INFLUENCE OF HALOTHANE AND ENFLURANE ON RESPIRATORY AIRFLOW RESISTANCE AND SPECIFIC CONDUCTANCE IN ANAESTHETIZED MAN

J. R. LEHANE, C. JORDAN AND J. G. JONES

SUMMARY

We have developed a method for the measurement of respiratory resistance and specific airways conductance (s. $G_{aw}$) using the forced airflow oscillation method, and have used it to study the effects of halothane and enfurane on airway mechanics in anaesthetized patients. Resistance ($R_n$) was determined over a range of lung volumes and s. $G_{aw}$ was obtained by computer-aided analysis of the hyperbolic relationship between $R_n$ and lung volume. Patients received diazepam orally, followed by thiopentone and pancuronium. The trachea was intubated and the lungs ventilated with 70% nitrous oxide in oxygen. After obtaining three baseline measurements of s. $G_{aw}$, 1.3% halothane (10 patients) or 2.5% enfurane (10 patients) was added to the inspired gas. Halothane caused an increase in s. $G_{aw}$ (bronchodilatation) of 47% ($P < 0.05$; paired t test) at 3 min and a non-significant increase of 72% at 15 min. Enfurane produced no significant increase in s. $G_{aw}$ at 3 and 8 min, but a 56% increase ($P < 0.02$) at 15 min. One patient responded to halothane with an increase in bronchomotor tone, manifest by a significant reduction in s. $G_{sw}$ ($P < 0.01$; two-sample t test). Enfurane did not cause bronchoconstriction in any patient. There was a significant reduction in resistance with halothane ($P < 0.05$; paired t test) and enfurane ($P < 0.01$). Expiratory reserve volume (ERV) was found to be small, and contributed to the high resistances observed: mean resistance 0.59 kPa litre$^{-1}$ s, range 0.15–1.71. Small changes in ERV were also shown to produce changes in resistance independent of changes in bronchomotor tone. Neither halothane nor enfurane produced significant mean changes in ERV.

Difficulty in inflating the lungs is a well-recognized complication of general anaesthesia and is often attributed to bronchospasm (Edwards et al., 1956). The volatile anaesthetic agents are generally considered to produce bronchodilatation (Aviado, 1975) and both halothane (Colgan, 1965; Gold, 1970) and enfurane (Rodriguez and Gold, 1976) have been recommended as particularly suitable for anaesthetizing patients with obstructive lung disease. There are, however, several case reports of bronchospasm induced by enfurane (Lowry and Fielden, 1976; Schwettmann and Casterline, 1976) and one of histamine release causing severe urticaria induced by halothane (Cole, 1964).

These anaesthetic agents may affect resistance to airflow through an effect on bronchial smooth muscle or elastic recoil pressure, or both. Lung recoil pressure depends on lung volume, and the relationship between airflow resistance and lung volume is hyperbolic (Briscoe and DuBois, 1958). We have shown that changes in lung volume which occur during anaesthesia may profoundly affect resistance to airflow (Lehane, Jordan and Jones, 1979) and therefore, in any study of the effects of anaesthetics on resistance, the effect of changes in lung volume must be considered.

The effect of a change in bronchomotor tone is to modify the shape of the hyperbola that describes the resistance–volume relationship (fig. 1). At a large lung volume the large distending force exerted by lung parenchyma on the airway wall minimizes the effect of active bronchoconstriction which consequently has only a small effect on airway resistance. Conversely, at a small lung volume the small distending force on the airway wall permits active smooth muscle contraction to produce a much larger effect on airway resistance. This change in the shape of the hyperbola may be quantitated by plotting the reciprocal of resistance, conductance, against lung volume. Changes in the slope of the resulting straight line, specific airways conductance (s. $G_{aw}$), may be used as an index of change in bronchomotor tone (fig. 2). The advantage of this approach is that a change in functional residual capacity, for example, has no effect on the slope of the conductance–volume plot and an acute change in slope implies a change in bronchomotor activity.
We have developed a method for measuring respiratory resistance ($R^*$) and $s.G_{aw}$ which is suitable for use during anaesthesia in man. This paper presents the results of a study of the effects of halothane and enflurane on $R_{rs}$ and $s.G_{aw}$ in anaesthetized patients.

