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## Feasibility of forced oscillatory assessment of respiratory mechanics across a laryngeal mask airway in rabbits

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## Feasibility of forced oscillatory assessment of respiratory mechanics across a laryngeal mask airway in rabbits

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Keywords: lung function, upper airway shunt, airway device, oscillometry, respiratory impedance

**Abstract**

**Objectives:** The forced oscillation technique (FOT) is the method of choice for assessment of respiratory tissue mechanics. A laryngeal mask airway (LMA) is increasingly used to secure the airways in subjects under sedation or general anesthesia. While FOT is routinely performed using an endotracheal tube (ETT), the accuracy of information about airway and tissue mechanics obtained with FOT using a LMA has not been characterized. Therefore, we compared the mechanical parameters obtained with FOT using LMA and ETT in rabbits. **Approach:** FOT was performed through a LMA at normal and reduced oscillatory amplitudes in anesthetized and mechanically ventilated rabbits ( $n = 9$ ) at positive end-expiratory pressures (PEEP) of 3 and 6 cmH<sub>2</sub>O. These measurements were repeated at normal amplitude for the same animal using an ETT. Airway resistance, inertance, respiratory tissue damping ( $G$ ) and elastance ( $H$ ) were measured under each condition by FOT. The potential bias of the distensible upper airways when FOT was applied using LMA was assessed with a simulation study. **Main results:** Values of parameters reflecting airway mechanics were significantly higher when measured using LMA at both PEEPs and oscillatory amplitudes than with ETT. Conversely, regardless of the condition, there was a correlation ( $r = 0.89$  both at normal and reduced amplitudes;  $p < 0.0001$ ) with good agreement (mean bias of 8.8 cmH<sub>2</sub>O/l and 11.3 cmH<sub>2</sub>O/l) in  $H$ , whereas  $G$  was systematically lower when obtained with LMA than with ETT at PEEP 3 ( $21.1\% \pm 7.2\%$  and  $9.6\% \pm 6.9\%$  at normal and reduced oscillatory amplitudes, respectively) and 6 cmH<sub>2</sub>O ( $15.1\% \pm 8.2\%$ ,  $1.6\% \pm 9.4\%$ ,  $p < 0.05$  for all). **Significance:** Mechanical properties of the airways and the respiratory tissues, particularly for respiratory tissue stiffness, can be reliably assessed using LMA. However, the involvement of a longer laryngo-tracheo-bronchial pathway when using LMA should be considered for airway resistance and inertance, whereas upper airway shunting may affect the assessment of respiratory tissue damping.

**Introduction**

Forced oscillation technique (FOT) is gaining increasing interest in both experimental and clinical settings for assessing the mechanical properties of the respiratory system (Brashier and Salvi 2015, Alblooshi *et al* 2017, Bates 2017). This increasing popularity can be attributed to the ability of the technique to partition the respiratory system mechanics into separate airways and tissue compartments without the need for cooperation from the subject. These features make FOT a useful tool in the assessment of respiratory mechanics during mechanical ventilation (Navajas and Farre 2001, Bayat *et al* 2009, Scholz *et al* 2011, Zannin *et al* 2012, Dellaca *et al* 2013). However, a secured airway with no leak or other mechanical artifact is required for successful FOT recording, a requirement which is currently guaranteed by endotracheal intubation (Navajas and Farre 2001, Scholz *et al* 2011) or tracheostomy (Bayat *et al* 2009, Zannin *et al* 2012, Dellaca *et al* 2013) in mechanically ventilated subjects.

The use of the laryngeal mask airway (LMA) is widely considered as an alternative to the endotracheal tube (ETT) for securing the airways during sedation and/or general anesthesia, both in experimental research (Bate-man *et al* 2005, Toman *et al* 2015) and in the clinical environment (von Ungern-Sternberg *et al* 2007, Park *et al* 2016, McNarry and Patel 2017, Mihara *et al* 2017). The ease of insertion and minimal adverse respiratory consequences (Park *et al* 2016, Xu *et al* 2016, Drake-Brockman *et al* 2017) have contributed to the generalized use of LMA for patients of all ages (von Ungern-Sternberg *et al* 2007) for elective and urgent situations and, more recently, for animal models, particularly if follow-up measurements are planned. Despite the increasing use of LMA, there have been no previous studies assessing the accuracy of FOT data for airway and tissue mechanics when obtained using LMA. Therefore, the present experimental study was designed to characterize the correspondence between the forced oscillatory mechanical parameters obtained by using LMA and ETT within the same rabbit.

