THE INFLUENCE OF BRONCHIAL SMOOTH MUSCLE TONE ON CRITICAL NARROWING OF DEPENDENT AIRWAYS

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SUMMARY

Critical narrowing of the dependent airways was examined in anaesthetised dogs with closed chests. Two techniques were used, (a) "closing" volume (CV), measured from the expired nitrogen plateau and (b) tantalum bronchography, to measure the calibre of airways of 3-8 mm diameter in the upper (UZ), middle (MZ) and lower (LZ) zones. The point of airway "closure" at the junction of phases III and IV of the alveolar plateau coincided with an inflection in the diameter-lung volume curve of the airways in the most basal zone of the lung. This was accompanied by a sudden large increase in the calculated resistance of the airways in LZ compared with UZ. Following stimulation of the vagi, CV increased and there was increased narrowing of airways, particularly in LZ. The addition of 0.5% halothane to the anaesthetic abolished the effect of vagal stimulation on CV and on airway resistance.

Experiments on lungs, whether isolated or in vivo with the chest wall opened, have shown that, as the volume decreases, there is a reduction in the diameter of both alveoli (Klingele and Staub, 1970) and conductive airways (Hahn, Graf and Nadel, 1976). In these experiments the pressure across the walls of the airways was evenly distributed and the changes in airway calibre occurred uniformly throughout the whole lung. However, when the chest wall is intact, the lungs are suspended from the chest wall in such a way that the upper parts of the lung are much more stretched than the dependent parts and it has been shown histologically that, with diminishing lung volume, alveoli in the dependent parts of the lung show much greater changes in diameter than those in the upper parts of the lung (Glazier et al., 1967). Direct demonstration of closure of dependent airways has not yet been reported, critical narrowing of conducting airways being deduced using a variety of techniques reviewed by Jones (1975). The expired tracer gas technique is used most widely; in this method the expired tracer concentration is analysed to find the point of inflection at the junction of phases III and IV of the alveolar plateau. This point is widely believed to represent the onset of closure in conducting airways in the dependent zone of the lung, phase IV of the alveolar plateau commonly being referred to as the "closing" volume (CV).

In most subjects the elasticity of the lung parenchyma is the major determinant of the lung volume at which dependent airways begin to close. Smoking or asthma, however, produce narrowing of small airways, resulting in an increase in the lung volume at which airway closure begins (McCarthy and Milic Emili, 1973), and it has been shown recently that the inhalation of a histamine aerosol results in an acute increase in the closing volume (Benson, Newberg and Jones, 1975). It is not clear from these experiments whether these acute changes in closing volume result from changes in the tone of airway smooth muscle, from an increase in airway mucus, or from a change in the mechanical properties of the lung. The functional consequences of the changes are relevant to the practice of anaesthesia, in which changes in the calibre of dependent airways may contribute to the abnormality of gas exchange which frequently occurs; these may cause trapping of soluble gas with subsequent absorption collapse which, in the period after operation, may predispose to pneumonitis and continued impairment of gas exchange. We also postulated that, during anaesthesia, stimulation of the powerful autonomic reflexes that follow mechanical irritation of the respiratory tract (Widdicombe and Sterling, 1970) may enhance the narrowing of airways in the dependent areas of the lung, but that this effect might be modified by the subsequent administration of volatile anaesthetic agents.
METHODS

