Comparison of the constant flow and occlusion methods for assessment of bronchoconstriction in guinea-pigs

A.M. Lorino, M. Benichou, T. Kochi, H. Lorino, J. Milic-Emili, A. Harf

Comparison of the constant flow and occlusion methods for assessment of bronchoconstriction in guinea-pigs. A.M. Lorino, M. Benichou, T. Kochi, H. Lorino, J. Milic-Emili, A. Harf.
ABSTRACT: Assessments of total respiratory compliance (C) and conductance (G) with the constant inspiratory flow and the occlusion methods were compared in the basal state and during histamine or serotonin induced bronchoconstriction in 22 normal, anaesthetized, paralysed, mechanically ventilated guinea-pigs. In the basal state, no significant difference was found between the C and G values measured by both methods. During drug-induced bronchoconstriction, small but significant differences were observed between the respiratory parameters measured by the two methods, and expressed as the percentage ratio (R) to the corresponding basal values (respectively RC_{CF} and RC_{OC}, and RG_{CF} and RG_{OC}). This discrepancy, which was independent of the drug and of the dose, was probably attributable to a modification of the visco elastic properties of the lung due to either the mechanical ventilation or the infused drug. Nevertheless, this study demonstrates that both methods can be considered as equivalent for bronchoconstriction assessment because very strong correlations were found between RC_{CF} and RC_{OC} ($r=0.96$, $p<0.001$) and between RG_{CF} and RG_{OC} ($r=0.97$, $p<0.001$), and because the slopes of the linear relationships were not significantly different from unity in both cases.
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INSERM U296, Département de Physiologie, Hôpital Henri Mondor, Créteil, France.

Correspondence: A.M. Lorino, Service d'Explorations Fonctionnelles, Hôpital Henri Mondor, 94010 Créteil, France.

Various methods have been proposed for assessing respiratory compliance (C) and conductance (G) in anaesthetized, paralysed, mechanically ventilated mammals [1–4]. Comparative studies of some of the methods [5–8] have shown that the technique of measuring the respiratory parameters greatly influences the values obtained.

Among the most frequently used methods are the occlusion [3, 9] and the constant flow [7] methods, which are schematically described in figure 1. The main advantage of the constant flow method lies in the fact that it does not need any interruption of the mechanical ventilation and can therefore be easily used for monitoring respiratory mechanics. Differences between the C and G values assessed by these two methods have been reported in some patients with respiratory failure [7] and attributed to recruitment of lung units during the first part of inflation.

The occlusion method is often considered as the reference because it allows partitioning of respiratory conductance into airway flow conductance and peripheral conductance [9]. It has, however, been pointed out that under conditions of severe bronchoconstriction [10], this partitioning becomes questionable, since alveolar pressure is not transmitted instantaneously to the airway opening: hence the occlusion method can only provide
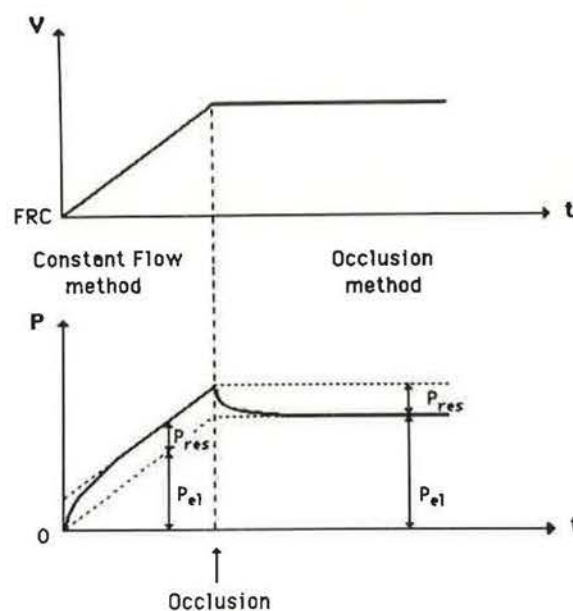

