Mecholyl aerosolized in the surrounding lung increases the resistance of the collateral pathways

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ABSTRACT: Collateral ventilation allows gas exchange in pulmonary units distal to an airway obstruction. Regional control of this airflow may be possible because smooth muscle exists in the wall of collateral pathways. Evidence of an intrasegmental cholinergic control of these pathways has been previously shown. We performed this study to investigate the possible control of collateral ventilation by cholinergic receptors situated in the surrounding lung. By using the wedged catheter technique, we measured collateral resistance before and after aerosolization of methacholine in the lung surrounding the wedged segment: both collateral resistance and the time constant for collateral ventilation increased, proving that a cholinergic stimulation in the surrounding lung can influence collateral pathways. Fast and complete reversibility was obtained after isoproterenol or atropine injection. Collateral obstruction would seem to be due, therefore, to a muscular spasm. The effective compliance of the wedged segment decreased during the spasm induced by mecholyl in the surrounding lung, and could be attributed to an increased Interdependence of this segment with surrounding segments. This effect was immediately reversed by intravenous bronchodilators. We conclude that cholinergic receptors on the smooth muscles of the external collateral channels can control collateral ventilation.

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The complete obstruction of an airway is not always followed by alveolar collapse; ventilation and gas exchange distal to an obstruction can be well preserved through the collateral ventilation [1]. Whether the ventilation that bypasses the obstructed airway is provided by alveolar pores, bronchial alveolar communications or respiratory bronchioles connecting terminal bronchioles from adjacent lung segments is not known [2], but bronchoalveolar channels and bronchioles probably provide the major pathways for collateral ventilation [3]. Since the bronchoalveolar channels and the bronchioles have a muscular wall of their own [4], regional control of airflow seems possible. Therefore, collateral pathways should be influenced by cholinergic and sympathetic stimulation and inhibition. This control may be located intrasegmentally (within the segment), intersegmentally, at the external opening of channels leading towards the surrounding lung or within the surrounding segments. Intrasegmental methacholine injection increases the resistance to collateral flow [5]. Control of the collateral channels by the surrounding lung could also occur, but has never been shown. In this study, we examine whether a cholinergic agent (methacholine), aerosolized throughout the lung (except in the isolated wedged segment), can increase collateral resistance. If this is the case, one could conclude that the cholinergic stimulation can limit the flow through collateral pathways in the external parts of the wedged segment.

The activity of methacholine on small airways and collateral pathways could be due to muscular constriction, mucus oedema or mucus plugging. If the variations observed after mecholyl were due only to muscular constriction, the intravenous injection of bronchodilators should reverse them. However, this would not be the case if these changes were caused either by mucosal oedema or by mucus plugging.

Material and methods

Twelve adult mongrel dogs were anaesthetized with pentobarbital (30 mg·kg⁻¹) and paralysed with pancuronium bromide (0.1 mg·kg⁻¹). The dogs were intubated and ventilated with the same tidal volume and rate as previously recorded during spontaneous ventilation, with periodical sighs. Airway opening pressure was measured at the endotracheal tube outlet by a Sunborn differential transducer, and oesophageal pressure was measured on the other side from a balloon (5 cm length; 0.5 ml content) placed in the lower third of the oesophagus [6]. The difference between these two pressures provides transpulmonary pressure (Pt). Flow was measured at the endotracheal tube outlet with a Fleisch pneumotachograph. The signal of Pt and flow were applied to an analogue
computer 'respiratory preamplifier UCB' as described by LULLING et al. [7] to obtain pulmonary resistance (Rt) and pulmonary dynamic compliance (Ct).