Dogs weighing 15–23 kg were anaesthetized with chloralose 50 mg kg$^{-1}$ i.v. and urethane 500 mg kg$^{-1}$ i.v. The dogs were paralysed by periodic injections of suxamethonium 4 mg kg$^{-1}$ i.v. and the lungs were ventilated with room air, using a Harvard respirator connected to a tracheal tube inserted via a cervical tracheostomy. Tidal volume was set at 10 ml kg$^{-1}$ and the rate adjusted to maintain normal $P_{a \text{CO}}$$_2$ values. Three dogs received also halothane 0.5% for 15 min before measurements of CV and airway resistance. Metabolic acidosis was corrected by intermittent i.v. injections of a solution of sodium bicarbonate 1 mmol litre$^{-1}$ according to the results of measurements of arterial pH. Incremental doses of anaesthetic agent were given in response to changes in heart rate or arterial pressure or the presence of lacrimation or salivation. End-tidal carbon dioxide was monitored continuously using a Beckman model LB2 infra-red analyser. Arterial pressure was recorded from a femoral artery catheter connected to a Statham model DB23 pressure transducer. Airway and oesophageal pressures were measured using a Statham model PM 131 TC differential pressure transducer.

All dogs were studied in the supine position. The closing volume was measured by a modification of the single breath oxygen test (Lemen et al., 1975): after three lung inflations to an airway pressure of 30 cm H$_2$O the airway pressure was reduced to −5 cm H$_2$O and the lungs were inflated with a volume of oxygen sufficient to achieve an airway pressure of 30 cm H$_2$O. This volume of oxygen was used for all subsequent CV manoeuvres. After inflation, slow controlled expiration at 0.1 litre s$^{-1}$ through a Fleisch No. 0 pneumotachograph was achieved by means of a needle valve and vacuum source. The end-point of expiration was an airway pressure of −20 cm H$_2$O and then when deflated stepwise to the point of maximum expiration at an airway pressure of −20 cm H$_2$O. A focal spot to film distance of 100 cm was used with 100–500 mA, 90–120 kV technique. The lateral radiographs at full inflation were divided into three equal horizontal zones, upper, middle and lower; and at least five airways, 3–8 mm diameter, were identified and measured in each zone using an eye-piece micrometer. The results of these measurements gave a mean diameter of all the measured airways in each horizontal zone. These measurements were compared with those obtained from radiographs taken at fixed volumes during expiration.

In each animal the vagus nerves were dissected out and studies of closing volume, airway resistance and lung recoil pressure were made before sectioning the nerves. These studies were repeated following vagal section and again when both nerves were stimulated electrically (model S4DR, Grass Instruments, Mass.) at 0, 3, 5 and 7 V, using square-wave pulses at 30 s$^{-1}$ with a 3-ms pulse width. In each case the period of stimulation was 10 s. Three animals were studied before and after adding halothane 0.5% to the anaesthetic; measurements were made of closing volume and airway resistance with and without electrical stimulation at 7 V.
RESULTS
The mean closing volume in eight dogs studied with the vagi intact was 28% of the expired volume with a range of 24–30%. After dividing the vagi there was no significant change in closing volume in any of the animals of this group. The alveolar nitrogen plateau, airway pressure and lung recoil pressure for one experimental animal are shown in figure 1.

The mean airway resistance was 1.6 cm H₂O litre⁻¹ s (SD 0.17). Following vagotomy, the mean resistance showed a 12% reduction to 1.4 cm H₂O litre⁻¹ s (SD 0.1). There was no change in the recoil pressure curve of the lung after sectioning the vagi.

Following vagal stimulation at 3 V there was no significant change in expired volume, closing volume, airway resistance or lung recoil pressure curve. Stimulation at 5 and 7 V produced a significant increase in closing volume and in airway resistance (fig. 2). With a 5-V stimulus the increase in closing volume exceeded the increase in airway resistance, but at 7 V the increase in resistance was greater than the increase in closing volume. At these levels of stimulation the heart rate slowed by about 20% with 5 V stimulation and there was marked bradycardia at 7 V. Stimulation of the vagi with more than 7 V produced a very large increase in airway resistance but the closing volume inflection point could not be identified. In some animals, although distinct inflections between phases III and IV were obtained at 7 V stimulation, a small increase of as little as 1 V gave a variable result: there was either a flat plateau or a changing slope throughout expiration. With 0.5% halothane the expired nitrogen signal was “noisy” but similar to that reported with sulphur hexafluoride (Newberg and Jones, 1974); nevertheless, the traces showed a clearly defined inflection point. The closing volume and airway resistances with halothane were indistinguishable from control observations with the vagi cut, and the increase in closing volume and airway resistance following 7 V stimulation was virtually abolished by halothane.

