Respiratory tissue properties derived from flow transfer function in healthy humans

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Respiratory tissue properties derived from flow transfer function in healthy humans. J. Appl. Physiol. 82(4): 1098–1106, 1997.—Assuming homogeneity of alveolar pressure, the relationship between airway flow and flow at the chest during forced oscillation at the airway opening {flow transfer function (FTF)} is related to lung and chest wall tissue impedance (Zti); FTF = 1 + Zti/Zg, where Zg is alveolar gas impedance, which is inversely proportional to thoracic gas volume. By using a flow-type body plethysmograph to obtain flow rate at body surface, FTF has been measured at oscillation frequencies (f os) of 10, 20, 30 and 40 Hz in eight healthy subjects during both quiet and deep breathing. The data were corrected for the flow shunted through upper airway walls and analyzed in terms of tissue resistance (Rti) and effective elastance (Eti,eff) by using plethysmographically measured thoracic gas volume values. In most subjects, Rti was seen to decrease with increasing f os and Eti,eff to vary curvilinearly with f os2, which is suggestive of mechanical inhomogeneity. Rti presented a weak volume dependence during breathing, variable in sign according to f os, and among subjects. In contrast, Eti,eff usually exhibited a U-shaped pattern with a minimum located a little above or below functional residual capacity and a steep increase with decreasing or increasing volume (30–80 hPa·l2) on either side. These variations are in excess of those expected from the sigmoid shape of the static pressure-volume curve and may reflect the effect of respiratory muscle activity. We conclude that FTF measurement is an interesting tool to study Rti and Eti,eff and that these parameters have probably different physiological determinants.

THERE EXIST INSTANTANEOUS DIFFERENCES between flow rate at the airway opening (Vao) and at the body surface (Vbs) that are due to changes in inspired and expired gas temperature and water pressure (P H2O) (2, 11), to departure from unity of the respiratory exchange ratio (17, 30), to gas compression within the chest (1, 12), and, to a small extent, to gas compression within the abdomen (8). During spontaneous breathing and, more generally, when the respiratory system is driven at the body surface, flow differences induced by gas compression inside the lung are related to airway impedance (Zaw) and to alveolar gas impedance (Zg); assuming that alveolar pressure is homogeneous [T-network model of DuBois et al. (13) (Fig. 1)], the flow transfer function (FTF) Vbs/Vao = 1 + (Zaw/Zg) (15); this relationship, which forms the basis for airway resistance measurements by body plethysmography, simply states that Vbs is distributed between the airway and the gas-compression pathway according to the ratio of their impedances. Symmetrically, when the respiratory system is driven by pressure oscillations at the airway opening (Eq. 1), airflow is distributed between the tissues and the gas-compression pathway, and the FTF = (Vao/Vbs) is given by

\[ \text{FTF} = 1 + \frac{\text{Zti}}{\text{Zg}} \]

where Zti is the impedance of the lung and chest wall tissues. In that instance, FTF is independent of Zaw, because it is implicitly assumed in the model that there is no flow loss through the airways (rigid airways and negligible gas compression). As Zg may easily be obtained from thoracic gas volume (TGV) [Zg = -j(\( \rho _b - \rho _H2O \))/(TGV \cdot \omega)], where j is the unit imaginary number, \( \rho _b \) the barometric pressure, and \( \omega = 2\cdot\pi\cdot f \), with f being the frequency, Eq. 1 provides a noninvasive way to study respiratory tissue properties. FTF data in humans in the 4- to 40-Hz frequency range have been incidentally reported in two studies (21, 25) devoted to respiratory input (Zin) and transfer (Ztr) impedances (FTF = Ztr/Zin). In this investigation, we have measured the FTF of healthy humans at 10, 20, 30, and 40 Hz, both during quiet breathing and during large tidal volume maneuvers. The results have been analyzed by using Eq. 1 to obtain the real part [Re(Zti)] or tissue resistance (Rti)] and the imaginary part [Im(Zti)] of Zti. The study revealed strikingly different volume dependencies of Rti and of tissue effective elastance (Eti,eff [Eti,eff = -Im(Zti) \cdot \omega]), which suggests that these properties have different physiological determinants.

MATERIALS AND METHODS

The study was performed in eight healthy subjects (5 men, 3 women), recruited from the laboratory staff, all trained to perform respiratory maneuvers. Their biometric characteristics and lung volumes are shown in Table 1.

