Assessment of bronchial reactivity by forced oscillation admittance avoids the upper airway artefact

R. Farré*, M. Rotger*, F. Marchal†, R. Peslin‡, D. Navajas*


ABSTRACT: The forced oscillation technique (FOT) allows easy assessment of bronchial reactivity. The use of a standard FOT generator (SG) results in changes in respiratory system resistance (ΔRs,SG) which are affected by an artefact caused by the extrathoracic upper airway (EUA). The aim was to improve the FOT assessment of bronchial reactivity with the SG by computing the change in FOT admittance (ΔA,SG), which is theoretically unaffected by this artefact.

ΔΔRs,SG and ΔA,SG after bronchial challenge in 17 children were compared with the values measured with a head generator (HG) FOT setup (ΔRs,HG and ΔA,HG, respectively), which were taken as a reference, since HG provides data virtually freed from the EUA artefact.

At 10 Hz, the SG significantly underestimated the resistance change: ΔRs,SG=1.77±0.62 versus ΔRs,HG=6.09±1.23 hPa L⁻¹ s⁻¹. ΔRs,SG and ΔRs,HG did not show a significant correlation. By contrast, the amplitude of the change in admittance measured by SG was close to the one obtained with the reference HG: |ΔA,SG|=29.5±4.6 versus |ΔA,HG|=32.7±3.9 mL hPa⁻¹ s⁻¹. |ΔA,SG| and |ΔA,HG| showed a significant correlation (r=0.65, p<0.01). Similar results were found up to 20 Hz.

The extrathoracic upper airway artefact was minimized when computing the change in admittance with the standard generator. This forced oscillation technique index may improve the sensitivity in assessing bronchial reactivity with the standard generator setup, which is the most common and easiest to use method for routine lung function testing.


The forced oscillation technique (FOT) allows a non-invasive assessment of respiratory mechanics with minimal cooperation from the patient. This is particularly useful when assessing respiratory function in patients who are unable to cooperate in performing forced spirometry according to the standard criteria, e.g. in patients with severe breathing impairment or in children. An additional feature of FOT, which contrasts with forced spirometry, is that it does not modify the bronchial tone since it is applied while the patient is breathing spontaneously, obviating the need for deep inspirations. This is of special relevance in the evaluation of bronchial challenge expected from the theoretical background. The practical improvement in the assessment of bronchial challenge expected from the theoretical background was substantiated by applying the method to the FOT data measured with the SG before and after bronchial challenge in children. The results were compared with

*Laboratori de Biofísica i Bioenginyeria, Facultat de Medicina, Institut d’Investigacions Biomèdiques Agustí Pi Sunyer (IDIBAPS), Universitat de Barcelona, Spain.  †Lab. Explorations Fonctionnelles Pediatriques, Hôtel d’Enfants, Centre Hospitalier Universitaire, Nancy, France.  ‡Unité 14 de Physio-pathologie Respiratoire, INSERM, Nancy, France.

Correspondence: R. Farré, Laboratori de Biofísica i Bioenginyeria, Facultat de Medicina, Casanova 143, E-08036 Barcelona, Spain. Fax: 34 934035260

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those obtained with the HG, which were taken as the reference, since they are virtually free of the upper airway artefact [18].

Methods

Rationale

The conventional method of assessing respiratory system impedance (Zrs) is based on applying a forced oscillation through a mouthpiece by means of an SG and computing Zrs,SG from the oscillatory pressure (P) and flow (V) signals recorded at the mouth. As illustrated in figure 1, measured Zrs,SG=P/V does not coincide with actual Zrs due to the shunt induced by the parallel impedance of the extrathoracic upper airway (Zeua) [21, 22]:

\[
Z_{rs,SG} = Z_{rs} \times \left(1 + \frac{Z_{rs}}{Z_{eua}}\right)^{-1}
\]  

(1)

Accordingly, the error induced by Zeua is higher as Zrs/Zeua increases. A bronchial challenge induces a change of impedance from the basal value Zrs to Zrs* and the values measured with the SG vary from baseline Zrs,SG to Zrs*,SG. It may be shown from equation 1 that the measured change in impedance (ΔZrs,SG=Zrs*,SG-Zrs,SG) is related to the actual change (ΔZrs=Zrs*-Zrs) according to:

\[
\Delta Z_{rs,SG} = \Delta Z_{rs} \times \left(1 + \frac{Z_{rs}}{Z_{eua}}\right)^{-1} \times \left(1 + \frac{Z_{rs}}{Z_{eua}}\right)^{-1}
\]  