Tantalum bronchograms
The mean value of the 3–8 mm airway diameters in the upper, middle and lower zones of the lung in three animals are shown in figure 3. The airway diameters of each zone are expressed as a percentage of the diameter at full inflation and the curves show the effect of change in lung volume and of vagal stimulation at 7 V.

The greatest change in airway diameter was found in the lower zone, where the diameter at maximum expired volume was 30% of that obtained at full inflation; in contrast, the minimum diameters in the upper and mid zones were 70% and 60% of control respectively. In figure 4A these data are expressed as an isovolume plot for airway diameter in the vertical plane of the supine lung. Assuming that airways at the dependent part of the lung collapse at minimum volume, a graphical model of the lung was constructed by extrapolating each isovolume line to a hypothetical uppermost and lowermost point of the lung; the volume isopleth at 0% VC is forced through an airway.
Vagal stimulation sufficient to produce a clearly identifiable inflection on the alveolar nitrogen plateau gave quite consistent changes in airway calibre. Change in airway diameter in the mid and lower zones was greater than that seen in the upper zone. This effect was dependent on lung volume; at full inflation there was no measurable effect of vagal stimulation on airway diameter in the upper and mid zone, but in the lower zone there was an 8% reduction in diameter of zero. This suggests that the reduction in airway diameter is fairly uniform at first, with the largest degree of reduction in the lower zone. Below 35% of the vital capacity (65% expired volume) the changes in diameter of airways in the lower zone occur much more rapidly than in the other two zones. For these three animals the mean closing volume was 29% of the expired volume and this coincided with the volume over which instability was observed in the lower zone. Over this volume range measurements of oesophageal pressure indicated that the elastic recoil pressure in the lower zone was 2 cm H₂O or less, and instability in the dependent airways is associated with this critically low recoil pressure.

![Airway Diameters from Tantalum Bronchograms](image)

**Fig. 3.** Airway diameters from tantalum bronchograms, plotted against expired volume in three dogs. Data for the upper (UZ), middle (MZ) and lower zones (LZ) of the supine lung, viewed laterally, are shown. Closed circles indicate vagi unstimulated, open circles vagi stimulated electrically.

![Airway Diameter Plots](image)

**Fig. 4.** A: The data from figure 3 were used to construct a graphical model to illustrate the effect of reduction in lung volume on the change in airway diameter extrapolated through the three zones. Airway diameters from figure 3 expressed as isovolume plots to show change in diameter down the lung from upper zone (UZ) to lower zone (LZ) during expiration to residual volume. Note the rapidly changing calibre in LZ in the last 25% of vital capacity (VC). B: The effect of vagal stimulation on the change in airway calibre during expiration.
compared with the unstimulated control. The reduction in diameter at maximum expired volume was least in the lower zone and largest in the upper two zones.

When airway diameter, following vagal stimulation, was expressed as a series of isovolume curves (fig. 4B) the general pattern of the curves was different from that seen in the isovolume curves of the unstimulated airways; there was no particular inflection on the curves to suggest a lung volume at which airways became unstable. In the experiments with vagal stimulation the closing volume increased from a mean value of 29% VC to a mean value of 38% VC. Extrapolation of these data to the most dependent part of the lower zone (fig. 5A) showed an inflection point at 30% VC (70% expired volume) on the diameter-volume curve of the unstimulated airway. This coincided with the onset of airway closure at a volume at which the diameter of the airways had decreased to about 58% of control. With vagal stimulation the closing volume, beginning at 38% VC, coincided with a reduction in airway calibre to about 45% of control.

