THE MECHANISM OF TACHYPNOEA IN PULMONARY MICROEMBOLISM AND PULMONARY INFLAMMATION

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We wished to study the mechanism responsible for the tachypnoea seen in microembolism and inflammation of the lung in man. We have made these two pathological conditions experimentally in the rabbit and cat.

1. PULMONARY MICROEMBOLISM

This was produced in the rabbit by the intravenous injection of plastic microspheres of 50 ± 10 μm diameter (3 M Co. Ltd.), given slowly over 3–4 min until the arterial pressure just began to fall. Animals with intact vagi developed rapid shallow breathing with little change in $PaCO_2$. The arterial oxygen tension was kept above 180 mm Hg by the addition of O_2 to the inspired air.

The lung merely showed a diffuse greyness due to the presence of columns of emboli (Fig. 1). Light microscopy did not reveal collapse, haemorrhage, infarction or substantial oedema.

2. LUNG INFLAMMATION

This was produced in the cat and the rabbit by the use of a 1% solution of carageenin, a polysaccharide obtained from a species of red algae, *Chrondrus crispis*. Carageenin produces an inflammatory reaction that resembles the acute inflammatory sequence typical of injury by microbial and non-microbial agents (Williams 1957). 10 ml of a sterile 1% solution of carageenin was injected via a small catheter inserted

through the trachea of anaesthetized cats or rabbits and pushed to the bottom of right or left lung. There was no way of knowing into which lung the catheter had gone. The lesions were allowed to develop over 1–7 days. They were confined to one lung and often one lobe (Fig. 2A). The architecture of the lung was shown to be intact histologically with an alveolar and interstitial infiltration with polymorphonuclear leucocytes on day 1, followed by a gradual replacement with histiocytes on days 2 and 3 (Fig. 2B) and fibroblasts on day 4. There was no fibrinous exudate in the alveoli, and there was no pleurisy.

The methods and results are fully described elsewhere (microembolism — Guz and Trenchard 1971, lung inflammation — Trenchard and Guz 1972). The plan in both sets of experiments was firstly to ascertain if vagus nerves were required for the rapid shallow breathing to occur. Secondly, if this were so, we wished to see if non-myelinated fibres within the vagus were necessary. Over 50% of the vagal afferent supply to the mammalian lung consists of non-myelinated fibres with a diameter of 1 μm or less (Agostoni et al. 1957). Activity in these fibres had been recorded by Paintal (1955, 1969) in response to pulmonary embolism with starch, intravenous phenyl diguanide and pulmonary congestion. Furthermore, Frankstein and Sergeeva (1966) had found suggestive evidence of increased activity in these fibres when the lungs were inflamed.

Differential vagal block

A differential block of the right vagus was established in our study by using anodal hyperpolarization (Mendell and Wall 1964). By gradual adjustment of the current it was possible to block myelinated fibres and leave the conduction of the non-myelinated 'C' fibres intact. The degree of block was assessed by eliciting electroneurograms across the area of block (Fig. 3). The left vagus was cut since we were not able to perform this differential block on both nerves simultaneously.

Under this degree of differential block, we established that the Hering–Breuer inflation and deflation reflexes were abolished, and the ventilatory response to intravenous phenyl diguanide was not only intact, but often enhanced. Thus, not only was the 'C' electroneurogram intact, but these fibres could transmit normally impulses arising from their pulmonary receptors (phenyl diguanide stimulation).