To study the resistance of the collateral pathways (Rcoll), we used Hilpert's technique as modified by SMITH et al. [5]. A double-lumen catheter (2 mm external diameter) was wedged into a peripheral bronchus under the direct vision of a fiberoptic bronchoscope. The catheter was pushed during lung inflation to assure perfect wedging. Wide variations in collateral ventilation are observed according to the lobe where the catheter is situated, with the longest time constant in the right middle lobe. We avoided this effect by wedging the catheter in the nondependent bronchi. One lumen provided a channel for the constant infusion of gas (V) while the second lumen allowed the measurement of pressure distal to the tip of the catheter (Pb). V was administered via a Fisher and Porter flowmeter (Flowrator tube No. FPI/16-20-6-5/36, air calibration G 9143 B, with sapphire and stainless steel beads, measuring flows between 0.05 and 7 ml·s⁻¹), into the wedged segment of the lung until a steady-state of end-expiratory Pb was reached (mean flow: 2 ml·s⁻¹). The ventilator was then stopped and measurements were made at functional residual capacity (FRC) to avoid changes due to the volume level [6]. When flow through the wedged segment was discontinued, Pb decayed as the obstructed segment emptied through the collateral pathways (fig. 1).

In some dogs, an obvious initial fast drop in Pb was followed by an exponential decline: the fast drop was attributed to the resistances in the intrasegmental airways, whereas the subsequent gradual decline of Pb was attributed to deflation of the distended obstructed segment through collateral channels [5] (fig. 1). When plotted as a percentage of pressure change on semilogarithmic paper, the gradual decline of Pb approximated a single exponential curve: thus the rate at which the pressure decreases can be conveniently described as the time it takes to decrease 63% (Tₑ) of the total decrease [9]. In some dogs, stopping the flow was associated with an obvious initial fast drop (fig. 1); this difference in the speed of Pb decline occurred in most control measurements, but was perceived only by calculation in some animals, and was not immediately obvious by inspection. To calculate intrasegmental airway resistance (Rsaw) and the mechanics of collateral ventilation, measurements of Pb were made every 0.2 s for 1 s after stopping the flow (fig. 1). The pressure in the obstructed segment of the lung prior to stop flow (Ps) was calculated from an extrapolation through zero time of the least-square linear regression of the logarithm of the 0.2 s measurements of Pb. Pb - Ps at zero time was assumed to represent the pressure drop in the airways during the constant flow [5, 10]. The control values of Rsaw are sometimes so low that they cannot be measured accurately [2].

The following calculations were made from the data:

\[ Q = 1 \text{ ml/s} \]

\[ \begin{align*}
\text{Pb} & = 12.5 \text{ cmH}_2\text{O} \\
\text{Ps} & = 7.5 \text{ cmH}_2\text{O} \\
\text{r} & = 0.96 \\
\text{T} & = 0.9 \text{ s} \\
\text{Rsaw} & = 4.25 \text{ cmH}_2\text{O/ml/s} \\
\text{Rcoll} & = 8 \text{ cmH}_2\text{O/ml/s} \\
\text{Cs} & = 0.112 \text{ ml/cmH}_2\text{O} \\
\end{align*} \]

Fig. 1. Diagram of an example of measurement (dog 7). The top panel shows the decay of Pb when flow is stopped, Q is the flow before stop. 't' is time (s). The middle panel shows the values of Pb (○) at 0.2 s intervals during the decay: the pressure in the obstructed segment of the lung prior to stop flow Ps (●), is calculated as described in the protocol; Pb - Ps at zero time is assumed to be the pressure drop in the airways during constant flow. 'r' is the regression coefficient of the decrease of pressure; T is the time constant of collateral ventilation; Rsaw is the computed resistance of small airways in the segment. Rcoll the collateral resistance and Cs the effective compliance of the segment.
- resistance to collateral ventilation $R_{coll} = \frac{P_x - P_y}{V}$;
- airway resistance within the obstructed segment $R_{aw} = \frac{P_b - P_x}{V}$. The theoretical definition of $R_{coll}$
is $R_{coll} = \frac{P_x - P_{av}}{V_{coll}}$, where $P_{av}$ is the alveolar pressure of the surrounding lung, but in practice $P_{av}$
is assumed to be equivalent to airway opening pressure (or atmospheric pressure in apnoea at FRC).

This assumption is valid in control conditions since $P_b$ decayed to atmospheric pressure. If constriction or closure between alveoli and airway opening occurs after challenge, the assumption will underestimate $P_{av}$ and overestimate $R_{coll}$. $R_{coll}$ would then represent the sum of collateral resistance and of the resistances of the pathways between alveoli and airway opening. The contribution of the latter resistances is small since their values are far lower.