Equipment. The subjects were seated in a 350-liter flow-type body plethysmograph (Emerson, Cambridge, MA) equipped with two layers of metal screen (area 144 cm2, resistance 0.083 hPa·s·l-1) and breathed outside the box. Vbs was derived from box pressure measured with a Validyne MP45 = 2-hPa differential transducer (Validyne, Northridge, CA) with respect to the pressure in a small reference chamber. The plethysmograph had a time constant (screen resistance × gas compressibility) of ~18 ms. Vao was measured with a heated Fleisch no. 2 pneumotachograph connected to a similar pressure transducer. Airway opening pressure (Pao) was also measured with a similar transducer and used, as indicated in Data analysis, to correct the FTF for the motion of upper airway walls. The responses of the three transducers were matched within 1% of amplitude and 2° of phase up to 40 Hz. The data were corrected for the relative frequency
response of the plethysmograph and of the Fleisch pneumotachograph (see Data analysis). Before each series of measurements, Vao and Vbs were calibrated by the integral method using a 1-liter syringe, and Pao was calibrated with a slanted fluid manometer.

Pressure oscillations at the airway opening were applied by using a 100-W loudspeaker enclosed in a box and connected to the pneumotachograph. The loudspeaker was supplied through a power amplifier with computer-generated sinusoidal signals. The subject breathed through a low-resistance high-inertance side tube branched in parallel with the loudspeaker. The distal end of the tube was connected to a small open reservoir where the gas was conditioned to BTPS so as to eliminate the component of the FTF related to the warming and humidification of inspired air in the airways.

Vbs, Vao, and Pao were digitized at a rate of 360 Hz by a 486-type personal computer equipped with a 12-bits analog-to-digital conversion board (PC-Lab, Digimétric, Perpignan, France).

Protocol. Measurements were performed in triplicate with superimposed pressure oscillations at oscillation frequencies (f os) of 10, 20, 30, and 40 Hz in random order. To facilitate the maneuvers, Vao and inspired volume (V), obtained by online digital integration of Vao, were displayed on the computer screen in front of the subject who supported his/her cheeks firmly with his/her palms. Each measurement included the recording of a few cycles of quiet breathing, followed by five to seven deeper breaths with three to four times larger tidal volumes, and, finally, by a slow vital capacity (VC) maneuver. Zero-flow offsets were also recorded as well as the flow signals when the subject was off the mouthpiece, which provided the FTF of the equipment. In most subjects, satisfactory measurements of the FTF could not be obtained during VC maneuvers because of glottic closure near total lung capacity (TLC) and/or near residual volume; then, VC maneuvers were only used to provide a volume reference.

Two additional measurements were also performed in all subjects. First, to correct the FTF for the motion of upper airway walls (see Data analysis), their impedance (Zuaw) was obtained by measuring the relationship between Pao and Vao at the same four frequencies during Valsalva maneuvers (20) while the subject supported his/her cheeks. Second, TLC was measured in triplicate by using a constant-volume body plethysmograph; this permitted computing TGV and Zg at any time during the measurements using the recorded VC maneuvers.

Data analysis. To correct for any difference in gain between the two flow channels and/or for small departures from BTPS conditions of inspired gas, the slope of the relationship between Pao and Vao at the same four frequencies during Valsalva maneuvers (20) was obtained by measuring the relationship between Pao and Vao at the same four frequencies during Valsalva maneuvers (20) while the subject supported his/her cheeks. Second, TLC was measured in triplicate by using a constant-volume body plethysmograph; this permitted computing TGV and Zg at any time during the measurements using the recorded VC maneuvers.

Table 1. Biometric characteristics and lung volumes of the subjects

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Gender</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>FRC, liters</th>
<th>VC, liters</th>
<th>TLC, liters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>50</td>
<td>171</td>
<td>92</td>
<td>1.96</td>
<td>5.13</td>
<td>6.12</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>58</td>
<td>168</td>
<td>66</td>
<td>3.28</td>
<td>4.27</td>
<td>5.70</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>34</td>
<td>171</td>
<td>70</td>
<td>2.82</td>
<td>4.33</td>
<td>5.94</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>65</td>
<td>168</td>
<td>71</td>
<td>2.69</td>
<td>4.84</td>
<td>6.31</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>40</td>
<td>155</td>
<td>48</td>
<td>3.12</td>
<td>3.54</td>
<td>5.13</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>30</td>
<td>160</td>
<td>56</td>
<td>2.60</td>
<td>3.80</td>
<td>5.38</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>58</td>
<td>178</td>
<td>55</td>
<td>5.39</td>
<td>5.09</td>
<td>7.43</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>34</td>
<td>187</td>
<td>84</td>
<td>3.45</td>
<td>6.10</td>
<td>7.53</td>
</tr>
</tbody>
</table>