METHODS

Patients
The study was approved by the Northwick Park Hospital Ethics Committee, and informed consent was obtained from each patient. Twenty patients aged between 18 and 60 yr were studied. They were not receiving any drugs and were non-smokers. There was no evidence of convulsive disorder, or of cardiac or respiratory disease. The patients were undergoing routine surgical procedures requiring general anaesthesia with tracheal intubation and neuromuscular blockade. They were randomly allocated to two groups of 10, one group to receive halothane, the other enflurane.

Resistance-volume plots
Plots of total respiratory resistance ($R_{rs}$) against volume over part of the vital capacity range were obtained using the modified anaesthetic circuit shown in figure 3. A tap was fitted to a Manley ventilator so that mechanical ventilation could be interrupted and replaced by a slow inflation or deflation of 3 litre min$^{-1}$. The forced airflow oscillation method (Goldman et al., 1970; Hyatt et al., 1970) was used to measure $R_{rs}$ during the deflation manoeuvre. The oscillating airflow was produced by a purpose-built, sinusoidal pump (developed by Division of Bioengineering, CRC, Harrow) delivering a stroke volume of 58 ml at a frequency of 3 Hz. Airway pressure was sensed with a pressure transducer (Pye Ether UP2) via a catheter the tip of which was at the distal end of the tracheal tube. A flow signal was obtained using a heated Fleisch No. 2 pneumotachograph and differential pressure transducer (Validyne MP 45–1). The pressure and flow signals were analysed electronically and $R_{rs}$ and the change in lung volume were derived. $R_{rs}$ was plotted as a function of lung volume on an X–Y recorder (Bryans 26000). The volume range studied was from 1 litre greater than FRC to near residual volume.

Specific airways conductance
Plots of conductance against volume may be obtained from the corresponding resistance–volume plots. However, the conductance–volume plot will be linear only if resistance tends to zero at large lung volume. It was necessary, therefore, to subtract the contributions to $R_{rs}$ which do not tend to zero at large lung volumes. This residual resistance may include the resistances of upper airway, lung tissue
and chest wall. We were able to exclude upper airway resistance by measuring airway pressure at the tip of the tracheal tube, but as it was not practical to measure alveolar pressure it was not possible to exclude lung tissue resistance. A computer-aided curve-fitting routine was therefore used to fit a hyperbola to the resistance–volume data in order to determine the residual or asymptotic resistance and to enable the derivation of specific airways conductance.

**Computer analysis**

The resistance–volume curves were sampled at 0.02-litre increments using a D-MAC digitizing table and stored on paper tape. The data were analysed by computer to derive the parameters of the hyperbola fitted to each plot. The three parameters derived (fig. 4) were asymptotic resistance ($R_A$), asymptotic volume (ERV, see below) and specific conductance ($s.G_{aw}$) where:

$$1/(R_{rs} - R_A) = s.G_{aw} \times (V_L + ERV)$$

and:

$$V_L = 0 \text{ at FRC where } V_L \text{ is lung volume}$$

$R_A$ represents the component of $R_{rs}$ which does not vary with lung volume (viz. resistance of lung tissue and chest wall). ($R_{rs} - R_A$) is the resistance of the distensible intrathoracic airways, and $1/(R_{rs} - R_A)$ is the conductance of these distensible airways. $s.G_{aw}$ is the slope of the plot of the conductance of these airways against $V_L$ over the range of $V_L$. In this method $s.G_{aw}$ is derived directly from the analysis of the hyperbolic plot of $R_{rs}$ and $V_L$.

The mean respiratory resistance over a tidal volume of 0.7 litre ($R_{vt}$) was calculated from the area under the fitted hyperbolic curve between the end-expiratory volume point and 0.7 litre above this point:

$$R_{vt} = \int_{0}^{0.7} R_{rs} \, dV_L/0.7$$

Expiratory reserve volume (ERV) is conventionally measured as the volume expired by a maximal expiratory effort from FRC. In this study ERV was defined as the volume asymptote of the $R_{rs}$–$V_L$ plots, which is the volume at which resistance could be infinite. This represents the maximum volume that could be expelled from the lung following the application of a large subatmospheric pressure to the airway of a paralysed patient and is likely to be larger than the ERV determined by spirometry.