Fig. 1. – Scheme of measurements of respiratory compliance (C) and conductance (G) by the constant flow and the occlusion methods, from elastic pressure ($P_{el}=V/C$), and resistive pressure ($P_{res}=\dot{V}/G$). V: insufflated volume; P: tracheal pressure, equal to the sum of P_{el} and P_{res}; FRC: functional residual capacity.

measurement of total respiratory conductance and elastance. With regard to the constant flow method, it has been reported that, during bronchoconstriction, the respiratory conductance values obtained may be affected by the possible presence of unequal time constants within the lung, contrary to those obtained by the occlusion method [9]. It therefore appeared interesting to find out whether these two methods provide comparable values for total respiratory parameters in normal animals on the one hand, and similar assessment of bronchoconstriction in the course of drug-induced bronchoconstriction on the other. We therefore investigated the suitability of these two methods for assessing bronchoconstriction in response to intravenous infusion of various doses of either histamine or serotonin, in guinea-pigs.

Methods

Animal preparation

We studied 22 male Hartley strain guinea-pigs with mean body weight (±SD) of 345 g (±23). Each animal was anaesthetized with pentobarbital (30 $mg \cdot kg^{-1}$ *i.p.*) and placed in the supine position. A tracheal cannula was inserted, and a jugular venous catheter (internal diameter 0.3 mm) was placed for drug (histamine or serotonin) infusion. The animals were then paralyzed (pancuronium bromide, 4 $mg \cdot kg^{-1}$ *i.p.*), and mechanically ventilated at a rate of 60 min^{-1} with a 6 $ml \cdot kg^{-1}$ tidal volume, corresponding to a constant inflation flow of 15 $ml \cdot kg^{-1} \cdot s^{-1}$, by a volumetric custom-made ventilator ensuring a constant inflation flow rate. This ventilation rate was previously checked to ensure normocapnia. The inspiratory to expiratory duration ratio was 2:3. A large inflation, to simulate a sigh, was manually performed every five minutes by occlusion of the expiratory valve during 3 respiratory cycles in order to prevent alveolar atelectasis. Rectal temperature was monitored continuously and maintained constant by a heated blanket (Animal Blanket Unit, Harvard). Respiratory compliance and conductance were determined as described later, by both the constant flow method (C_{CF} and G_{CF}) and the occlusion method (C_{OC} and G_{OC}).

Experimental procedures

The animals were randomly divided into groups 1 and 2 respectively. After a 10 min stabilization period, the first set of values for respiratory compliance and conductance was estimated and taken as basal values for all animals, using both methods. Immediately thereafter, animals of group 1 had a histamine solution (drug 1) administered intravenously *via* the jugular catheter as a continuous 5 min infusion, at a constant mass flow of either 100 $ng \cdot kg^{-1} \cdot s^{-1}$ (dose 1) or 150 $ng \cdot kg^{-1} \cdot s^{-1}$ (dose 2), the dose being randomly assigned. The mechanical parameters were continuously monitored using the constant flow method, and assessed to have reached a plateau when their respective variations had been lower than 5%

for 60 s. The response to the bronchial challenge was then assessed by respiratory compliance and conductance, which were measured again by both methods and expressed as the percentage ratio (R) to the corresponding basal values (respectively RC_{CF}, RG_{CF}, and RC_{OC}, RG_{OC}). Following this, the 5 min infusion having been completed, about 10 min were allowed for the respiratory parameters to return to their basal values. The recovery to control conditions was first assessed by the constant flow method, and then verified using the occlusion method. Next, another histamine infusion was administered, at a constant mass flow corresponding to the dose which had not yet been administered, and the response to the bronchial challenge assessed as previously described. Animals of group 2 were submitted to the same experimental protocol, the infused drug used being serotonin (drug 2).