(2)

Consequently, the change in impedance measured with the SG (ΔZrs,SG) is also affected by the upper airway artefact. This is illustrated in figure 2a, which shows a representative example of the different impedances, represented as respiratory system resistance (Rrs) and reactance (Xrs) (Rrs=Rrs1×Rrs; where j=(-1)^{1/2}), involved in a FOT measurement before and after bronchial challenge in adults [3]. From the mean measured values with the SG at 6 Hz (Zrs,SG=2.9 j × 0.6 hPa·L^{-1}·s and Zrs*,SG=5.7 j × 1.8 hPa·L^{-1}·s), the actual pre- and postchallenge impedances were estimated (equation 1) assuming a value of Zeua=20 j × 15 hPa·L^{-1}·s at this frequency [16]: Zrs=3.3 j × 0.5 hPa·L^{-1}·s and Zrs*=7.7 j × 2.9 hPa·L^{-1}·s. As expected, the change from pre- to postchallenge impedances measured by the SG effectively underestimated the actual change (equation 2).

To improve the detection of the changes induced by a bronchial challenge when using the SG it was proposed to compute the change in respiratory admittance (Ars), which is the reciprocal of Zrs. According to figure 1, the admittances measured with the SG before and after challenge (Ars,SG=1/Zrs,SG and Ars*,SG=1/Zrs*,SG respectively) are the addition of the actual respiratory admittances (Ars=1/Zrs and Ars*=1/Zrs*, respectively) and the admittance of the extrathoracic upper airway (Ars*SG=Ars+Zeua):

\[
Ars,SG = Ars + Zeua
\]  

(3)

\[
Ars*,SG = Ars* + Zeua
\]  

(4)

where Zeua is expected to be unaffected by the bronchial challenge. Consequently, the change in admittance due to the bronchial challenge measured by the SG (ΔArs,SG=Ars*,SG-Ars,SG) coincides with the actual change of respiratory admittance (ΔArs=Ars*-Ars):

\[
\Delta Ars,SG = \Delta Ars
\]  

(5)

as is illustrated in figure 2b. This figure shows that, in contrast to that found in impedance data (fig. 2a), the effect of the extrathoracic upper airway shunt on actual Ars and Ars* is additive (equations 3 and 4). Therefore, the absolute...
change in admittance is not influenced by $\Delta eua$. Consequently, assessing the effects of the bronchial challenge by means of the change in admittance measured with the SG allows an unbiased estimation of the actual change in the mechanical properties of the respiratory system.

In addition to the fact that the measurement of the absolute change in admittance ($\Delta Z_{RS,SG}$) is unbiased (equation 5), it should be pointed out that its relative change:

$$\frac{\Delta Z_{RS,SG}}{Z_{RS,SG}} = \Delta Z_{RS} \times \left(1 + \frac{Z_{RS}}{Z_{EUA}}\right)^{-1}$$

(6)

exhibits an error that depends on the baseline impedance ($Z_{RS}$). Consequently, the error factor $(1 + Z_{RS}/Z_{EUA})^{-1}$ is the same for the different successive measurements with increased dose of the challenge agent. By contrast, the magnitude of error in the relative change in impedance:

$$\Delta Z_{RS,SG}/Z_{RS,SG} = \Delta Z_{RS} \times \left(1 + Z_{RS}^*/Z_{EUA}\right)^{-1}$$

(7)

depends not on the value of the baseline impedance, but on the actual impedance after each dose of bronchial challenge agent ($Z_{RS}^*$). Moreover, the magnitude of the error, in the relative change in admittance (equation 6) is expected to be lower than the error in the relative change in impedance (equation 7) because the error factor, $(1 + Z_{RS}/Z_{EUA})$, is expected to be smaller than $(1 + Z_{RS}^*/Z_{EUA})$. Since a broncho-provocation results in an increase in impedance ($Z_{RS}^* > Z_{RS}$).

**Patient measurements**

To substantiate the practical improvement when using the change in forced oscillation admittance measured by the SG ($\Delta Z_{RS,SG}$) to assess bronchial reactivity, the FOT data obtained with SG and HG during bronchial challenge in 17 children were re-analysed [18]. All the patients, aged 2–9 yrs, presented with a history of mild-to-severe asthma and were referred to the laboratory for assessment of airway reactivity. These patients had been free of respiratory symptoms for three weeks preceding the challenge, and $\beta$-agonists were withheld for at least 12 h prior to the test. The study was approved by the Regional Committee on Human Subjects Experimentation.