**DISCUSSION**

This study demonstrated the relative contributions of the two main determinants of closing volume: (a) changes in airway calibre attributable to the elastic properties of the lung parenchyma and (b) intrinsic changes in airway calibre, produced by changes in vagal activity. In this group of anaesthetized animals the size of the closing volume with the vagus intact was unchanged following vagal section. CV increased with vagal stimulation but the increase was almost completely eliminated by the inhalation of 0.5% halothane. In these experiments the airway resistance showed a pattern of changes similar to those in closing volume but, because of the geometry of the airways, the resistance method is most sensitive to changes in the calibre of airways 5 mm or more in diameter (Macklem and Mead, 1967).

The dissociation of the effect of vagal tone on closing volume and airway resistance might also be explained by the different effects of vagal tone on airways of different size (Cabezas, Graf and Nadel, 1971). While vagal stimulation constricts all airways from the trachea to bronchioles 0.5 mm in diameter, the greatest degree of narrowing is in the 1–5 mm range. In our study, with the chest closed, it was too difficult technically to produce satisfactory pictures of airways smaller than 2 mm in diameter. When the vagi were stimulated at more than 7 V there was a marked increase in airway resistance but the closing volume inflection point could not be identified on the alveolar plateau. Widespread airway narrowing leads to a greater degree of air trapping in the dependent lung, regional differences in residual volume and, after a breath of oxygen, there is little or no vertical gradient in
nitrogen concentration. Despite extensive airway closure, there is no tracer gas gradient in the lung with which it can be demonstrated. In these circumstances a bolus method rather than a resident gas technique might have demonstrated a closing volume inflection (Benson, Newberg and Jones, 1975). In some of our animals, vagal stimulation produced a very steep alveolar nitrogen plateau, suggesting a wide distribution of the emptying time constants of terminal airway units.

The effect of halothane on closing volume and airway resistance is not surprising in view of previous studies of the effects of this anaesthetic on airway calibre (Hickey et al., 1969). In this study there was no significant effect of 0.5% halothane on the size of the closing volume or airway resistance of the vagotomized dog, but the increase in these variables with vagal stimulation at 7 V was virtually abolished by halothane. We did not study the effects of halothane on the closing volume or resistance following maximum vagal stimulation. The effect of halothane is probably directly on airway smooth muscle because it has been shown by Hickey and others (1969) that the bronchoconstrictive effect of histamine is antagonized by halothane. However, the bronchoconstrictor effect of severe hypocapnia is not reversed by halothane (Patterson et al., 1968).

This study showed also that, in the supine dog, the magnitude of the change in diameter of the airways during expiration depends upon their location in the vertical plane. Thus the uppermost airways change least and the lowermost dependent airways change most. When the data were replotted as a set of iso-volume curves, the change in calibre of the airways was seen to decrease suddenly in the lower zone, a point of instability being demonstrated which coincided with the onset of phase IV of the alveolar plateau. Instability of airway diameter is compatible with the hypothesis that the airways are held open by the elastic tissue of the lung parenchyma. Because of the vertical gradient of elastic recoil pressure, the distending pressure in the dependent lung is much less than in the upper parts of the lung; when this pressure decreases to about 20 cm H₂O the sudden large reduction in diameter of these dependent airways causes a disproportionately large increase in resistance of the lower zone airways. Calculations were made of the regional differences in resistance assuming laminar flow conditions in small airways. At 75% expired volume the resistance in the basal zone (BZ) airways was about 10 times greater than those in UZ and the difference that this would produce in regional time constants would be sufficient to alter suddenly the pattern of regional emptying without airway closure actually occurring. If the data extrapolated to the most basal zone are used to calculate the ratios of resistance UZ to BZ, then there is a very striking take-off in this ratio below 30% VC without vagal stimulation, and below 50% VC with stimulation. The tantalum bronchographic technique cannot be used as a method for identifying the site of airway closure because the method cannot discriminate between an open or closed lumen. Even when there is no further reduction in the diameter of an airway there is no certainty that its lumen has been occluded. These data are confined to 4–8 mm diameter airways as a model of other airways. It is, of course, quite possible that airways less than 4 mm in diameter might actually occlude, but the large regional change in resistance is quite sufficient to alter the emptying time constants of the upper and lower zone and produce an abrupt change in slope of the alveolar plateau.