## Methods

### Animal preparation

The experimental protocol was part of a research project approved by the Experimental Ethics and the Animal Welfare Committees of the Canton of Geneva, Switzerland (No. GE/197/17, approved on the 28 of November 2017). New-Zealand White rabbits ( $n = 9$ ; weight mean and range 3865 g, 3470–4190 g) of both sexes were used. Anesthesia was induced with intramuscular ketamine (15 mg/kg) and xylazine (3 mg/kg) and was maintained with intravenous 1% propofol (1 ml/kg/h) and remifentanyl (75  $\mu$ g/kg/h) through the ear vein. The airway was secured by a non-inflatable rabbit-specific LMA device with an anatomical seal (V-gel, R5, Docsinnovent Ltd., London, UK). Volume-controlled mechanical ventilation was started with a pediatric ventilator (SERVO-i, Maquet Critical Care, Solna, Sweden) with a tidal volume of 7 ml/kg, fraction of oxygen in the inspired air of 40% and positive end-expiratory pressure (PEEP) of 3 cmH<sub>2</sub>O. The ventilation frequency was adjusted to target an end-tidal CO<sub>2</sub> of 5.5%–6%, resulting in 30–40/min. After completing the acquisition of the first set of data for respiratory system impedance (see below), mechanical ventilation was maintained using the LMA while a surgical tracheostomy was performed under local anesthesia achieved with a subcutaneous injection of 0.5% lidocaine (up to 1 ml). As soon as an uncuffed ETT (3.5 mm ID, 5 cm length) was secured, the LMA was removed and mechanical ventilation was provided using the ETT with the same ventilation parameters. Body temperature was maintained between 38 °C and 39 °C using a homeothermic blanket system (Harvard Apparatus Co. Inc., South Natick, MA) and controlled rectally by a thermal sensor. Electrocardiogram was continuously monitored by means of needle electrodes and a PowerLab data acquisition system (ADInstruments, Dunedin, New Zealand).

### Measurement of total respiratory system mechanics

The mechanical impedance of the respiratory system ( $Z_{rs}$ ) was measured by FOT as detailed previously (Bayat *et al* 2009). Briefly, the airway opening was connected from the ventilator to a loudspeaker-in-box system at end expiration, which generated a small-amplitude pseudorandom signal with frequency components between 0.5 and 20.75 Hz. The pressure oscillations were led through a polyethylene wave-tube (internal diameter 3.75 mm, length 1 m). The lateral pressures at the loudspeaker ( $P_l$ ) and at the tracheal ( $P_{ao}$ ) ends of the wave-tube were measured by miniature pressure transducers (Honeywell Differential Pressure Sensor, model 24PCEFA6D, Charlotte, North Carolina, USA) and the total respiratory impedance was calculated as the load impedance of the wave-tube (Petak *et al* 1997, Bayat *et al* 2009). The impedance of the airway device ( $Z_t$ ) was measured separately after completing the *in vivo* experiments and  $Z_{rs}$  data were obtained by correcting the impedance measurements with this instrumental impedance by serial subtraction of  $Z_t$  from the uncorrected impedance data.

A well-validated model containing a modified airway and a constant-phase tissue compartment (Hantos *et al* 1992b, Thamrin *et al* 2005) was fitted to the averaged  $Z_t$ -corrected  $Z_{rs}$  spectra in each condition by minimizing the squared sum of the differences between the measured and the modeled impedance data:

$$Z_{rs} = R_{aw} (1 + \beta\omega^2) + j\omega I_{aw} + (G - jH) / \omega^\alpha$$

where  $j$  is the imaginary unit,  $\omega$  is the angular frequency, and  $\alpha = 2/\pi \arctan(H/G)$ . As it has been validated in earlier studies,  $R_{aw}$  and  $I_{aw}$  represent primarily the resistance and inertance of the airways, while tissue parameters characterize the damping ( $G$ ) and elastic ( $H$ ) properties of the respiratory tissues (Hantos *et al* 1992b, Petak *et al* 1997, 1998, Bayat *et al* 2009). Tissue hysteresivity ( $\eta$ ), which reflects the coupling between the dissipative and elastic properties in the respiratory tissues, was calculated as  $G/H$  (Fredberg and Stamenovic 1989). The empirical parameter  $\beta$  has no physiological meaning and allows for a more accurate model fitting in the presence of a slight frequency dependence of  $R_{aw}$  (Thamrin *et al* 2005). Frequency points corrupted by the heart or its upper harmonics were omitted from the model fits (Hantos *et al* 1992b, Petak *et al* 1997, 1998, Bayat *et al* 2009).