Full details of the method, including the computer analysis, will be presented elsewhere (Jordan et al., in preparation).

**Procedure**

Premedication was with diazepam 0.2 mg kg$^{-1}$ orally. Anaesthesia was induced with thiopentone 3.5–4 mg kg$^{-1}$ i.v. and maintained with 70% nitrous oxide in oxygen. Pancuronium 0.12 mg kg$^{-1}$ provided neuromuscular blockade. After tracheal intubation, ventilation was adjusted to maintain end-tidal $P_{CO_2}$ at 5 kPa (measured with a Godart infra-red analyser corrected for the effects of nitrous oxide).

At least three baseline resistance–volume plots were obtained during the following 15 min. Ten patients subsequently received 1.3% halothane and 10 received 2.5% enflurane. Inspired and end-tidal concentrations of the volatile agents were measured using a mass spectrometer (BOC Medishield). At least three further resistance–volume plots were obtained during the following 15 min.

All the measurements were completed before the commencement of surgery.

**Statistical analysis**

Following the introduction of both volatile agents, the degree of change in both resistance and specific conductance was found to be dependent on the initial values. After logarithmic transformation, the differences in these variables were found to be normally distributed and independent of the initial values. Statistical analyses of changes in $R_{vt}$ and $s.G_{aw}$ were therefore performed on the logarithmic data and Student's $t$ tests were applied.
RESULTS
Patients in the two groups were well matched for age, weight and height (table I). There were no significant differences in end-tidal concentration of the volatile anaesthetics when expressed as a fraction of minimal alveolar concentration (MAC assumed to be 0.8% halothane and 1.68% enflurane) during the period of measurement (fig. 5).

TABLE I. Anthropometric data (SD); two groups of 10 patients

<table>
<thead>
<tr>
<th></th>
<th>Halothane</th>
<th>Enflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>42.6 (11.5)</td>
<td>42.9 (9.8)</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>72.1 (11.6)</td>
<td>67.5 (12.6)</td>
</tr>
<tr>
<td>Mean height (cm)</td>
<td>168 (11)</td>
<td>167 (10)</td>
</tr>
<tr>
<td>Per cent of average weight for height and age</td>
<td>107 (17)</td>
<td>101 (14)</td>
</tr>
</tbody>
</table>

Fig. 5. Mean end-tidal concentration (± SEM), expressed as a fraction of 1 MAC for halothane (O) and enflurane (●).

Resistance–volume plots
Typical plots are shown for two patients in figure 6A and B. These illustrate the hyperbolic relationship between resistance and volume and also show the effects of halothane administration. In both cases there was a reduction in resistance over the tidal volume range \( R_{VT} \) following halothane administration. In figure 6A, there was only a small increase in ERV (20 ml) and the reduction in \( R_{VT} \) from 0.68 to 0.22 kPa litre\(^{-1}\) s resulted mainly from a change in the shape of the curve. This shape change was a result of a change in bronchomotor tone, with s.\( G_{aw} \) increasing from 4.56 to 28.8 kPa\(^{-1}\) s\(^{-1}\). In figure 6B, \( R_{VT} \) changed from 0.73 to 0.27 kPa litre\(^{-1}\) s and there was displacement in the curve to the left which resulted in ERV increasing by 0.2 litre. This volume change accounted for most of the reduction in \( R_{VT} \), but there was also a decrease in bronchomotor tone with s.\( G_{aw} \) increasing from 6.21 to 19.9 kPa\(^{-1}\) s\(^{-1}\).

Specific conductance
Figure 7 shows mean changes in \( \log_{10} s.\( G_{aw} \) \) from the baseline derived from mean values obtained during nitrous oxide anaesthesia. Administration of both halothane and enflurane was accompanied by an increase in s.\( G_{aw} \) indicating bronchodilatation, which was significant for halothane at 3 min \( (P<0.05) \) and for enflurane at 15 min \( (P<0.02, \) paired t test \).