M, male; W, female; FRC, functional residual capacity; VC, vital capacity; TLC, total lung capacity.
As the head of the subject was inside the plethysmograph, some of the flow through the pneumotachograph was shunted directly to the box by the vibrations of upper airway walls (mouth floor, pharynx, residual motion of supported cheeks). The effect of the shunt is to bias the measured FTF (FTFm) toward unity, and its magnitude is related to the ratio of Zuaw to respiratory system Zin (Zin = Pao/V˙ao). Zin values were, therefore, similarly computed from Pao and V˙ao on a cycle-per-cycle basis and used to correct the FTF with the following relationship

$$\text{FTF} = \frac{\text{FTFm} \cdot (1 - H)}{(1 - \text{FTFm} \cdot H)}$$  \hspace{1cm} (2)

where $H = \text{Zin}/\text{Zuaw}$. The real (Re) and imaginary (Im) parts of the corrected FTF and instantaneous TGV were used to compute Rti and Im(Zti) from Eq. 1 according to

$$\text{Rti} = \text{Im(FTF)} \cdot (\text{Ps} - \text{PH}_2\text{O})/(\text{TGV} \cdot \omega)$$  \hspace{1cm} (3)

$$\text{Im(Zti)} = (1 - \text{Re(FTF)}) \cdot (\text{Ps} - \text{PH}_2\text{O})/(\text{TGV} \cdot \omega)$$  \hspace{1cm} (4)

Im(Zti) was expressed in terms of tissue effective elastance [Eti,eff = -Im(Zti) · ω]. Also, combining the values of Eti,eff at different frequencies and assuming mechanical homogeneity of the tissues, tissue compliance (Cti) and inertance (Iti) were computed by linear regression of Eti,eff vs. $\omega^2$ according to

$$\text{Eti,eff} = \frac{1}{\text{Cti}^2} \cdot \omega^2 \cdot \text{Iti}$$  \hspace{1cm} (5)

RESULTS

Time plots of V˙ao, V, Re(FTF), and Im(FTF) in a representative subject are shown in Fig. 2. All variables have been low-pass filtered with a cut-off frequency of 1 Hz to eliminate the superimposed oscillations on V˙ao and V and smooth the FTF data. It may be seen that both Re(FTF) and, to a lesser extent, Im(FTF) undergo systematic variations during the breathing cycle, which are clearly related to the amplitude of the tidal volume. Re(FTF), Im(FTF), and the derived Rti and Eti,eff were averaged over the whole respiratory cycles during the periods of quiet breathing (QB) and of deep breathing (DB). Mean data in the group are shown in Table 2, and individual values of Rti as a function of $f_0$, and of Eti,eff as a function of $\omega^2$ during QB are shown in Fig. 3. Eti,eff is shown as a function of $\omega^2$, rather than as a function of

<p>| Table 2. Mean values of FTF and derived tissue properties during quiet and deep breathing |
|---------------------------------|---------------------------------|----------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>$f_0$, Hz</th>
<th>Re(FTF)</th>
<th>Im(FTF)</th>
<th>Rti, hPa·s·l⁻¹</th>
<th>Eti,eff, hPa/l</th>
<th>Re(FTF)</th>
<th>Im(FTF)</th>
<th>Rti, hPa·s·l⁻¹</th>
<th>Eti,eff, hPa/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.086 ± 0.030</td>
<td>0.283 ± 0.070</td>
<td>1.23 ± 0.46</td>
<td>22.5 ± 8.8</td>
<td>1.129 ± 0.026</td>
<td>0.326 ± 0.059</td>
<td>1.38 ± 0.45*</td>
<td>31.0 ± 8.4*</td>
</tr>
<tr>
<td>20</td>
<td>1.046 ± 0.051</td>
<td>0.429 ± 0.155</td>
<td>0.94 ± 0.41</td>
<td>13.1 ± 14.7</td>
<td>1.110 ± 0.054</td>
<td>0.505 ± 0.131</td>
<td>1.06 ± 0.37</td>
<td>24.7 ± 16.0*</td>
</tr>
<tr>
<td>30</td>
<td>0.899 ± 0.058</td>
<td>0.503 ± 0.142</td>
<td>0.73 ± 0.26</td>
<td>-33.5 ± 21.6</td>
<td>0.972 ± 0.060</td>
<td>0.569 ± 0.151</td>
<td>0.82 ± 0.30†</td>
<td>-13.4 ± 18.7*</td>
</tr>
<tr>
<td>40</td>
<td>0.662 ± 0.128</td>
<td>0.685 ± 0.237</td>
<td>0.73 ± 0.29</td>
<td>-97.2 ± 49.8</td>
<td>0.756 ± 0.145</td>
<td>0.722 ± 0.254</td>
<td>0.78 ± 0.31</td>
<td>-75.4 ± 54.9*</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td>0.0004</td>
<td>0.03</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0005</td>
<td>0.01</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are means ± SD of average values over breathing cycles in 8 subjects. $f_0$, oscillation frequency; Re and Im, real and imaginary parts of flow transfer function (FTF), respectively; Rti, tissue resistance; Eti,eff, tissue effective elastance. P values denote statistical significance of differences among frequencies (1-way analysis of variance); paired t-test for differences between quiet and deep breathing: *P < 0.05, †P < 0.01.
because it is expected to be linearly related to $\omega^2$ if the tissues behave homogeneously (Eq. 5). $R_{ti}$ decreased with increasing frequency in all subjects, and the trend was statistically significant in the group. $E_{ti,eff}$, which includes both the elastance and a negative frequency-dependent inertial component (Eq. 5), decreased considerably as expected from 10 to 40 Hz. In two subjects, however, it increased slightly from 10 to 20 Hz. The tissue resonant frequency ($E_{ti,eff} = 0$) was between 20 and 30 Hz in all but one subject (Fig. 3). When $E_{ti,eff}$ was analyzed by linear regression according to Eq. 5, $C_{ti}$ ranged from 0.019 to 0.060 l/hPa (mean ± SD 0.032 ± 0.016 l/hPa) and $I_{ti}$ ranged from 0.09 to 0.33 Pa·s²·l⁻¹ (mean ± SD 0.21 ± 0.10 Pa·s²·l⁻¹).