### Simulation study

Because of its anatomical position when in use, measurements through LMA may involve an upper airway shunt, which potentially biases  $Z_{rs}$  data obtained in the frequency range studied (Cauberghs and Van de Woestijne 1983, Peslin *et al* 1984, Desager *et al* 1999). Upper airway shunting can be attributed to the loss of oscillatory airflow in motions of the tissue compartment proximal to the LMA (i.e. the laryngeal and vocal cavities and the trachea), as this shunted airflow cannot participate in lung expansion during FOT measurements. In agreement with earlier studies (Peslin *et al* 1984, Desager *et al* 1999), this phenomenon was modeled (figure 4(A)) with a lumped shunt impedance ( $Z_s$ ) placed in parallel with the respiratory impedance distal to the shunt ( $Z_{rs,l}$ ). The frequency dependence of the real and imaginary parts of  $Z_s$  have been shown to mirror each other with a ratio of approximately 0.2 (Cauberghs and Van de Woestijne 1983). Accordingly, a constant-phase tissue impedance with a  $G/H$  ratio of 0.2 was considered to model this shunting compartment. Since estimates for  $Z_s$  are only available for humans (Cauberghs and Van de Woestijne 1983), the magnitudes of  $G$  and  $H$  were scaled up proportionally by a factor reflecting differences in anatomical structure and body-size between humans and rabbits. Accordingly,  $Z_s$  10, 20, 40 and 80 times higher than that obtained in humans with supported cheeks have been applied for rabbits (Cauberghs and Van de Woestijne 1983).  $Z_{rs}$  obtained with ETT are not subjected to this phenomenon, as the impedance data obtained under this condition directly reflect the mechanical properties distal from the tip of the ETT, where no significant shunting is expected.

### Experimental protocol

The experimental protocol was designed to compare respiratory mechanical measurements obtained using LMA and ETT. Since significant turbulences are expected around the LMA device and these turbulences lead to a nonlinear relationship between pressure and flow, the protocol included the investigation of the dependence of the  $Z_{rs}$  estimates on two oscillatory amplitudes. Accordingly, two sets of  $Z_{rs}$  data were collected through the secured LMA with an amplitude comparable to that applied using the ETT (1.5 cmH<sub>2</sub>O peak-to-peak), and with reduced amplitude (1 cmH<sub>2</sub>O peak-to-peak) while a PEEP of 3 cmH<sub>2</sub>O was maintained. Each data set consisted of four 8 s data epochs. To investigate whether the elevated PEEP affects these  $Z_{rs}$  estimates, the same sequence was repeated at a PEEP of 6 cmH<sub>2</sub>O. Measurements were repeated for the same animal at PEEP 3 and 6 cmH<sub>2</sub>O after replacing the LMA with an ETT and applying the normal oscillatory amplitude (resulting in 1.5 cmH<sub>2</sub>O peak-to-peak oscillatory). No amplitude dependence was involved here, as the gas flow in the trachea around the uncuffed ETT was shown to be laminar with a linear pressure–flow relationship (Hantos *et al* 1992a).

### Statistical analyses

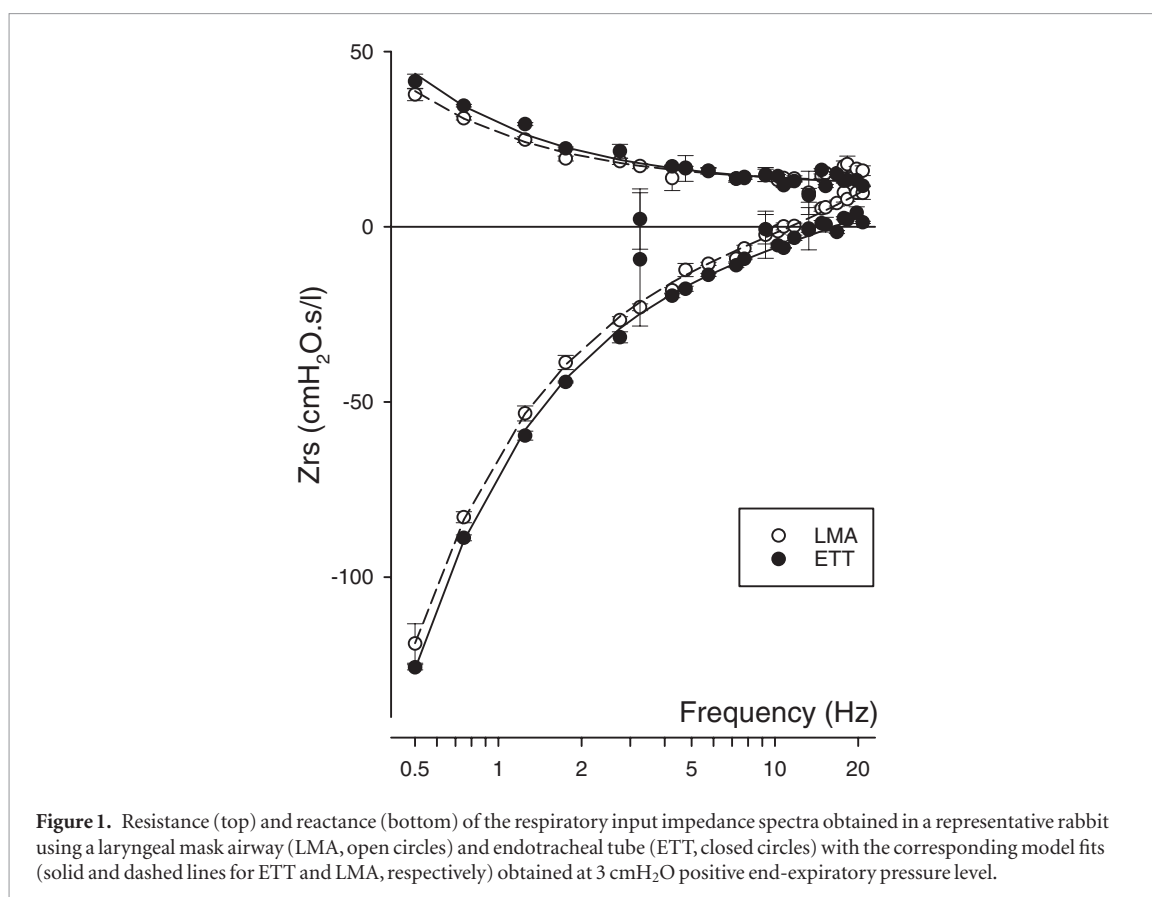
Scatters in the parameters are expressed as standard-deviation values. The Kolmogorov–Smirnov test was used to test data for normality. The effects of airway device and PEEP on the respiratory mechanical parameters were assessed using two-way repeated measures analysis of variation (ANOVA) with Holm–Sidak post-hoc analyses. Pearson product moment tests were used to assess correlations, and Bland–Altman analysis was performed to assess the agreement between the respiratory tissue parameters ( $G$  and  $H$ ) measured using LMA and ETT; such analyses were not performed for the airway parameters due to the predictable difference based on the variable anatomy. Sample size was estimated using repeated measures ANOVA (Barker Bausell and Li 2002) for the primary variable  $R_{aw}$ , and the estimate indicated a minimum number of nine animals was required to provide a statistically significant difference with a power of 0.8 and alpha of 0.05. The statistical tests were performed with a significance level of  $p < 0.05$ .