The responses of the individual patients to halothane and enflurane are shown in figure 8A, B. There was considerable variability in response to both agents at 3 min and this variability subsequently increased with halothane, and reduced with enflurane.
HALOTHANE AND ENFLURANE ON AIRWAY CALIBRE

**Fig. 7.** Mean changes in $sG_{aw}$ from baseline values during nitrous oxide anaesthesia. The left y-axis indicates difference in log$_e$ $sG_{aw}$, and the right y-axis, the analog of the left y-axis, indicates percentage change in $sG_{aw}$ (halothane (○) and enfurane (•), ± SEM).

The two-sample $t$ test, applied to the data from each patient individually, showed significant increases in $sG_{aw}$ in six of 10 patients given halothane and three of 10 given enfurane. In one patient given halothane there was a significant decrease in $sG_{aw}$ ($P<0.01$), but in no patient given enfurane was there a significant decrease in $sG_{aw}$.

**Fig. 8.** A: Changes in $sG_{aw}$ in each patient with halothane. (○ = significant change, $P<0.05$); B: Changes in $sG_{aw}$ in each patient with enfurane. (○ = significant change, $P<0.05$.)

**Mean resistance over the tidal volume range ($R_{VT}$)**

Figure 9 shows mean respiratory resistance over the tidal volume range ($R_{VT}$) before and during the administration of halothane and enfurane for individual patients. Halothane produced a significant mean decrease of $30\%$ (change in log$_e R_{VT}$ from control = 0.36, SEM 0.15, $P<0.05$, paired $t$ test) and enfurane produced a mean decrease of $20\%$ (change in log$_e R_{VT}$ = 0.22, SEM 0.06, $P<0.01$).

**Fig. 9.** Respiratory resistance ($R_{VT}$) before and during administration of halothane and enfurane in individual patients.

**Expiratory reserve volume (ERV)**

There were no significant mean group changes in ERV following the introduction of either volatile agent. Halothane was associated with an increase in ERV in three patients (+0.055, +0.075 and +0.350 litre), and a decrease in four ($-0.035$, $-0.040$, $-0.045$ and $-0.109$ litre). Enflurane was associated with an increase in four patients (+0.030, +0.040, +0.060 and +0.100 litre), and a decrease in two

**Fig. 10.** A: Correlation between ERV during anaesthesia and age of patient. (1 = ERV < 0.05 litre.) B: Correlation between ERV and % of normal expected weight. (1 = ERV < 0.05 litre.)
During nitrous oxide in oxygen anaesthesia ERV was less than 0.25 litre in 10 of the 20 patients. There was a significant negative correlation with age (P<0.01) (fig. 10A) and with weight (P<0.05) (fig. 10B) when the latter was expressed as a percentage of average weight for age and height.

**DISCUSSION**

This is the first study of airflow resistance in anaesthetized patients to distinguish between the effects of changes in bronchomotor tone and changes in lung volume. The resistance-volume plots obtained in this study confirm, in anaesthetized patients, the hyperbolic relationship previously described for conscious man (Briscoe and DuBois, 1958). This hyperbolic relationship has a number of important implications. First, it is clear that changes in lung volume such as are known to occur during anaesthesia may produce very large changes in respiratory resistance without the need to invoke changes in bronchomotor tone. Second, the magnitude of the effect of any given change in lung volume on resistance is dependent on the initial lung volume so that, at small lung volumes, small changes in volume will have a much greater effect on resistance than the same change at a larger lung volume. Third, the magnitude of the effect of a change in bronchomotor tone is also dependent on lung volume so that, at large lung volumes, even large changes in s.Gw produce only small changes in resistance, whereas, at small lung volumes, small changes in s.Gw may produce large changes in resistance. This is illustrated in figure 11 which shows the effect of three levels of bronchomotor tone at large and small ERV. It will be seen that, at any given s.Gw, resistance is greater at the smaller ERV and that the difference in resistance produced by a change in s.Gw is greater at small lung volume. Therefore it is essential to take account of the effect of lung volume whenever lung volumes are small and to note that when bronchospasm complicates general anaesthesia a small lung volume is likely to make an important contribution to airflow resistance.