Determination of the respiratory parameters

Tracheal pressure (P) was measured with a differential pressure transducer (Validyne MP45±5 kPa) connected to the tracheal cannula. Inspiratory flow ($\dot{V}$) was measured by a pneumotachograph (Fleisch # 000) connected to a differential pressure transducer (Validyne MP45±0.2 kPa). Two identical occlusion valves (Burkert, type 311C, closure time of 15 ms) were placed, one on the inspiratory and the other on the expiratory circuit of the ventilator in order to allow rapid occlusion. The equipment flow resistance, including the tracheal cannula, was linear over the experimental flow range and amounted to 0.004 $kPa \cdot ml^{-1} \cdot s$. The dead space of measuring equipment was 0.4 ml.

Pressure and flow signals were low-pass filtered (second order, 20 Hz cut-off frequency), and then sampled at 64 Hz for 5 s by a 12-bit, 4 channel analogue/digital converter (Gauthier, France). Samples were fed into an Apple GS microcomputer. The two signals' baselines, corresponding respectively to barometric pressure and zero flow, were established before starting mechanical ventilation. P and $\dot{V}$ were then referenced to their baseline, and on-line integration of $\dot{V}$ by the trapezoidal rule yielded the instantaneous inspiratory volume V.

Respiratory compliance and conductance measurement was based on the general equation of motion of the respiratory system:

$$P = (1/C)V + (1/G)\dot{V}$$

The constant flow method used in this study was that proposed by ROSSI *et al.* [7]: during a constant flow inflation, respiratory compliance (C_{CF}) can be estimated as the inverse of the slope of the regression line of P on V, and respiratory conductance (G_{CF}), as the ratio of the constant flow to the intercept of the regression line on the pressure axis (fig.1). For each cycle, automated data analysis was performed, over the 40–90% range of inspiratory time, when both pressure and volume always varied linearly with time. The conductance values were corrected for that of the equipment. The correlation

coefficient allowed appreciation of the quality of the fit. Values obtained for compliance and conductance were then averaged over the 5 s period of data acquisition.

The occlusion method [9] was applied at the end of relaxed inflation (fig. 1): the valve occlusion was manually driven by means of an electric switch. The occlusion was maintained during a two second period in the course of which the tracheal pressure always reached a plateau. The respiratory compliance (C_{OC}) was computed by dividing the inflated volume by the elastic pressure (difference between the plateau pressure and the end-expiratory pressure measured during the last ventilatory cycle prior to occlusion). The respiratory conductance (G_{OC}) was obtained by dividing the constant inspiratory flow preceding the occlusion by the resistive pressure (difference between the peak inflation pressure and the end-plateau pressure). The conductance values were corrected for that of the equipment but not for the finite time closure of the valves which has been reported to affect the airway conductance values obtained [11]. For each animal, at least three relaxed inflations were analysed at the basal state, all separated by about ten regular mechanical ventilation cycles in the course of which respiratory parameters were measured by the constant flow inflation method. During drug-induced bronchoconstriction, we retained for analysis the occlusions separated by sequences of regular mechanical ventilation that provided stable respiratory parameters with the constant flow method, in order to ensure that a comparable degree of bronchoconstriction was assessed by both methods.

For each animal, at the end of histamine or serotonin infusion, the absence of intrinsic positive end-expiratory pressure (PEEPi) was verified as follows: the respiratory circuit was occluded at the end of the expiratory phase, and after a two second equilibration period, the tracheal pressure was measured and found equal to barometric pressure.

Statistical analysis

Statistical analysis was performed using Students' t test for paired data and analysis of variance and covariance, with self-pairing and repeated measures, completed as necessary by paired t tests. Regression analysis was done by the least-squares method.

Results

When the constant flow method was applied, the correlation coefficient of the linear regression of P on V was higher than 99.7% in all animals, both in the basal state and during drug-induced bronchoconstriction.

The mean basal values ($\pm$SD) for respiratory compliance and conductance obtained by the constant flow and the occlusion methods are reported in table 1: no significant difference was found between C_{CF} and C_{OC}, nor between G_{CF} and G_{OC}.