Slightly but significantly larger values of $R_{ti}$ were found during DB than during QB. $E_{ti,eff}$ was also significantly larger during DB, and the corresponding $C_{ti}$ and $I_{ti}$ were slightly lower, averaging $0.025 ± 0.014$ l/hPa and $0.19 ± 0.10$ Pa·s²·l⁻¹, respectively.

The variations of $R_{ti}$ during the respiratory cycle were, in general, weak and varied among subjects, as illustrated in Fig. 4 by the data obtained at 20 Hz. In four subjects, $R_{ti}$ decreased with increasing lung volume at all frequencies during QB, whereas in others it varied very little and in either direction, depending on frequency. The results were similar during DB, except for a more frequent and stronger negative volume dependence of $R_{ti}$ below normal FRC. On average, the slopes of the $R_{ti}$-V relationships, obtained by linear regression over the entire respiratory cycle, were negative (Table 3), did not vary significantly with the $f_{so}$, and tended to be steeper, although not significantly so, during DB than during QB (Table 3). The $R_{ti}$-V relationship also exhibited in most instances some degree of

![Fig. 3](image-url)  
**Fig. 3.** Frequency dependence of tissue resistance ($R_{ti}$, left) and variations of effective elastance ($E_{ti,eff}$, right) with square of circular frequency ($\omega^2$) in 8 subjects. Data are mean values during quiet breathing cycles. Subjects are represented by same symbols in both graphs.

![Fig. 4](image-url)  
**Fig. 4.** Plots of $R_{ti}$ as a function of absolute lung volume in 8 subjects obtained with an oscillation frequency of 20 Hz during quiet breathing (thick lines) and during deep breathing (thin lines). Three to five consecutive respiratory cycles have been ensemble-averaged.
counter clockwise hysteresis, with slightly larger values of $R_{ti}$ at the same volume during the expiratory than during the inspiratory phases; at mid inspiration, the differences averaged 8.6% during QB and 10.5% during DB.

The variations of $E_{ti,eff}$ during the respiratory cycle were stronger and much more systematic than those of $R_{ti}$ (Fig. 5). In all subjects and at all frequencies, $E_{ti,eff}$ was higher at end inspiration than at end expiration during QB. In several subjects, however, the $E_{ti,eff}$-$V$ relationship was U shaped, exhibiting a minimum a little above FRC. A U-shaped relationship was also seen in six out of eight subjects during DB. In some instances, particularly at low frequencies during QB, the $E_{ti,eff}$-$V$ relationship also exhibited some degree of clockwise hysteresis, with larger $E_{ti,eff}$ values at the same lung volume during inspiration than during expiration; in most cases, however, the relationships were eight shaped with clockwise looping at high lung volume and counterclockwise looping at low lung volume; this was systematically the case when the relationship was U shaped (Fig. 5). We measured by linear regression the slopes of the right part of the loops, over the volume range where $E_{ti,eff}$ exhibited a positive volume dependence during both respiratory phases. These slopes tended to be a little larger during QB than during DB and increased significantly with frequency during DB (Table 3).