The expiratory reserve volumes observed in this study were very small. Whilst it is known that a change in posture from erect to supine produces a reduction in ERV (Blair and Hickham, 1955), it is not known whether the small ERV measured in our anaesthetized patients resulted from the supine posture, the state of anaesthesia or both these factors. It is established that anaesthesia usually causes a decrease in functional residual capacity (Hewlett et al., 1974a, b) which must also further reduce ERV if residual volume remains constant. The possibility that ERV is reduced during anaesthesia remains unconfirmed in individual patients in this study because measurements of ERV were not made in the conscious supine state. Obesity and advancing age are both known to be associated with reduction in ERV (Cotes, 1979) and in our study during anaesthesia the ERV in patients more than 50 yr, or more than 110% of average weight, was less than 0.25 litre. The addition of halothane or enflurane produced no significant mean changes in ERV in the grouped data, but the small changes which occurred in individual patients were sufficient to produce important changes in airflow resistance because of the small initial ERV. This effect of anaesthesia on ERV in some subjects, while of considerable interest in terms of its effects on lung mechanics and gas exchange, is not easily explained. A possibility is that changes in central blood volume may cause a change in thoracic gas volume (Jones et al., 1979). It is clearly important to make measurements of ERV and FRC with and without volatile agents to attempt to elucidate this mechanism.

There can be no doubt that, in most patients, bronchomotor tone was substantially reduced by the administration of halothane and enflurane, although one patient given halothane showed a significant decrease in s.Gw indicating bronchoconstriction. The effect of enflurane was smaller but more consistent than that of halothane. Although the average response was a reduction in bronchomotor tone, the decrease in resistance which occurred was not completely accounted for by these changes in tone. Paradoxically, in some patients, there was an increase in bronchomotor tone which was not accompanied by an
increase in resistance. This paradox is fully explained by the increase in ERV which occurred in these patients and which was sufficient to increase airway calibre and offset the effect of bronchomotor tone. In one patient given halothane, the opposite effect was noted in that an increase in \( s.G_{aw} \) failed to reduce resistance because there was a concomitant reduction in ERV. These results emphasize the importance of determining the effects of changes in lung volume if changes in airway resistance are to be interpreted.

The observation that halothane reduces airways resistance in man is broadly in agreement with the findings of Rügheimer, Himmel and Greiner (1974), Rolly and Thomas (1975) and Morr-Strathmann, Welte and Lawin (1977), but conflicts with the findings of Patterson and others (1968) and Brakensiek and Bergman (1970). Our finding that enflurane also reduces resistance is in agreement with those of Rolly and Thomas (1975) and Morr-Strathmann, Welte and Lawin (1977), but is in conflict with the finding of Rügheimer, Himmel and Greiner (1974). The differences in the results are most likely to be a result of methodological differences in resistance measurement and the failure of other workers to take into account the effects of changes in lung volume.

Attempts to elucidate the mechanism of action of halothane on bronchomotor tone in animals and man have also yielded conflicting results. It has been suggested that halothane causes bronchodilatation. Klide and Aviado (1967) found evidence in intact dogs that this was mediated by beta-adrenergic stimulation, whereas Fletcher, Flacke and Alper (1968), using isolated guineapig tracheas, and Hickey and others (1969), using intact dogs, concluded that it was a result of a non-specific direct effect on the smooth muscle cell. Fletcher, Flacke and Alper (1968) found that the relaxation in isolated guineapig tracheal muscle was not blocked by beta-adrenergic blockade, whereas Boissier and others (1968) found that, in guineapig lung in situ, beta blockade gave a bronchoconstrictor effect with halothane. Brakensiek and Bergman (1970) and Patterson and others (1968) found that halothane produced little effect on bronchial smooth muscle alone (Tattersfield, 1979). Our results show that, during anaesthesia in man, such an assumption is unwarranted.

