viscoelastic constants of the respiratory system in both normal subjects and patients with acute lung injury.

References

3. D’Angelo E, Calderini E, Torri G, Robatto FM, Bonò D,