Unilateral distribution of a vagus nerve in the lung

Much of the thinking in the experiments on lung inflammation depends on evidence that a vagus nerve is distributed wholly or at least predominantly to one lung. There is considerable physiological data to suggest that this is so (Klassen et al. 1951, Troelstra 1960, Guz et al. 1966).
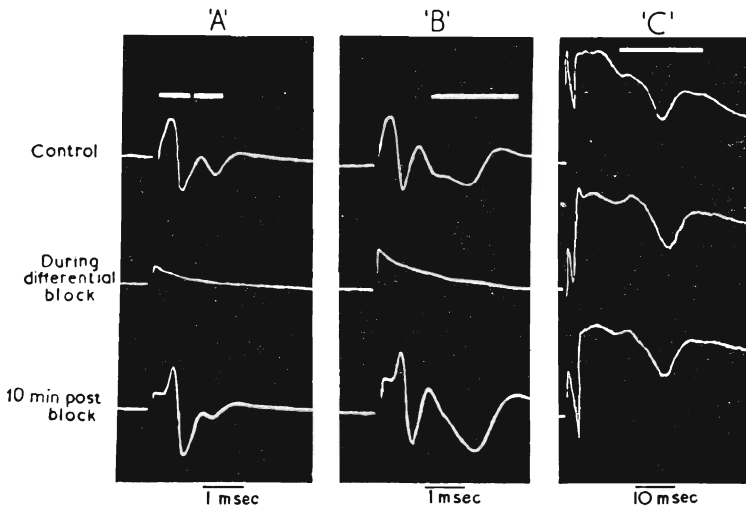
Fig. 3. Effect of a differential block of conduction by direct current on the 'A', 'B' and 'C' waves of the cervical vagal electroneurogram, and their subsequent recovery. The horizontal bars above the records indicate respectively the 'A' and 'Aδ' waves (left-hand column), the 'B' wave (middle column) and the 'C' wave (right hand column). In each trace the stimulus is shown first as a brief downwards deflexion (break in base line) followed by a slowly declining upwards deflexion. The artifact became successively larger with the 'B' and 'C' waves because of the increase in stimulating voltage necessary to elicit these waves. The 'C' wave is therefore superimposed on a large declining artifact. Note that during the block the 'A' and 'B' waves are eliminated leaving only the stimulus artifacts, while the 'C' wave is almost unchanged. (From Guz and Trenchard 1971).

RESULTS

Microembolism

Tachypnoea did not develop when rabbits ($n = 5$) had both vagi cut. Tachypnoea developed to the same degree in rabbits ($n = 6$) with the differentially blocked vagus, as in control rabbits ($n = 10$). If the differentially blocked vagus is cut then the respiratory frequency falls; this does not happen when a differentially blocked vagus is cut from a control rabbit (Fig. 5).

Lung inflammation

Conscious cats. Serial measurements, in duplicate, of respiratory frequency (counted over at least 1 min) and rectal temperature were made 2–4 times a day throughout the study. One of the vagus nerves was cut in the neck prior to the beginning of the study. Carageenin was then given via the trachea as described above, and the serial measurements of

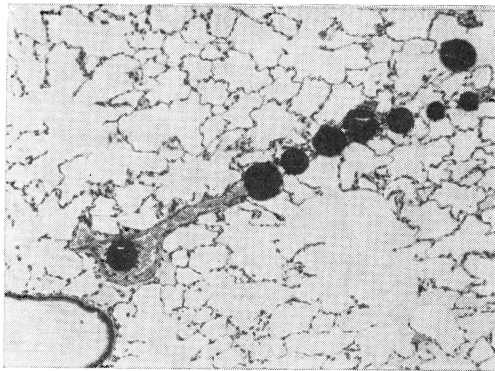Fig. 1. A group of inert carbon coated plastic microspheres impacted in a vessel of average diameter 30 μm in the lung of a rabbit. Emboli that have been sectioned centrally have a diameter of 50±10 μm. Note the distortion of the alveolar wall by the spheres.   ×120.
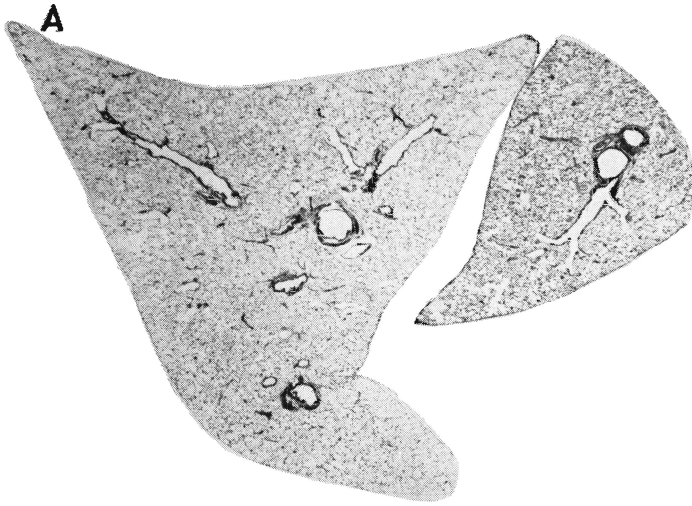
Fig. 2*A*. Mild inflammation 24 hr after instillation of carageenin. The lower lobe (right) alone is inflamed, whereas the upper lobe (left) is normal.   ×3.
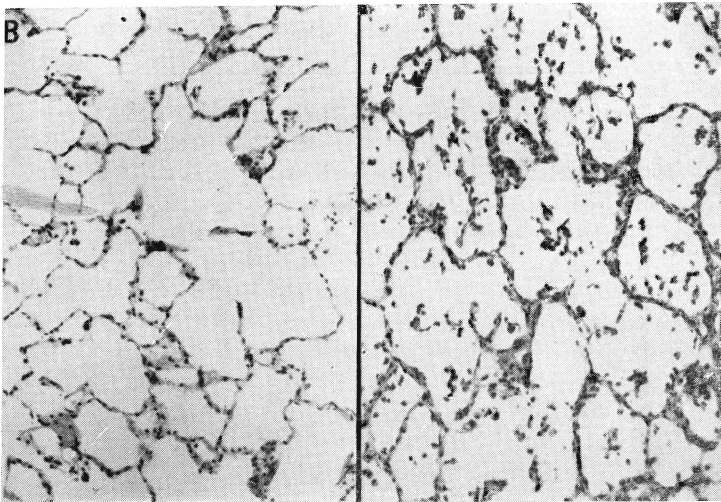