## Results

Forced oscillatory measurements using ETT were successfully obtained in all rabbits. A leak precluded the recording of technically acceptable impedance data at PEEP 6 cmH<sub>2</sub>O for one rabbit when using the LMA.

Figure 1 provides  $Z_{rs}$  data obtained using LMA and ETT with a representative rabbit at PEEP 3 cmH<sub>2</sub>O. The slight deviation in the low-frequency resistance indicates a somewhat lower tissue resistive contribution when the airways were secured using LMA. The quasi-parallel shift in the reactance curve implies minor deviations in the tissue elastic and in the inertive properties between the measurement modes. The model fitted well to the impedance curves with no systematic error.

Airway and respiratory tissue parameters measured at normal (3 cmH<sub>2</sub>O) and elevated (6 cmH<sub>2</sub>O) PEEP levels using ETT and LMA with the two oscillatory amplitudes are depicted in figure 2. Significantly higher  $R_{aw}$  and  $I_{aw}$  values were obtained with the supraglottic device at both PEEP levels and oscillatory amplitudes ( $p < 0.001$  for both). Mild, but statistically significant lower tissue damping ( $G$ ) was obtained using the LMA at the lower PEEP ( $p < 0.001$ ); this significant difference was found only at the normal oscillatory amplitude at the elevated PEEP ( $p < 0.01$ ). While elevation of PEEP decreased  $H$  significantly ( $p < 0.001$ ), there was no evidence for a significant difference in  $H$  at any PEEP or oscillatory amplitudes. These differences in  $G$  and  $H$  resulted in



significantly lower  $\eta$  at PEEP 3 cmH<sub>2</sub>O ( $p < 0.01$ ), with no evidence for a difference in this parameter at PEEP 6 cmH<sub>2</sub>O. The change in the oscillatory amplitude through the LMA had a significant effect on Raw ( $p < 0.02$ ) and  $G$  ( $p < 0.01$ ) when PEEP 3 cmH<sub>2</sub>O was maintained.