- time constant for collateral ventilation ($T_{coll}$): $T_{coll}$ is defined as the time for $P_x$ to decrease 63% during the single exponential decrease of $P_b$. Since the time constant is determined by the product $R_{coll} \times C_s$ (effective compliance of the segment), the compliance of the obstructed segment $C_s = T_{coll} \times R_{coll}$ [9].

As in previous studies, wide variations of the control values were observed: this range depends on the volume of the wedged segment, the volume of the surrounding segment and their relationships to the pleura. Therefore most results will be expressed as a percentage of the control values, to compensate for their fluctuations. The statistical significance was tested by using a variance analysis. The study has been performed in 12 dogs according to this protocol: the measurements were performed before and after a bronchospasm induced by aerosolized methacholine. The drug was aerosolized in the tracheal tube, during mechanical ventilation, with a DeVilbiss 42 nebulizer (mass median diameter of the aerosol particle, MMAD: 3.8 μm; geometric standard deviation, GSD: 2.8 μm, allowing maximal bronchopulmonary deposition) for 2 min, with concentrations increasing from 0.25 to 50 mg·ml⁻¹, to the point where no further increase of $R_t$ could be registered; the measurements were performed 2 min after the end of the aerosol.

The reversibility of the increase in $R_t$ observed after mecholyl aerosol was tested by injecting 0.4 mg isoproterenol intravenously in seven dogs, immediately after the measurements. In four other dogs, 0.5 mg atropine was injected intravenously. The measurements were repeated 4 min after (7–8 min after the end of the challenge). In some dogs where bronchodilators were not injected, the increase of $R_{coll}$ was still stable at 13 min.

Results

The results for the twelve dogs after aerosolized mecholyl are summarized in figure 2. During the induced bronchoconstriction, we observed a mean increase of $R_t$ from 2.2 to 6.9 cmH₂O·l⁻¹·s (p < 0.01). The mean $C_l$ decreased significantly from 137 to 41 ml·cmH₂O⁻¹ (p < 0.001). $R_{aw}$ varied in various directions without any significant tendency. A systematic increase in collateral resistance (mean: +1370%) followed the aerosol. The range of control values was so wide (fig. 3) that the statistics had to be computed from logarithmic values to allow us to test for significant differences (p < 0.01). In figure 3, we plotted the $R_{coll}$ values after mecholyl challenge against their values in control conditions (logarithmic scale): all values after mecholyl are above the line of identity. $T_{coll}$ also increased significantly (mean: +83%) (p < 0.05), with the exception of two dogs (fig. 2). Since mean $R_{coll}$ had increased more than mean $T_{coll}$, mean $C_s$ decreased significantly (mean: −44%; p < 0.01).

The results of the effects of isoproterenol on mecholyl-induced spasm in seven dogs are summarized in figure 4. After an increase in $R_t$ of 146% after mecholyl aerosol (p < 0.02), we observed a rapid decrease to nearly control values with isoproterenol.
Fig. 3. Effect of aerosolized metholyl on the collateral resistance, $R_{coll}$. Metholyl values are on the ordinate, and controls, on the abscissa. Identity line is shown, and all points are above.

The same evolution was observed on $C_l$ measurements, with a decrease of 70% after metholyl ($p<0.01$), increasing to nearly control values after isoproterenol ($p<0.05$). No significant change was observed in $R_{saw}$ (but measurable control values in four dogs only). However, $R_{coll}$, the mean of which had increased markedly after metholyl, decreased significantly towards control values after isoproterenol injection ($p<0.01$ versus metholyl, NS versus control values). The increase in mean $T_{coll}$ (+52%) after metholyl (five out of seven dogs) was reversed after isoproterenol (NS). After the decrease of $C_s$ due to metholyl ($-45$%; $p<0.05$), the injection of isoproterenol restored the mean $C_s$ to control values ($p<0.05$, statistics on logarithmic values).