**DISCUSSION**

In a previous study from the same laboratory (25), Re(FTF) and Im(FTF) had been found in 10 healthy men to average 1.068 and 0.286, respectively, at 10 Hz; 1.095 and 0.490, respectively, at 20 Hz; and 1.008 and 0.610, respectively, at 30 Hz during QB. These numbers are similar to those observed in this study (Table 2), except for Re(FTF) at 30 Hz, which was slightly and significantly larger ($P < 0.05$, $P < 0.01$). In contrast, the values of $V_{bs}/V_{ao}$ (1/FTF) observed by Mishima et al. (21) correspond to substantially larger Re(FTF) (1.19 and 0.88 at 10 and 40 Hz, respectively) and to larger

![Figure 5](http://jap.physiology.org/)

**Table 3. Volume dependence and hysteresis of $R_{ti}$ and $E_{ti,eff}$ during quiet and deep breathing**

<table>
<thead>
<tr>
<th>$f_{m}$</th>
<th>Quiet breathing</th>
<th>Deep breathing</th>
<th>Eti,eff Quiet breathing slope</th>
<th>Deep breathing slope</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>EIDiff</td>
<td>Slope</td>
<td>EIDiff</td>
</tr>
<tr>
<td>10</td>
<td>-0.112 ± 0.168</td>
<td>11.7 ± 5.4</td>
<td>-0.215 ± 0.099</td>
<td>8.7 ± 10.8</td>
</tr>
<tr>
<td>20</td>
<td>-0.061 ± 0.247</td>
<td>8.0 ± 4.4</td>
<td>-0.127 ± 0.107</td>
<td>5.3 ± 7.4</td>
</tr>
<tr>
<td>30</td>
<td>-0.082 ± 0.118</td>
<td>9.1 ± 2.5</td>
<td>-0.145 ± 0.100</td>
<td>14.5 ± 8.7</td>
</tr>
<tr>
<td>40</td>
<td>-0.145 ± 0.102</td>
<td>5.7 ± 3.5</td>
<td>-0.192 ± 0.089</td>
<td>13.6 ± 8.0*</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>0.049</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SD in 8 subjects. Slope, regression coefficient of $R_{ti}$ (hPa·l$^{-2}$·s) and $E_{ti,eff}$ (hPa/l$^2$) as a function of volume; for $E_{ti,eff}$, it is the slope of that part of the relationship with a positive volume dependence. EIDiff, % difference between expiratory and inspiratory $R_{ti}$ values at mid tidal volume. P values denote statistical significance of differences among frequencies (1-way analysis of variance); NS, not significant. Paired t-test for differences between quiet and deep breathing: *$P < 0.05$, †$P < 0.01$.
Table 4. FTF in 2 representative subjects, uncorrected and corrected for upper airway shunt

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>f_n (10 Hz)</th>
<th>f_n (20 Hz)</th>
<th>f_n (30 Hz)</th>
<th>f_n (40 Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Re(FTF)</td>
<td>Im(FTF)</td>
<td>Re(FTF)</td>
<td>Im(FTF)</td>
</tr>
<tr>
<td>Uncorrected</td>
<td>1.078</td>
<td>0.277</td>
<td>1.061</td>
<td>0.473</td>
</tr>
<tr>
<td>Corrected</td>
<td>1.066</td>
<td>0.281</td>
<td>1.009</td>
<td>0.469</td>
</tr>
<tr>
<td>5</td>
<td>Re(FTF)</td>
<td>Im(FTF)</td>
<td>Re(FTF)</td>
<td>Im(FTF)</td>
</tr>
<tr>
<td>Uncorrected</td>
<td>1.110</td>
<td>0.209</td>
<td>1.074</td>
<td>0.381</td>
</tr>
<tr>
<td>Corrected</td>
<td>1.102</td>
<td>0.215</td>
<td>1.044</td>
<td>0.374</td>
</tr>
</tbody>
</table>

Re(FTF) and Im(FTF) at high frequency (0.83 at 40 Hz) than seen in this study. These differences may be related to methodological differences: BTPS conditions of the inspired air were not fully achieved in our previous work (25) or, presumably, in the work by Mishima et al. (21), where the inspired gas only passed through a heated pneumotachograph. In this study, we solved the problem both by conditioning the inspired air to BTPS and by correcting the V˙ao data for any residual difference between the low-frequency components of the two flows. More importantly, Mishima et al. did not correct their data for the upper airway shunt. The influence of this factor is illustrated in Table 4, which shows corrected and uncorrected data in two representative subjects. It may be seen that the effect of the correction is weak at low frequency but becomes quite substantial at 30 and 40 Hz. Specifically, the uncorrected upper airway shunt is responsible for an overestimation of both Re(FTF) and Im(FTF), which could explain the larger values found by Mishima et al. at high frequency. Although correction for the upper airway shunt appears necessary, one should point out, however, that the correction used in this study may be less than perfect; indeed, it has been shown that Zua, as measured during Valsalva maneuvers, is slightly overestimated, probably because of the active contraction of the muscles in the face and neck (24); then, our FTF could be slightly undercorrected.