Whatever the method used, the respiratory compliance values obtained during drug-induced bronchoconstriction

were significantly dependent on the factor drug ($p<0.001$) and on the factor dose ($p<0.001$), while the respiratory conductance values were independent of the factor drug but significantly dependent on the factor dose ($p<0.001$). The values of RC_{CF} and of RG_{CF} measured after each dose of the two drugs are provided in table 2.

Table 1. – Basal values of respiratory compliance and conductance obtained by both methods

	Constant flow method	Occlusion method
C ml·kPa^{-1}	3.76±0.48	3.72±0.44
G ml·kPa^{-1}·s^{-1}	30.9±3.7	30.5±4.6

Mean values±SD for total respiratory system compliance (C) and conductance (G) obtained in the basal state (n=22).

Table 2. – Values of respiratory compliance and conductance obtained by the constant flow method during drug-induced bronchoconstriction

	Histamine		Serotonin	
	dose 1	dose 2	dose 1	dose 2
RC_{CF} %	77±7	57±9	86±4	73±7
RG_{CF} %	69±13	45±16	64±16	42±10

Mean values±SD for respiratory compliance (RC_{CF}) and conductance (RG_{CF}) during drug-induced bronchoconstriction, measured by the constant flow method, and expressed as a percentage of the corresponding basal values (n=11). Dose 1 and dose 2 correspond to a continuous 5 min infusion of drug, at a constant mass flow of 100 and 150 ng·kg^{-1}·s^{-1} respectively.

During histamine- or serotonin-induced bronchoconstriction, very strong correlations were found between RC_{CF} and RC_{OC} on the one hand (r=0.96, p<0.001), and between RG_{CF} and RG_{OC} on the other (r=0.97, p<0.001), as illustrated by figures 2 and 3. The slopes of the linear relationships were not significantly different from unity in both cases.

Significant differences were, however, observed between the two methods for assessment of respiratory responses, but these differences were found to be independent of the factor drug, on the one hand, and of the factor dose, on the other. The values for compliance, expressed as a percentage of the basal values, were lower with the constant flow method ($RC_{CF}<RC_{OC}$, p<0.001), while those for conductance were higher ($RG_{CF}>RG_{OC}$, p<0.001). Although significant, the differences in bronchoconstriction assessment by both methods were very small since the mean difference between RC_{OC} and RC_{CF} was only 3.1%, and that between RG_{CF} and RG_{OC}, 2.8%.
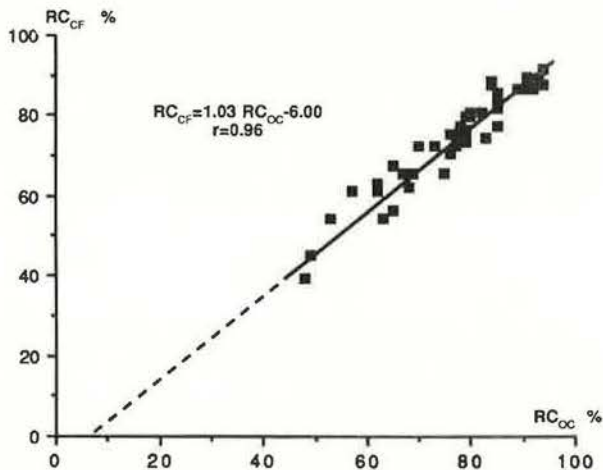
Fig. 2. – Identity plot between respiratory system compliances measured during drug-induced bronchoconstriction, with the constant flow method (RC_{CF}) and with the occlusion method (RC_{OC}), and expressed as a percentage of the corresponding basal values. Values obtained in the 22 animals for both drugs and both doses. Solid line: regression relationship over the actual data range; r: coefficient of correlation.
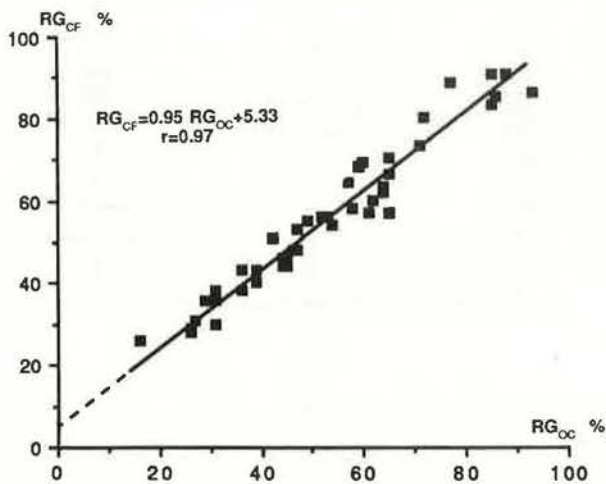