The FOT system and the signal processing used in the measurements have been described in detail previously [18]. Briefly, respiratory impedance was computed from at least two 16 s records of the pressure and flow signals sampled when applying a pseudorandom forced oscillation while the patient was breathing spontaneously. The experimental system could apply the forced oscillation through a mouthpiece while the patient’s cheeks were supported, i.e. SG, and the oscillation pressure could also be applied around the head to minimize the shunt of the extrathoracic upper airway, i.e. HG. In each patient, SG and HG measurements were taken in a random order and the time interval between the two techniques was 2–3 min.

After baseline measurements of $Z_{RS,SG}$ and $Z_{RS,HG}$, the patient was subjected to a bronchial challenge with acetylcholine or to a specific allergen. Aerosols were delivered with a Wright nebulizer (Harlow, UK). Acetylcholine (11 patients) was given at a dose of 0.5 or 1 mg. Aerosols of allergenic extracts of house dust mites (five patients), and alternaria (Pasteur, Paris, France) (one patient) were given in cumulative doses, starting from 0.5 IR for mites, and from a solution of 2.5% (w/v) for alternaria. FOT was applied 10 min after inhalation of the last dose of the test.

Impedance data (10–20 Hz) were first analysed according to the most conventional procedure, to quantify the changes induced by the bronchial challenge, i.e. by computing the change in the resistance, both for SG ($\Delta R_{RS,SG}$) and HG ($\Delta R_{RS,HG}$). To verify the improvement when using admittance for assessing bronchial challenge, the amplitude of the change in admittance measured with the SG ($\Delta Z_{RS,SG}$) was compared with the one obtained from the reference head generator ($\Delta Z_{RS,HG}$). This allowed us to employ a unique FOT index to quantify the change in respiratory mechanics after bronchial challenge. The analysis was carried out for the relative changes in resistance ($\Delta R_{RS,SG}/R_{RS,SG}$ and $\Delta R_{RS,HG}/R_{RS,HG}$) and admittance ($\Delta Z_{RS,SG}/Z_{RS,SG}$ and $\Delta Z_{RS,HG}/Z_{RS,HG}$). Data are expressed as mean±SEM. Differences between means were analysed with paired Student’s $t$-tests and were considered statistically significant at $p<0.05$.

**Results**

The mean±SEM of baseline respiratory impedance measured by the conventional generator ($Z_{RS,SG}$) and with the head generator ($Z_{RS,HG}$) are shown in figure 3a. As expected, $R_{RS}$ was scarcely affected by the upper airway

![Fig. 3. - Respiratory system resistance ($R_{RS}$) and reactance ($X_{RS}$) at baseline (a) and after bronchial challenge (b), measured by the standard generator (SG) and by the head generator (HG). Values are mean±SEM. $\bigcirc$: $R_{RS,SG}$; $\Delta$: $X_{RS,SG}$; $\bullet$: $R_{RS,HG}$; $\bigtriangleup$: $X_{RS,HG}$.](image-url)
shunt, especially at the lowest frequencies. By contrast, $X_{rs,SG}$ measured by the SG was lower and showed smaller frequency dependence than the reference $X_{rs,HG}$. Also, in accordance with previous data, figure 3b shows that the difference between the results obtained with SG and HG increased after the bronchial challenge. The discrepancies between the resistances measured with both variants of the technique increased with frequency.

Figure 4 illustrates that, at all the investigated frequencies, the increase in resistance was considerably underestimated when measured by the SG as compared with the results obtained with the reference HG. For instance, at 10 Hz, $\Delta R_{rs,SG}=1.77\pm0.62 \text{ hPa-L}^{-1}\cdot\text{s}$ and $\Delta R_{rs,HG}=6.09\pm1.23 \text{ hPa-L}^{-1}\cdot\text{s}$. At this frequency, $\Delta R_{rs,SG}$ exhibited a lower statistical significance ($t=2.8$) than $\Delta R_{rs,HG}$ ($t=5.0$). The difference between $\Delta R_{rs,SG}$ and $\Delta R_{rs,HG}$ was statistically significant ($p<0.01$). Both changes in resistance did not show significant correlation.