The values of Rti derived from Im(FTF) have the same order of magnitude as those obtained by analyzing the frequency dependence of respiratory Ztr of healthy adults with DuBois’ six-coefficient model (12): 0.70 ± 0.28 (18), 1.01 ± 0.26 (26), 1.10 ± 0.35 (27), 1.03 ± 0.17 (29), and 0.62 ± 0.19 hPa·s·l⁻¹ (31). This is noteworthy, since the two methods are fundamentally different: indeed, contrary to the approach used in this study, the analysis of Ztr data requires specific assumptions concerning the properties of the airway and tissue compartments and the additional assumption that the coefficients are not frequency dependent. Also, our Rti data are about a little larger than the values of chest wall resistance (Rw) derived from chest wall impedance measurements around 4 Hz (6, 16, 22, 28) or measured with the interruption technique (9); this is not surprising, since tissue resistance of human lungs has been shown to get extremely small above a few hertz at normal distending pressures (28, 32). Similarly, Cti and Iti, derived from the frequency dependence of Eti,eff (Eq. 5), are in good agreement with the data obtained by other forced-oscillation approaches on the same frequency range in healthy humans: for instance, mean values of Iti and Cti derived from Ztr data range from 0.10 to 0.21 Pa·s²·l⁻¹ and 0.021–0.035 l/hPa, respectively (18, 26, 27, 29, 31).

An advantage of the FTF over the usual Zin or Ztr is that Rti and Eti,eff may be obtained noninvasively at any frequency. As shown in Fig. 3, Rti exhibited a substantial degree of negative frequency dependence in most subjects, which is in agreement with previous observations (21, 25, 28); in addition Eti,eff tended to vary curvilinearly with ω², with a larger negative frequency dependence above than below 20 Hz. These data are inconsistent with the simple resistance-inertance-compliance model (Eq. 5) but may be explained by a two-compartment, six-coefficient (bitissular) model (25) accounting for the asynchronous deformation of different parts of the chest wall documented above 3 Hz (4–6, 13). The number of frequencies recorded in this study is too low for accurate analysis of the data with a six-coefficient model. An example, however, chosen among the subjects who departed most from homogeneous behavior, is shown in Fig. 6. It may be seen that the association in parallel of a pathway with a low resonant frequency and of a pathway with a large resonant frequency gives a very good fit to the data. This is in agreement with our previous observations (25).

The most interesting piece of information in this study is the fact that tissue properties varied systemati-

![Image](http://jap.physiology.org/DownloadedFrom/http://jap.physiology.org/DownloadedFrom)
cally during the respiratory cycle in a volume-dependent manner and that these variations were quite different for $R_{ti}$ and $E_{ti,eff}$. Variations of tissue properties during the respiratory cycle may be expected on several grounds. One should first rule out, however, artifactual variations. Conceivably, errors on plethysmographically measured TLC could be responsible for absolute errors on $R_{ti}$ and $E_{ti,eff}$ and for small variations during the cycle. Indeed, both properties are computed by using instantaneous values of TGV (Eqs. 2 and 3) derived from TLC and integrated $V_{ao}$; for a given absolute error on TLC, the relative error in TGV would vary systematically during the cycle, provoking some volume dependence of $R_{ti}$ and $E_{ti,eff}$. The variations, however, would be similar for the two parameters, which does not fit our findings, and would not exceed a few percent per liter of tidal volume for a 10% error on TLC.