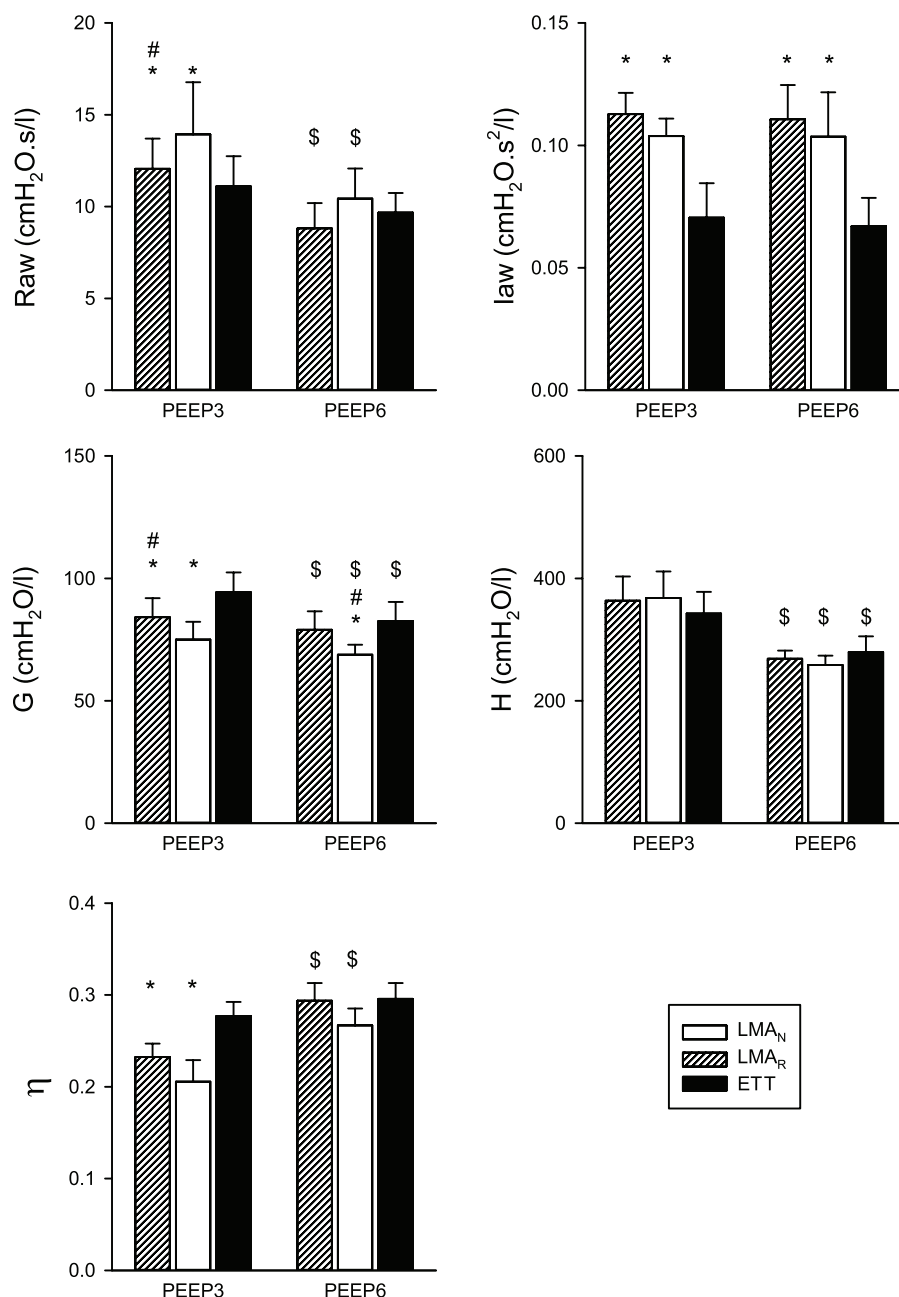
Relationships between the viscoelastic tissue parameters  $G$  and  $H$  obtained with the two recording methods (LMA and ETT) and the corresponding Bland-Altman plots are given in figure 3. A moderate relationship was observed for  $G$  obtained with the two airway devices at the higher ( $r = 0.70$ ,  $p < 0.01$ ) and lower ( $r = 0.64$ ,  $p = 0.01$ ) oscillatory amplitudes. Bland-Altman analyses revealed that the oscillatory amplitude had a marked effect on the mean bias in  $G$  ( $-14.7$  versus  $-5.1$  cmH<sub>2</sub>O/l at normal and reduced amplitudes, respectively), with fairly similar limits of agreement ranges (25.9 versus 28.9 cmH<sub>2</sub>O/l). Strong and significant correlations were observed in  $H$  independent of the oscillatory amplitude ( $r = 0.89$  at both normal and reduced amplitudes;  $p < 0.0001$  for both). The Bland-Altman analysis for  $H$  indicated a small mean bias at normal (8.8 cmH<sub>2</sub>O/l) and reduced (11.3 cmH<sub>2</sub>O/l) oscillatory amplitudes, with limits of agreement of 132.8 and 108.8 cmH<sub>2</sub>O/l, respectively.

The results of the simulation study are summarized in figure 4. Increasing the effects of the upper airway shunt (i.e. decreasing the magnitude of  $Z_s$ ) resulted in proportionally greater decreases in  $G$  than in  $H$ , with maximum relative changes of 19.4% and 12.9%, respectively. These disproportional changes decreased  $\eta$  by 8.2%.

## Discussion

Forced oscillatory mechanical parameters characterizing the airway and respiratory tissue compartments were compared in the present study with measurements taken from the same animal through a conventionally applied tracheostomy tube (ETT), and a supraglottic airway device (LMA) at normal and elevated PEEP levels. The results demonstrated the feasibility of collecting sensible forced oscillatory data using a LMA, as well as close agreement of respiratory system elastance between ETT and LMA. However, values for parameters reflecting airway mechanics were significantly higher and tissue damping was somewhat lower with the LMA than those obtained with the ETT.