The results obtained when assessing the effects of the bronchial challenge by means of the change in absolute oscillatory admittance are shown in figure 5 for all the investigated frequencies. At 10 Hz, which is a representative frequency, the change in admittance measured by the SG ($|\Delta A_{rs,SG}|=29.5\pm4.6 \text{ mL-hPa}^{-1}\cdot\text{s}^{-1}$) was very close to the one measured by the reference HG ($|\Delta A_{rs,HG}|=32.7\pm3.9 \text{ mL-hPa}^{-1}\cdot\text{s}^{-1}$), the difference being not significant. The statistical significance was similar for both SG ($t=6.4$) and HG ($t=8.4$) and the t-values were much higher than the ones corresponding to the changes in resistance. $|\Delta A_{rs,SG}|$ and $|\Delta A_{rs,HG}|$ showed a significant correlation ($r=0.65$, $p<0.01$).

Figure 6 shows the results obtained in the patients when computing the relative changes of resistance ($\Delta R_{rs,SG}/R_{rs,SG}$ and $\Delta R_{rs,HG}/R_{rs,HG}$) and admittance ($|\Delta A_{rs,SG}|/|A_{rs,SG}|$ and $|\Delta A_{rs,HG}|/|A_{rs,HG}|$). As expected (equation 6), the percentage change in resistance was underestimated by the SG, showing lower statistical significance for SG ($t=3.0$) than for HG ($t=5.3$). By contrast, the percentage change in admittance computed from the SG was only slightly, although significantly, underestimated when compared with the reference value from the HG (27±3% and 33±4%, respectively). Similarly, as found in the case of the absolute changes (figs. 4 and 5), the statistical significances of the relative changes in admittance ($t=8.7$ for SG and $t=8.5$ for HG) were much higher than those of the relative changes in resistance.

**Discussion**

The theoretical prediction that computing the change in FOT admittance after a bronchial challenge from data obtained with the SG is free of the upper airway artefact (equation 5) was verified in children, in whom the FOT is
most affected by this artefact. Indeed, previous data indicate that in children the ratio $Z_{rs}/Z_{eua}$ which is the factor quantifying the amount of artefact (equation 1), is greater than in adults [17]. The results from the present study (fig. 5) confirmed that the absolute change in admittance measured with the SG was very close to the one detected with the HG, which is a measurement virtually unaffected by the artefact [18]. The rationale behind the use of the change in admittance to avoid the upper airway artefact is applicable both in bronchoprovocation and in bronchodiagnosis tests [20, 23]. One of the two hypotheses employed to derive equation 5 is that the effect of the extrathoracic upper airway can be modelled as a pure lumped shunt impedance ($Z_{eua}$). This assumption is based on data indicating that the role played by the serial component of the extrathoracic upper airway is small both in children [17] and adults [16]. The second hypothesis is that the impedance of the extrathoracic upper airway is unaffected by the bronchial challenge agent, which is a reasonable assumption since most conventional agents used in bronchial challenge, e.g. histamine and methacholine, have been shown to induce effects mainly at the level of central and peripheral airways [24]. As for the rationale, it should be noted that oscillatory admittance contains exactly the same information as impedance since they are reciprocal complex magnitudes. Consequently, both pre- and postchallenge admittances are affected by the upper airway artefact (equations 3 and 4). However, the key issue of the present work consists in processing the data (by computing $\Delta Z_{rs,SG}$ instead of $\Delta Z_{rs}$) to quantify the changes in the mechanical properties of the respiratory system with a FOT index which is theoretically free of the upper airway artefact (equation 5). Although equations 1–5 are valid regardless of the frequency, the analysis of the FOT data was carried out taking into account the technical reliability of FOT measurements in children [25]. Indeed, at low frequencies (<10 Hz) it is difficult to obtain a satisfactory signal-to-noise ratio owing to the relatively high breathing rate of these patients. Moreover, measurements at high frequencies (>20 Hz) are more difficult in children than in adults given their higher impedance. On the one hand, the effects of possible limitations in the common-mode rejection ratio of transducers are enhanced. On the other hand, as the frequency increases the impedance of the extrathoracic upper airways, $Z_{eua}$ may become even lower than the respiratory impedance, especially after challenge ($Z_{rs}$*), with the result that data measured with the SG may be considerably artefactual (equation 1). Accordingly, the data analysis was focused from 10 to 20 Hz, which is a frequency range similar to the one commonly employed for quantifying bronchial challenge by FOT in children and in adults.

In conclusion, it is suggested that using the absolute or relative change in oscillatory admittance as an index for assessing bronchial reactivity eliminates, or markedly reduces, the upper airway artefact when using the forced oscillation technique standard generator. Thus, this could allow us to increase the sensitivity and specificity of the forced oscillatory technique to a degree resembling that found when using the head generator [20], but with the advantage of employing the forced oscillatory technique setup which is the more common and easiest method to use for routine lung function testing.

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