Fig. 3. – Identity plot between respiratory system conductances measured during drug-induced bronchoconstriction, with the constant flow method (RG_{CF}) and the occlusion method (RG_{OC}), and expressed as a percentage of the corresponding basal values. Values obtained in the 22 animals for both drugs and both doses. Solid line: regression relationship over the actual data range; r: coefficient of correlation.

Discussion

Among the numerous methods proposed to assess respiratory mechanics in anaesthetized mechanically ventilated mammals, the occlusion method is the only one which allows partitioning of respiratory conductance into central and peripheral components [9]. However, this partitioning becomes dubious during severe bronchoconstriction [10]. Furthermore, in the course of bronchial challenge, the time necessary for respiration parameters to reach a plateau, and the duration of the plateau may vary among animals. Thus, a method like the constant inspiratory flow method, which allows respiratory mechanics monitoring without the need to interrupt the

mechanical ventilation, appears attractive. The constant flow and occlusion methods have already been compared in the basal state in patients with respiratory failure [7] but never in normal mammals or during drug-induced bronchoconstriction.

With regard to the constant inspiratory flow method, the high value of the correlation coefficient of the linear regression of P on V illustrates the fact that the pressure signal is a linear function of time, and ensures that the steady state was virtually reached over the inspiratory phase selected for analysis. In this connection, it has to be noted that for ventilators providing a constant inspiratory flow i.e. a ramp of volume instead of a ramp of pressure, the time constant of the respiratory system is that of the visco-elastic component, which is smaller than one of those obtained for a ramp in applied pressure, as demonstrated in the Appendix. Thus, it does not appear surprising that the steady state was reached early, and that stress relaxation did not affect in any way the respiratory parameters, whatever the method used (see Appendix).

Under such conditions, assuming that a single-compartment model correctly describes the mechanical behaviour of the total respiratory system, the absence of a significant difference between the respiratory parameter values assessed by both methods can be considered as the expected result, as demonstrated in the Appendix. Our results are in agreement with those of Rossi et al. [7] obtained in patients with acute respiratory failure, and ventilated under positive end-expiratory pressure (PEEP) conditions. The underestimation of occlusion compliance observed by the same authors in patients ventilated under zero end-expiratory pressure (ZEEP) conditions was explained by recruitment of new lung units during lung inflation, since it disappeared when patients were ventilated under PEEP conditions. It is likely that, in our normal guinea-pigs, no recruitment of new lung units occurred during the very beginning of inflation in the basal state.

The doses of histamine and of serotonin used here were chosen in order to ensure moderate bronchoconstriction. Indeed, we previously observed that, during severe bronchoconstriction, the inspiratory pressure signal becomes a curvilinear function of time up to the end of the inflation phase: under such conditions, either the steady state is not reached, due to the presence of large and unequal time constants within the lung, or the respiratory mechanical parameters can no longer be considered as constant over the tidal volume range. The comparison of the two methods then becomes impossible: indeed, on the one hand the constant flow method cannot be applied, and on the other, the interpretation of the resistive and elastic pressures provided by the occlusion method becomes dubious as well as the respiratory parameter values derived from them.