It is of interest to compare these data on conducting airway instability with those of Klingele and Staub (1970) who examined the instability of alveoli in isolated lungs undergoing slow deflation. Some of their data are plotted in figure 5. In the ratio D/MD, D represents alveolar diameter and MD alveolar mouth diameter. The inflection at 50% lung volume represents a sudden reduction in mouth diameter. One might suppose that small airways at the lung base, intermediate in size between alveolar ducts and 4–8 mm airways, might also show an inflection point at a similar volume between 50 and 30% of lung volume.

With vagal stimulation, airway narrowing was extensive in all three zones but the instability observed in the unstimulated airways had disappeared. Bronchoconstriction has been suggested as a mechanism that stabilizes airways against collapse (Jones, Fraser and Nadel, 1975). Timoshenko (1936) has shown that the ability of a tube to collapse increases with diameter and is inversely proportional to the thickness of the wall. Thus, if bronchoconstriction occurs, the quotient diameter/wall thickness changes to give conditions much less favourable to collapse. Nevertheless, closing volume increased significantly in all animals, which suggested that the onset of the “closing” volume phenomena may well be a result of sudden large changes in regional airway resistance as much as to collapse of dependent airways. Subsequently, as lung volume is reduced during phase IV of the alveolar plateau there may be actual closure of dependent airways with consequential trapping of gas in upstream alveoli.
There is still controversy about the evidence for airway closure. Several very ingenious experiments have been published which strongly support the idea of actual occlusion of basal airways (Burger and Macklem, 1968; Engel, Grassino and Anthonisen, 1975). Both of these studies concluded that there was unequivocal evidence of airway closure. However, in both cases the lungs were held at very low volumes well within the closing volume, at a point at which few would disagree that some airways may have closed. Other workers have pointed out that inflection on the alveolar plateau can be produced by increasing expiratory flow (Jones and Clarke, 1969, 1970; Hyatt, Okeson and Rodarte, 1973) and dynamic compression of dependent airways is a likely explanation in these circumstances. Our conclusion is that a change in regional emptying pattern can be produced at any lung volume by sudden changes in flow. This results from regional differences of airway resistance produced by dynamic compression of airways. At slow rates of flow there is a point during expiration at which, because of the lower basal recoil pressure, dependent airways have narrowed to such an extent that sudden large changes in regional airway resistances occur, giving an inflection on the alveolar plateau at the onset of phase IV. With further reduction in volume some dependent airways may close also. The model proposed originally for the susceptibility of dependent airways to critical narrowing was a gravity-related gradient of pleural pressure down the lung, but this is now regarded as an oversimplification. This gradient is certainly not constant in any given lung, but can be altered by changing the shape of the chest wall and diaphragm (Grassino and Anthonisen, 1975; Roussos et al., 1976). Martin, Das and Young (1976), on the other hand, have pointed out that phase IV on the expired tracer gas plateau can be obtained not only from samples obtained at the mouth, but from intrapulmonary sampling of the expirate from lungs, lobes, segments and even subsegments of lobes. This raises serious questions about the origin of the phase IV phenomenon. Nevertheless, our study has demonstrated (a) a vertical gradient of airway diameters in the supine lung, (b) a preponderance of the effect of vagal stimulation in the lower zone where lung elastic recoil pressure is least and (c) changes in closing volume with vagal stimulation in keeping with the predominance of changes in calibre of dependent lung airways. The virtual abolition of many of these effects by halothane lends further support to its clinical use in the management of patients requiring tracheal intubation for the treatment of severe bronchospasm.