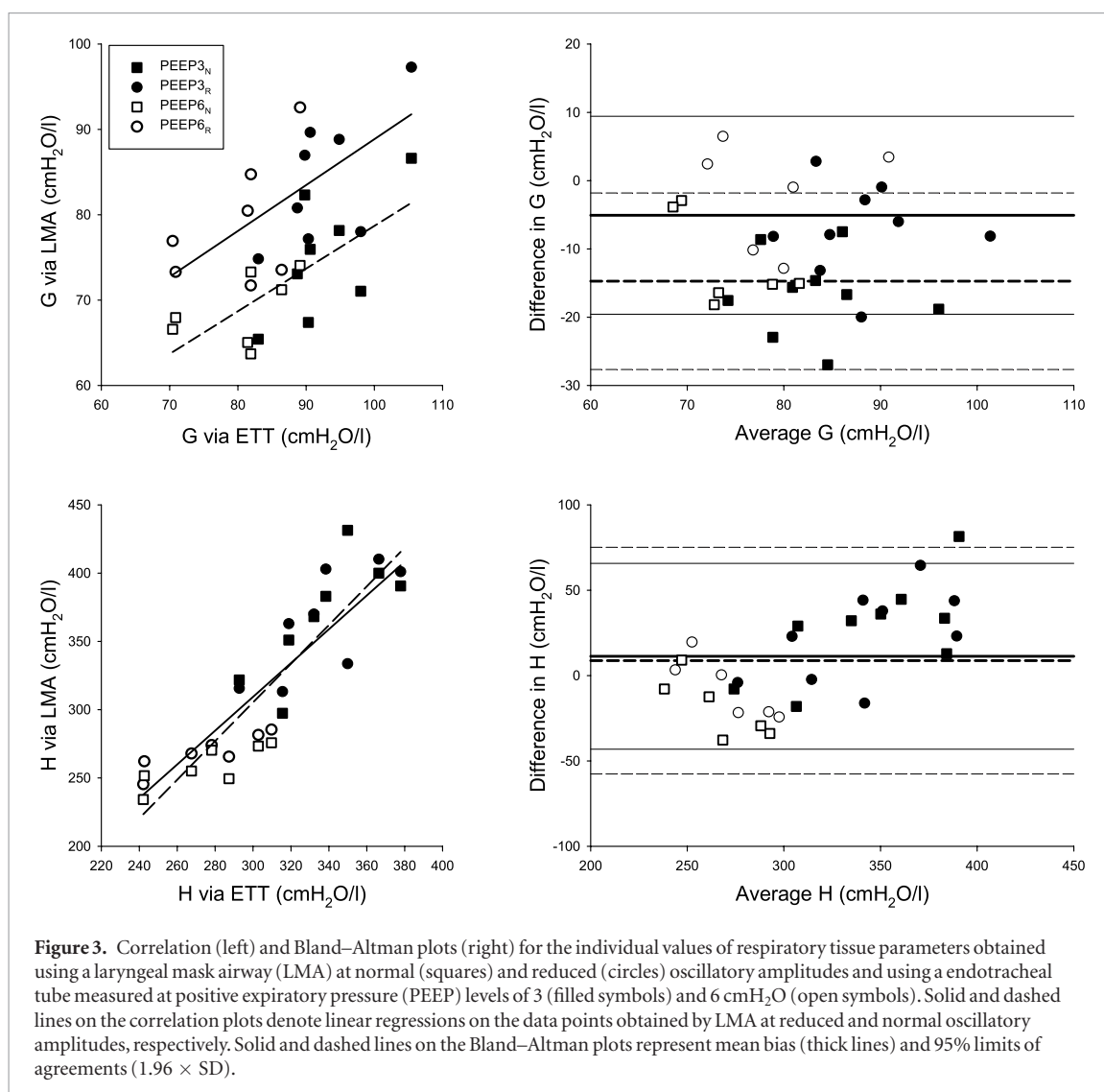
The rationale of the study was motivated by the fact that, although LMA is gaining increasing popularity to secure the airways during sedation and/or general anesthesia (Bateman *et al* 2005, Toman *et al* 2015, Park *et al* 2016, McNarry and Patel 2017, Mihara *et al* 2017), the feasibility of measuring airway and respiratory tissue mechanics with this supraglottic device has not previously been studied. The LMA was successfully inserted in all animals at normal PEEP, and technical difficulty obtaining sealed contact with the larynx was observed in one



**Figure 2.** Airway and respiratory tissue mechanical parameters (mean and standard deviation,  $n = 9$ ) obtained using a laryngeal mask airway (LMA) at normal (LMA<sub>N</sub>, white bars) and reduced (LMA<sub>R</sub>, white hatched bars) oscillatory amplitudes, and using an endotracheal tube (ETT, filled bars) measured at positive expiratory pressure (PEEP) levels of 3 and 6 cmH<sub>2</sub>O. Raw: airway resistance; law: airway inertance; G: tissue damping; H: tissue elastance;  $\eta$ : tissue hysteresivity ( $G/H$ ). \* $p < 0.05$  versus ETT within a PEEP level, # $p < 0.05$  between LMA<sub>N</sub> and LMA<sub>R</sub> within a PEEP level, \$ $p < 0.05$  between PEEP levels within a measurement condition.