In the present study, the drugs selected to induce bronchoconstriction were histamine, which constricts both central and peripheral airways, and serotonin, which predominantly constricts central airways [12]. Indeed, we wanted to ensure that bronchoconstriction assessment was, whatever the method used, independent of the specific

effects of each drug on the respiratory parameters. Therefore, the significant effect of the factor drug on the respiratory compliance parameter only may be easily explained by the predominant effects of each drug: histamine infusion reduces lung compliance and conductance comparably, while serotonin infusion reduces lung compliance less markedly than conductance [12]. Both drugs leave chestwall compliance and conductance values unaffected. The significant effect of the factor dose illustrates the fact that for higher doses bronchoconstriction is more severe.

Whatever the drug used, and whatever the dose of this drug, very strong correlations were observed between RC_{CF} and RC_{OC} on the one hand (fig. 2) and between RG_{CF} and RG_{OC} on the other (fig. 3), and the values of the slopes of the regression lines were not significantly different from unity. These results validate the assessment of bronchoreactivity in the course of moderate bronchoconstriction by the constant flow inflation method. Nevertheless, the two methods provide small but significantly different assessments of this reactivity: using the constant flow instead of the occlusion method, the animals appear a little more reactive if the respiratory response is assessed from changes in compliance, while they appear a little less reactive if the response is assessed from changes in conductance. This very small discrepancy of about 3% is not attributable to lung unit recruitment, which requires an additional pressure to reopen airways and/or air-spaces [7], and which would have resulted in an overestimation of resistive pressure appreciated by the constant flow method, and in a decrease in compliance estimated by the occlusion method. It is more likely that, in some animals, the visco-elastic properties of the lungs may have been altered by the infused drug or the mechanical ventilation, thus leading to a small increase in the time constant of the visco-elastic component. Under such conditions, in spite of the high correlation observed, the linear regression analysis used in the inflation method may have taken into account the very end of the transient phase when the exponential function of equation 2 (Appendix) could not yet be disregarded. The fact that the steady state was not completely achieved could have resulted in a small underestimation of respiratory compliance and thus a small overestimation of respiratory conductance. Consequently, the constant flow method could present limitations in assessing severe bronchoconstriction due to the presence of unequal time constants within the lung. However, it is worth noting that the small discrepancies observed between the two methods were found, in this study where mild degrees of bronchoconstriction were induced, independent of the dose.

In conclusion, this is the first study comparing the constant flow and the end-inflation occlusion methods in the basal state and during drug-induced bronchoconstriction, in normal guinea-pigs. The main advantages of the constant flow method are its applicability to ventilated animals without the need to interrupt mechanical ventilation, and therefore its adequacy for respiratory parameter monitoring in the course of bronchial challenge. Our observations indicate that both methods provide comparable results in the basal state as well as during drug-induced mild bronchoconstriction. The respiratory mechanical parameters and the degree of bronchoconstriction can therefore be accurately assessed by the constant flow inflation method, provided that assessments are made during the phase of inflation corresponding to the steady state period.

Appendix

Consider the physical model proposed by BATES et al. [13] to describe the mechanical behaviour of the lung (fig. 4). This model is one of the simplest which accounts for stress relaxation. It may be used to describe the mechanical behaviour of the respiratory system in guinea-pigs whose chest wall compliance and conductance are markedly higher than their pulmonary compliance and conductance [14], and therefore contribute little to the tracheal pressure required for a given ventilation.
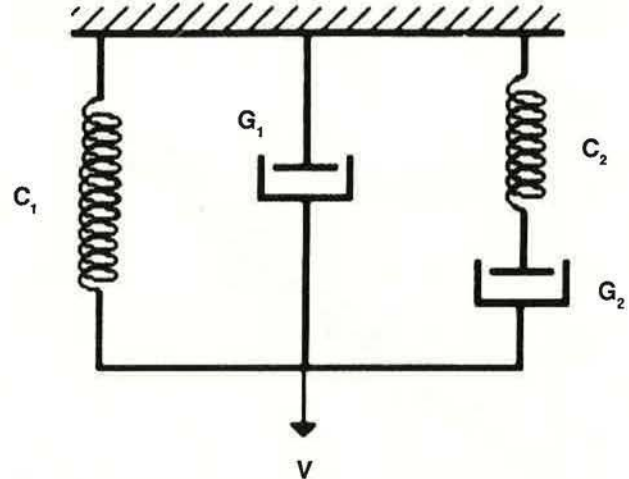

Fig. 4. – Four-element visco elastic model of respiratory system mechanics. G_1: airway conductance; G_2: tissue conductance; C_1: respiratory system compliance; C_2: tissue compliance generating stress relaxation; V: volume.