In conclusion, we have developed a method for the measurement of changes in bronchomotor tone which allows for the effect of lung recoil pressure. We have used the method to study the effects of halothane and enflurane on the airways of anaesthetized patients. Both agents produced significant bronchodilatation, although the effect of halothane was more marked than that of enflurane. Changes in lung volume sometimes reversed the effects of changes in bronchomotor tone. There was much greater variability in response to halothane and one patient showed significant bronchoconstriction with this agent.

ACKNOWLEDGEMENTS
We would like to thank Anne Rhodes for digitizing the data, the C.R.C. Division of Computing and Statistics for help in data analysis, Abbott Laboratories for supplies of enflurane and Brenda Dobson and Norma Saunders for secretarial help.

REFERENCES


HALOTHANE AND ENFLURANE ON AIRWAY CALIBRE

and Pancuronium. The Trachea was intubated, and the lungs were inflated with 70% nitrous oxide in oxygen. After establishment of the three basic measurements of s.Gaw, Halothane (10 patients) or Enfluran (10 patients) was added to the inhaled gas at 1.3% (10 patients) or 2.5% (10 patients). Halothane caused an increase in s.Gaw (bronchodilation) of 47% (P<0.05; paired t-Test) after 3 min, and a non-significant increase of 72% after 15 min. Enfluran caused no increase after 3 and 8 min, but a 56% (P<0.02) increase after 15 min. One patient reacted to Halothane with an increase of bronchomotor tone, manifested by a significant reduction of s.Gaw (P<0.01; paired t-Test with two samples). Enfluran did not cause broncho-constriction in any patient. There was a significant decrease in resistance with Halothane (P<0.05; paired t-Test) and Enfluran (P<0.01). The expiratory reserve volume (ERV) was small and contributed to the high resistance observed: average resistance was 0.59 kPa s^-1 L^-1, range 0.15-1.71. Small changes in ERV also produced changes in resistance, independent of changes in bronchomotor tone. Neither Halothane nor Enfluran produced significant changes in ERV.

INFLUENCIA DEL HALOTANO Y ENFLURANO EN LA RESISTENCIA DEL FLUJO DE AIRE RESPIRATORIO Y LA CONDUCTABILIDAD ESPECÍFICA EN EL SER HUMANO ANESTESIADO

SUMARIO

Hemos elaborado un método de medición de la resistencia respiratoria y de la conductabilidad específica de las vías respiratorias (s.Gaw) al usar el método de oscilación del flujo de aire forzado, el cual hemos empleado para estudiar los efectos de halotano y enfurano sobre la mecánica de las vías respiratorias en pacientes anestesiados. Se determinó la resistencia respecto de una serie de volúmenes pulmonares y se obtuvo s.Gaw mediante un análisis por computadora de la relación hiperbólica entre Rₐₐ y el volumen del pulmón. Se administró diazepam oralmente a los pacientes, seguido por tiopentona y pancuronio. Se les intubó la tráquea y se les ventiló los pulmones mediante oxígeno al 70% en oxígeno. Después de obtener tres mediciones básicas del s.Gaw, se añadió al gas inspirado halotano al 1.3% (10 pacientes) o enfurano al 2.5% (10 pacientes). El halotano causó un aumento del s.Gaw (broncodilatación) de un 47% (P<0.05; ensayo t emparejado) a los 3 min y un incremento insignificante del 72% a los 15 min. El enfurano no produjo aumento significativo del s.Gaw a los 3 y 8 min, pero sí un incremento del 56% (P<0.02) a los 15 min. Un paciente tuvo una respuesta al halotano que resultó en un aumento del tono broncomotor que se manifestó por una disminución significante del s.Gaw (P<0.01; ensayo t sobre dos muestras). El enfurano no provocó ninguna bronco-constricción en ninguno de los pacientes. Hubo una reducción significativa de la resistencia con el halotano (P<0.05; ensayo t emparejado) y con el enfurano (P<0.01). El volumen del aire de reserva (VAR) comprobó ser bajo y contribuyó a las altas resistencias observadas: la resistencia media era de 0.59 kPa-litro^-1 s, extensión de 0.15-1.71. Pequeñas alteraciones del VAR también produjeron cambios en la resistencia, independientes de las variaciones del tono broncomotor. Ni el halotano ni el enfurano produjeron cambios medios significativos en el VAR.