Provided that alveolar pressure is homogeneous, mechanical inhomogeneity of the tissues, as discussed above, could not be responsible for artifactual volume dependence of $R_{ti}$ and $E_{ti,eff}$ if the local properties are constant. However, it may conceivably influence the data in two ways. First, some artifactual variations may be expected in a system with several lung compartments in parallel if the inspired gas distribution between the compartments, and, therefore, the ratio of the local TGVs vary systematically during the cycle. Indeed, the “weight” of each compartment in the overall FTF depends on its TGV; if, for instance, compartment 2 has a much lower elastance than compartment 1 and takes most of the inspired volume, one may expect $E_{ti,eff}$ to decrease with increasing lung volume. Would the two compartments breathe out of phase, this mechanism could also explain some looping in the $R_{ti}$-V and $E_{ti,eff}$-V relationships. We did some computer simulation with a model including two T networks in parallel, with the same airway resistance, airway inertance, $R_{ti}$, and $FRC$ ($1.0$ hPa·s·l$^{-1}$, $0.02$ hPa·s$^{-2}$·l$^{-1}$, $1.0$ hPa·s·l$^{-1}$, 2 liters, respectively), which only differed by their Cti ($0.1$ and $0.01$ l/hPa, respectively). With a tidal volume of 1 liter and a breathing frequency of $0.25$ Hz (91% of the tidal volume in compartment 1), $E_{ti,eff}$ decreased with increasing volume with a slope of $-3$ to $-4$ hPa/l$^2$, depending on the $f_{res}$, which is one order of magnitude less than the observed $E_{ti,eff}$ slopes (Table 3). It is, therefore, quite unlikely that inhomogeneous inspired gas distribution is responsible for much of the observed volume dependence of tissues properties. Second, if two compartments with similar or different properties have different volume dependencies of these properties, the volume dependence of the global $E_{ti,eff}$ may have little to do with that of the local elastances; it could even happen that the increase of a local elastance paradoxically results in a decrease of $E_{ti,eff}$ at some frequencies. This is due to the fact that the imaginary part of the impedance of two resistance-inertance-elastance pathways does not increase monotonously with frequency and may present a wavy pattern between the resonant frequencies of the two compartments (25); then, the increase of a local elastance may shift the curve in such a way that, at a given frequency, $E_{ti,eff}$ will be decreased. We have not found situations where this would also be the case for $R_{ti}$. Although this factor may have influenced our $E_{ti,eff}$ volume dependencies, it is unlikely that it was of much importance for two reasons: 1) the $E_{ti,eff}$-V loops were not different in the two subjects who exhibited a strong negative frequency dependence of $R_{ti}$ and a strong nonlinearity of the $\text{Im}(Z_{ti})\omega^2$ relationship (1st and 2nd subjects of 1st row in Fig. 5); and 2) although the $E_{ti,eff}$-V slopes tended to increase with increasing frequency (Table 3), the changes were moderate, and in all subjects the right part of the loops had a positive slope at all frequencies.

In most subjects, $E_{ti,eff}$ was seen to present a minimum at some volume slightly above (3 cases) or below (3 cases) FRC. One may assume that in the two other subjects the minimum was located below the volume range explored during the maneuvers. $E_{ti,eff}$ increased rather sharply with decreasing or increasing volume on either side of the minimum. $E_{ti,eff}$ depends on tissue elastance ($E_{ti} = 1/C_{ti}$) and $I_{ti}$, and its volume dependence reflects that of both properties; there is little reason, however, to expect that $I_{ti}$ (which is related to the mass of the tissues) will vary much with lung volume. To test that expectation, we computed separately $E_{ti}$ and $I_{ti}$ by combining the data obtained at different $f_{res}$ values using Eq. 5 in the six subjects in whom that equation appeared to be an acceptable model [almost linear decrease of $\text{Im}(Z_{ti})$ with $\omega^2$]; $E_{ti}$ and $I_{ti}$ were obtained by linear regression of $E_{ti,eff}$ vs. $\omega^2$ by using the values of $E_{ti,eff}$ at different times of ensemble-averaged breathing cycles (32 points/cycle). A representative example of the $E_{ti}$-V and $I_{ti}$-V loops obtained in that manner is shown in Fig. 7. It may be seen that the volume dependence of $I_{ti}$ is very weak during both QB and DB and that the variations of $E_{ti}$ are very similar to those of $E_{ti,eff}$ (Fig. 5, 3rd subject in lower row). In the part of the loops with a positive volume dependence, the slopes in the six subjects averaged $56.1 \pm 31.9$ hPa/l$^2$ for $E_{ti}$, compared with $56.4 \pm 28.8$ hPa/l$^2$ for $E_{ti,eff}$ at $10$ Hz during QB; the corresponding numbers during DB were $33.3 \pm 13.5$ hPa/l$^2$ for $E_{ti}$ and $40.7 \pm 23.7$ hPa/l$^2$ for $E_{ti,eff}$ at $10$ Hz. Most of the variations of $E_{ti,eff}$, therefore, reflect changes in lung and chest wall elastic properties.