The results of the effects of atropine on metholyl-induced bronchospasm are summarized in figure 5 (four dogs). After an increase of $142$% ($p<0.02$) due to metholyl, mean $R_l$ decreased significantly ($-52$%) after atropine. $C_l$ decreased after metholyl ($-54$%; $p<0.05$) and increased again after bronchodilators with wide variation (NS). No significant changes were observed in mean $R_{saw}$ (three dogs only). After a metholyl-induced increase in three out of four dogs (mean $86$%; NS), mean $R_{coll}$ decreased significantly after atropine ($-63$%; $p<0.01$). $T_{coll}$ increased after methacholine (mean: $+148$%; $p<0.05$); it diminished after atropine in three dogs. $C_s$ increased after atropine ($p<0.05$), since a significant decrease of $R_{coll}$ accompanied a smaller decrease of $T_{coll}$.

Discussion

The collateral pathways between a segment and the surrounding lung could theoretically be divided into three zones, according to the control of their aperture. Their calibre could be controlled either by tension exerted by fibres from the lung surrounding the wedged segment, as in case of lung volume and $P_l$ changes, by tension exerted by lung fibres within the wedged segment, or finally by tension within the walls of the channels. The fibres of the walls of the channels can be located intrasegmentally, intersegmentally or at the external opening of the channels in the surrounding lung. These last fibres are supposed to be the most sensitive to the aerosolized metholyl which reaches only the non-wedged lung.

Of course, the resistance of the airways and collateral pathways of the surrounding lung will also
decrease the Rcoll by acting on the tension exerted by fibres from the surrounding lung. Since we observed co-


collar pathways of the obstructed segment and to influence Tcoll and Cs. Nevertheless, since atropine, as well as isoproterenol, were able to immediately reverse the constrictive action of mecholyl on Rcoll and Cs, this constrictive action must be attributed to a direct effect on the smooth muscle tone, and not to other more persistent phenomena like mucosal oedema or mucus plugging.

**Conclusion**

Mecholyl aerosolized in the surrounding lung increased the collateral resistance of a wedged segment. This effect could be immediately inhibited by intravenous injection of isoproterenol or atropine. We conclude that cholinergic receptors on smooth muscles can control the collateral ventilation at the external way out of the collateral channels, in the surrounding lung. Their action must be additional to that of intrasegmentally or intersegmentally located cholinergic receptors described in previous studies [5].
References


RÉSUMÉ : La ventilation collatérale permet des échanges gazeux entre une unité isolée de la voie bronchique par obstruction et les unités pulmonaires adjacentes. Contrairement à ce qui est le cas pour les unités collatérales, le contrôle de la résistance collatérale dépend à la fois de la compliance du segment et de sa perméabilité à l'air. En cas d'obstruction, la ventilation collatérale du poumon apparaît comme l'entraînement d'un spasme cholinergique du segment adjacent, mais les récepteurs cholinergiques situés dans les unités adjacentes n'ont pas moins une partie du contrôle. Nous avons tenté d'élucider ce point en utilisant chez le chien la mesure de la résistance collatérale par la technique du cathéter bloqué. Cette technique permet la mesure de la résistance collatérale, de la constante de temps de la ventilation collatérale du segment et de sa compliance effective. Après induction d'un spasme cholinergique par aérosol de méthylxyl dans le poumon adjacent, ces paramètres ont été mesurés ; des mesures ont ensuite été faites après des injections ultérieures d'isoproterénol ou d'atropine. L'aérosol de méthylxyl augmente la résistance collatérale et la constante de temps, ce qui montre que la stimulation cholinergique des segments environnants entraîne une contraction des voies collatérales. Le fait qu’une réversibilité rapide et complète survienne après injection d’isoproterénol ou d’atropine démontre que l’obstruction de la voie collatérale est due à un spasme des muscles lisses, et non à des phénomènes comme l’œdème de la muqueuse ou des bouchons de muqueuses. La compliance du segment bloqué a également diminué durant le spasme cholinergique du poumon avoisinant, ce qui peut être attribué à l'interdépendance entre ce segment et le poumon environnant. Cet effet a aussi été immédiatement inhibé par les bronchodilatateurs. On peut en conclure que les récepteurs cholinergiques des muscles lisses situés sur le versant externe des canaux collatéraux peuvent aussi exercer un contrôle sur la ventilation collatérale du poumon.