REFERENCES


**INFLUENCE DE LA TONALITE DES MUSCLES LISSES BRONCHIALES SUR LE RETRECISSEMENT CRITIQUE DES PASSAGES D'AIR TRIBUTAIRES**

**RESUME**

Le rétrécissement critique des passages d'air tributaires a été étudié sur des chiens anesthésiés dont la poitrine était fermée. Deux techniques ont été utilisées: (a) volume de fermeture (CV), mesuré à partir du plateau de l'azote expiré et (b) la bronchographie au tantale, pour mesurer le calibre des passages d'air de 3-8 mm de diamètre dans les zones supérieures (UZ), moyennes (MZ) et basses (LZ). Le point de “fermeture” des passages d'air à la jonction des phases III et IV du plateau alvéolaire a coïncidé avec une inflexion de la courbe diamètre/volume du poumon des passages d'air de la zone la plus basique des poumons. Ceci a été accompagné d'une importante augmentation soudaine de la résistance calculée des passages d'air par rapport à celle des passages d'air des UZ. Après stimulation du nerf vague, le CV a augmenté et il y a eu une augmentation du rétrécissement des passages d'air, particulièrement dans les LZ. L'addition de 0,5% d'halothane à l'agent anesthésiant a annulé l'effet de la stimulation du nerv vague sur le CV et sur la résistance des passages d'air.

**EINFLUSS DES GLATTEN BRONCHIALMUSKELTonus’ AUF KRITISCHE VERENGUNG DER ABHÄNGIGEN LUFTWEGE**

**ZUSAMMENFASSUNG**

Die kritische Verengung der abhängigen Luftwege wurde bei Hunden mit geschlossenem Brustraum in narkotisiertem Zustand untersucht. Zwei Methoden wurden benutzt: (a) “Schliessvolumen” (CV), gemessen am Ausatmungs-Stickstoffplateau, und (b) Tantal-Bronchographie zur Messung des Durchmessers der 3-8 mm starken Luftwege der oberen (UZ), mittleren (MZ) und unteren (LZ) Zonen. Der Punkt der Luftweg-“Schliessung” bei dem Zusammentreffen von Phase III und IV der alveolären Kurvenhöhe erfolgte gleichzeitig mit einer Inflektion der Durchmesser-Lungenvolumskurve der Luftwege in der basalsten Lungenzone. Dies war begleitet von einem plötzlichen starken Anstieg des berechneten Luftwegwiderstandes in LZ verglichen mit UZ. Nach Stimulierung der Vagi kam es zu einem Anstieg von CV und zu einer wachsenden Verengung der Luftwege, besonders in LZ. Die Beigabe von 0,5% Halothan zum Narkosemittel eliminierte die Wirkung vagaler Stimulierung auf das CV und auf den Luftwegwiderstand.

**LA INFLUENCIA DEL TONO DEL MUSCULO LISO BRONQUIAL SOBRE EL ESTRECHAMIENTO CRITICO DE VIAS RESPIRATORIAS DEPENDENTES**

**SUMARIO**

Se examinó el estrechamiento crítico de las vías respiratorias dependientes en perros anestesiados con tórax cerrado. Se emplearon dos técnicas, (a) de volumen de “cierre” (CV) medido de la meseta de nitrógeno expirado y (b) broncografía de tantalo, para medir el calibre de las vías respiratorias de 3-8 mm de diámetro en las zonas superior (UZ), media (MZ) e inferior (LZ). Los puntos de “cierre” de las vías respiratorias en la unión de las fases III y IV de la meseta alveolar coincidió con la inflexión en la curva de diámetro-volumen pulmonar de las vías respiratorias en la zona más basal del pulmón. Esto fue acompañado por un gran aumento repentino en la resistencia calculada de las vías respiratorias en la LZ en comparación con la UZ. Tras el estimulo del vago, el CV aumentó así como el estrechamiento de las vías respiratorias, especialmente en la LZ. Agregando un 0,5% de halotano a la anestesia, se eliminó el efecto del estímulo vagal sobre el CV y la resistencia de las vías respiratorias.