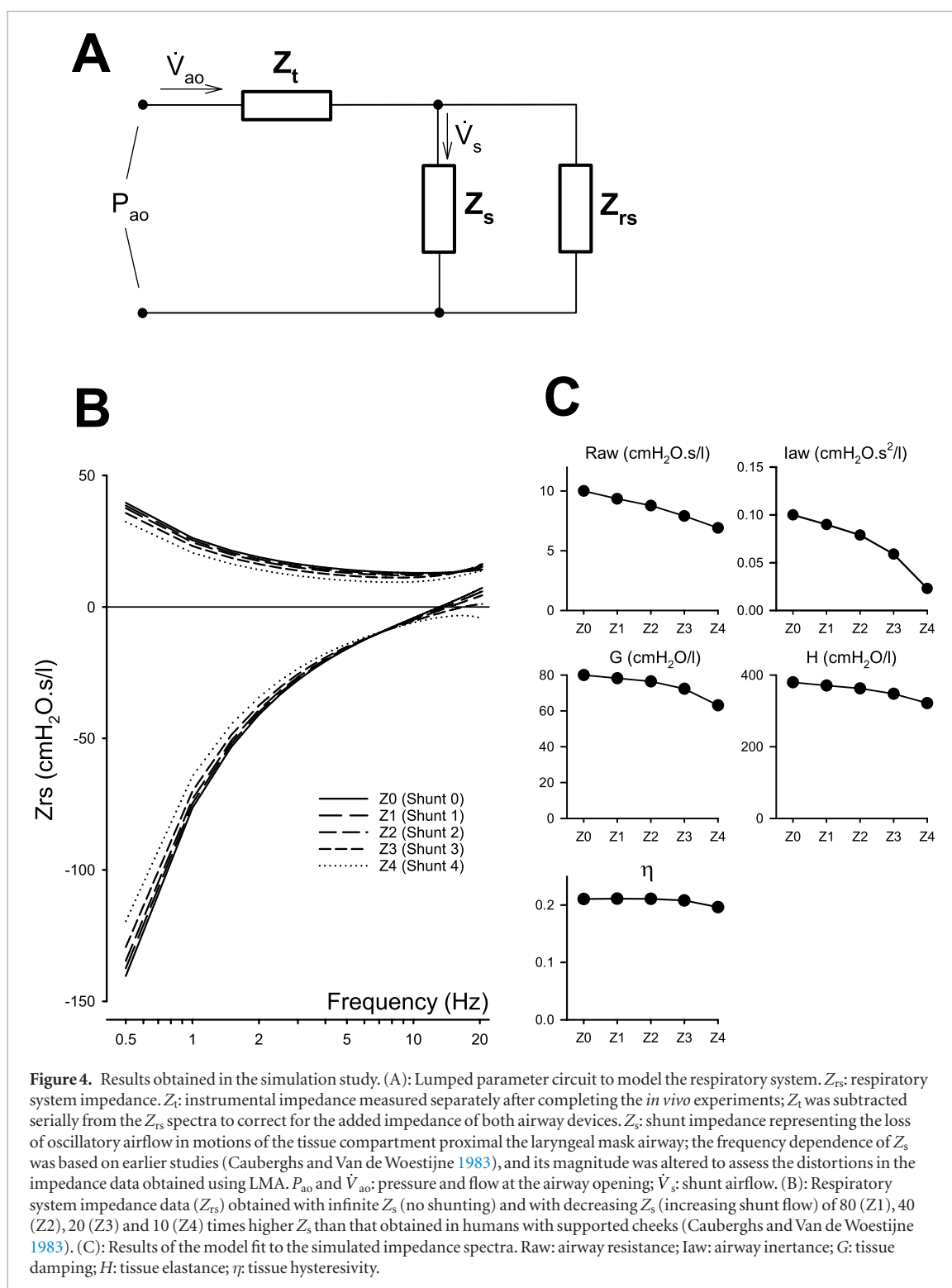
rabbit at the higher PEEP. It is important to note that even a slight leak around the LMA distorts the frequency dependence of the  $Z_{rs}$  spectra, ultimately biasing model parameter estimates. Such an artifact would have given an additional rise in the low frequency resistance and subsequent artifactual increase in  $G$ , as well as a decrease in the reactance, thereby decreasing  $H$  (Hantos *et al* 1997). Since such a changing pattern was not observed in any of the other rabbits, it can be concluded that the LMA provided a tight seal even at the elevated PEEP level.