A first obvious cause for these variations is the sigmoid shape of the respiratory static pressure-volume curve. From the model and the data of Paiva et al. (23) in healthy humans, the change in lung elastance would be $-10\%$ for a 1-liter volume change on either side of $FRC$ and $25\%$ for a 2-liter volume change; even if the same degree of nonlinearity was present in the chest wall, the corresponding slope of the $E_{ti,eff}$-V relationship would only be $-3$ to $8$ hPa/l$^2$, which is much lower than actually observed (Table 3). The static pressure-volume curve reflects respiratory tissue elasticity during muscular relaxation. Elastic loading experiments suggest that the effective total respiratory elastance may be substantially larger during active breathing, in relation to the force-length
relationship of respiratory muscles and to chest wall
distortion from its passive configuration (7, 19). In
addition, there is direct evidence that sustained respira-
tory muscle contraction increases both Rw and chest
wall elastance (3): a muscular effort of 10 hPa in either
direction would double Rw and increase chest wall
elastance by a factor of five or more. Whereas these
variations are much larger than those expected from
elastic loading experiments (7), they would well explain
the large volume dependence of Eti, eff observed in this
study: most of the pressure developed by respiratory
muscles at usual breathing frequencies being in phase
with volume, so would be the resulting variations of
Eti, eff. The U-shaped characteristic of the Eti, eff-V
relationship could reflect inspiratory muscle activity
above normal FRC and expiratory muscle activity at
lower volume. This mechanism would also explain
the observation of higher Eti, eff during the active inspira-
tory phase than during expiration. This interpretation,
however, remains hypothetical. Indeed, from the data
of Barnas et al. (3), one would also expect Rti to exhibit
some volume dependence in relation to respiratory
muscles contraction. This was not observed, which
might mean that Rti has something to do with the state
of respiratory muscles when measured with low oscilla-
tion frequencies [≤ 4 Hz, Barnas et al.] but not when
measured at the frequencies used in this study. Al-
though there is evidence that Rti is mostly located in
the chest wall (28), its precise physical meaning re-
ains to be established.

If one assumes that the cyclic variations of Eti, eff
observed in this study are largely related to the activity
of respiratory muscles, one may wonder about their
physiological significance. A mechanism by which they
may play an important role during breathing has been
pointed out by Barnas et al. (3). The rib cage and
abdomen-diaphragm pathways act like parallel pumps
operating on the lungs to produce flow; to behave
properly, such a system requires that the internal
impedance of both pumps be large compared with that
of the lung; indeed, if one of the pumps had a compar-
tively low impedance, it would be driven by the other
and decrease the total flow output instead of increasing
it. The same reasoning applies to parts of the chest wall
which, at a given time, are not acting as a pump but
must offer a high enough impedance to simply resist
the changes in intrathoracic pressure; this increased
impedance may be provided by the contraction of
muscles acting as fixators (10). Whether the changes
seen in Eti, eff reflect an increased internal impedance
of the muscles as they contract or the stiffening by
fixators of some part of the chest is open to question.
Whatever the case, the observed variations of tissue
elastance may be beneficial and prevent paradoxical
motion when intrathoracic pressure is lowered during
inspiration or increased at low lung volumes: an in-
crease in elastance by 30 hPa/l, as we have seen to occur
in our subjects during a quiet inspiration (Fig. 5),
corresponds to an increase in impedance by 20 hPa·s·l
at a breathing frequency of 15 breaths/min; that change
is sufficiently large compared with normal lung imped-
ance at the same frequency (~ 5 hPa·s·l -1) to be a very
effective stabilizing mechanism. Whereas a high inter-
nal impedance of the pumps may be beneficial, it is also
costly in term of energy expenditure; the corresponding
work, however, does not appear in the conventional
pressure-volume diagrams because it is performed
inside the pressure generator itself; it only contributes
to lowering what is measured as the efficiency of
respiratory muscles. It is one of the merits of ap-
proaches in which external generators are used, such
as the forced-oscillation method, to reveal otherwise
inapparent mechanical features of the respiratory sys-
tem.

In summary, we have developed and tested a noninva-
sive method to measure respiratory tissue properties.
The method does not assume that the tissues behave
homogeneously, and the data are little influenced by
inspired gas maldistribution. The method is well suited
to study the frequency dependence of tissues properties
as well as their time, volume, or flow dependence. We
have also observed a volume dependence of Eti, eff to be
much larger than expected from the passive properties
of the respiratory system, which may reflect the effect
of respiratory muscles activity. In contrast, Rti varied
little with lung volume, which suggests that the two
properties have different physiological determinants.

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