In such a model, G_1 corresponds to airway conductance; C_1 to respiratory system static compliance; G_2 to tissue conductance, and C_2 to the tissue compliance which generates stress relaxation.

The equation of motion of the model may be easily obtained as:

$$P+C_2/G_2 \cdot \dot{P}=1/C_1 \cdot V+(1/G_1+1/G_2+C_2/C_1 \cdot G_2) \cdot \dot{V}+C_2/G_1 \cdot G_2 \ddot{V} \quad (1)$$

where $\dot{P}$ and $\dot{V}$ are, the first time derivatives of P and V respectively, and $\ddot{V}$, of the second time derivative of V.

In response to a ramp-applied volume, V=at, corresponding to a constant inspiratory flow $\dot{V}$=a, the term including $\ddot{V}$ vanishes and the respiratory system reaches its steady state with a time constant equal to $-C_2/G_2$, which corresponds to that of stress relaxation, according to the following equation:

$$P=a/G_1+a/G_2[1-\exp(-tG_2/C_2)]+(1/C_1)at \quad (2)$$

In response to a ramp-applied pressure, the steady state is reached with two time constants t_1 and t_2 which are both real and negative, and verify $t_1 < -C_2/G_2 < t_2$. It is thus reached less rapidly than in response to a ramp-applied volume.

If a ramp-applied volume is applied (equation 2), when the steady state has been reached, the exponential function becomes negligible, and the constant flow inflation method allows determination of $C_{CF}=C_1$, as the inverse of the slope of the linear regression of P on V, and of $1/G_{CF}=(1/G_1+1/G_2)$ as the ratio of the intercept on the pressure axis to the constant flow. If an occlusion is performed, the ratio of resistive pressure to constant flow, after the steady state has been reached, similarly provides $1/G_{OC}=(1/G_1+1/G_2)$, and that of inflation volume to elastic pressure, $C_{OC}=C_1$.

During the steady state, the two methods can therefore be expected to provide similar assessments of respiratory compliance and conductance.

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Comparaison des methodes à débit constant et des methodes d'occlusion pour l'appreciation de la broncho constriction chez le cobaye. A.M. Lorino, M. Benichou, T. Kochi, H. Lorino, J. Milic-Emili, A. Harf

RÉSUMÉ: Les valeurs de compliance (C) et de conductance (G) du système respiratoire obtenues par deux méthodes (méthode de débit inspiratoire constant et méthode d'occlusion) ont été comparées à l'état de base, et au cours de tests de bronchoprovocation à l'histamine et à la sérotonine chez 22 cobayes normaux, anesthésiés et ventilés. A l'état de base, aucune différence significative n'a été trouvée entre les valeurs de C et de G déterminées par chacune des deux méthodes. Au cours des tests de bronchoprovocation, des différences faibles, mais significatives, ont été observées entre les mêmes paramètres respiratoires mesurés par les deux méthodes et exprimés en pourcentage de leurs valeurs de base respectives (RC_{CF} et RC_{OC}, RG_{CF} et RG_{OC}). Ces petites différences, indépendantes et de la drogue et de la dose, sont vraisemblablement dues à une modification des propriétés viscoélastiques du poumon, induites soit par la ventilation mécanique, soit par la substance perfusée. Cette étude démontre cependant que les deux méthodes peuvent être considérées comme équivalentes pour l'évaluation de la bronchoconstriction, parce que d'une part, de très fortes corrélations ont été trouvées entre RC_{CF} et RC_{OC} (r=0.96, p<0.001) et entre RG_{CF} et RG_{OC} (r=0.97, p<0.001), et que d'autre part les pentes des droites de régressions ne sont pas significativement différentes de l'unité.