Our findings on the forced oscillatory mechanical parameters obtained with an ETT show excellent agreement with previous results obtained for rabbits with similar experimental conditions using an ETT (Bayat *et al* 2009, Tolnai *et al* 2018). Comparing the airway parameters obtained in the present study revealed significantly higher Raw and law values for the LMA measurements than those obtained with the ETT after the corresponding instrumental resistance and inertance were removed from these estimates. These findings were expected and can be explained by the obvious differences between the two airway devices. Whereas measurements with LMA include airways from the laryngeal cavity to the terminal bronchioles, airway parameters obtained with the ETT incorporate airway compartments distal from the lower trachea. Indeed, estimating the magnitude of additional



Raw and Iaw due to this anatomical difference (Peslin and Fredberg 1986) revealed a difference of  $2 \text{ cmH}_2\text{O} \cdot \text{s/l}$  for Raw (length of the airway segment 5 cm, ID = 0.35 cm) and  $0.017 \text{ cmH}_2\text{O} \cdot \text{s/l}$  for Iaw (estimated additional air volume of 7 ml with LMA). This calculation confirmed that the involvement of a longer central airway segment with LMA can fully explain the observed differences in the airway parameters. Furthermore, the amplitude-dependence of Raw estimates when LMA was applied at low PEEP is also worth noting. This finding can most likely be attributed to the presence of a nonlinear phenomenon due to airflow turbulences around the LMA and indicates the use of reduced oscillatory amplitudes with this airway device for accurate assessment of airway resistance without compromising signal-to-noise ratio. A slight frequency-dependence of the real part of  $Z_{rs}$  at higher frequencies was observed, particularly when LMA was applied. This phenomenon was described to occur in rats (Thamrin *et al* 2005), dogs (Jackson and Lutchen 1987), rabbits (Frey *et al* 1998) and humans (Dorkin *et al* 1988) with different frequency characteristics. The apparent frequency dependence during the application of LMA but not ETT might be related to acoustic resonance. Differences in mean path lengths travelled by the oscillatory waveform and different resonant properties of the tubing and measured airway components between the LMA and ETT circuits affect the frequency range in which this frequency-dependent component occurs (Thamrin *et al* 2005). This necessitated the use of a modified airway compartment to improve the quality of the model fitting with the constant-phase model. However, the empirical parameter  $\beta$  has no direct physiological interpretation, and only allows for taking the curvilinear elevation of the real part at higher frequencies into account.

Viscoelastic parameters reflect the dissipative ( $G$ ) and elastic ( $H$ ) properties of the respiratory tissues. Accordingly, these parameters are expected to be independent of the techniques to secure the airways. This anticipated finding was confirmed for  $H$  where close correlation was associated with good agreement at both PEEP levels. However,  $G$  values were significantly lower with the LMA than those obtained with the ETT when comparable oscillatory amplitudes were led through the two devices (17%), and this difference decreased to about half when the oscillatory amplitude was reduced using the LMA (9%). This amplitude-dependence of the difference suggests the involvement of a non-linear biasing phenomenon in the  $G$  estimates when FOT was applied through the



LMA. Since compliant tissue compartments exist at the tip of the LMA device, such biasing phenomenon may be related to upper airway shunting, which has been demonstrated to distort the forced oscillatory  $Z_{rs}$  spectra (Cauberghs and Van de Woestijne 1983, Peslin *et al* 1984, Desager *et al* 1999). In an attempt to clarify the potential involvement of shunting, a simulation study was performed using realistic impedance data to model the load ( $Z_{rs}$ ) and shunt ( $Z_s$ ). The results of this modeling revealed that upper airway shunting led to a greater underestimation for  $G$  than for  $H$ , confirming that the differences in  $G$  can be attributed, at least partially, to the influence of the upper airways when FOT was applied through a LMA. Furthermore, increasing shunting effects also led to more prominent frequency-dependence in the real part of  $Z_{rs}$  at higher frequencies (figure 4(B)). This also indicates the potential contribution of the upper-airway shunting to the differences between FOT measurements with the two airway devices.



In summary, the results of the present study demonstrate that mechanical properties of the airways and the respiratory tissues can be reliably assessed using a LMA. The longer upper airway compartment should be taken into account in the interpretation of the airway resistance and inertance. While respiratory tissue stiffness can be accurately assessed using an LMA, upper airway shunting may slightly bias the estimates of respiratory tissue damping. LMA is less invasive and its application results in significant reduction in the incidence of postoperative respiratory complications compared to the use of ETT. Thus, application of this airway device offers a suitable alternative to ETT, particularly in animal studies where a follow-up of changes in respiratory mechanics is of interest.

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## Disclosures

Authors have no perceived or potential conflict of interest related to the present paper.

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