Fig. 2*B*. Inflamed lung (right) compared with normal lung (left) from *A*. Note the infiltration with macrophages and polymorphs in the interstitial spaces and within alveoli. Note the absence of fibrin.   ×120.

PaO_2 did not fall below 80 mm Hg; the $PaCO_2$ was 40 mm Hg before carageenin, and remained between 40 and 35 mm Hg for the duration of the study in the one control cat. In the one experimental cat the $PaCO_2$ fell sharply to 32 mm Hg, where it remained for the next 5 days. This evidence therefore suggests that alveolar hyperventilation as well as tachypnoea depends on the integrity of an ipsilateral vagus.

Anaesthetized rabbits. Rabbits, in whom lung inflammation had been induced as described above were studied under chloralose anaesthesia (40 mg/kg) 1–5 days after the instillation of carageenin. The side of the lung inflammation could not be determined without radiology and this was not used. The left vagus was cut and a differential block of the right vagus nerve was then established. This nerve was then cut. If the lung lesion had been induced on the right side ($n = 16$), then the respiratory frequency fell. By contrast, if the lung lesion had been induced on the left side ($n = 4$), there was no fall in respiratory frequency (Fig. 5).
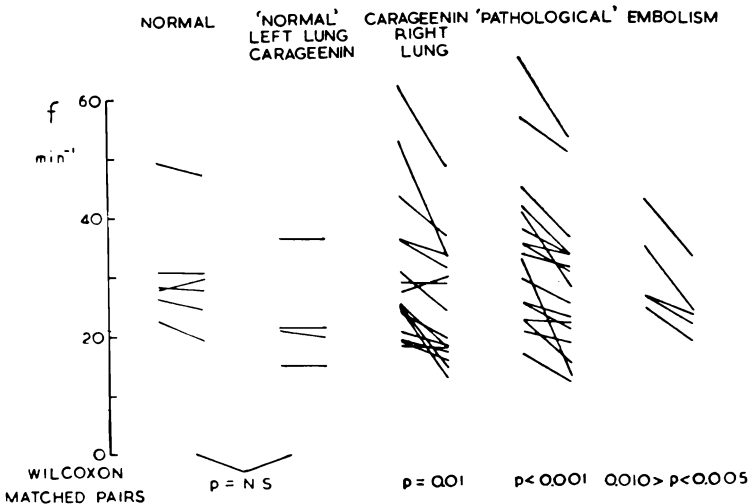

Fig. 5. Effect on respiratory frequency of cutting a differentially blocked right vagus nerve in the rabbit. Left vagus nerve cut prior to study. The lines join points on the left pre-section with points on the right post-section. The studies are grouped under self-explanatory headings. The 'pathological' group is a mixed collection of spontaneous patchy atelectasis, lung oedema, haemorrhage and infarction. The significance of the change with section is given below using the Wilcoxon Matched Pairs Test. NS, not significant.

CONCLUSION

This evidence suggests that the abnormal vagal input to the medulla from an inflamed lung is coming predominantly via non-myelinated 'C'

fibres at least in the rabbit experiments. The evidence does not exclude a contribution from the small myelinated 'irritant' fibres (Mills et al. 1970).

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