Studies on the action of bronchial muscle

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IT IS appropriate, in celebrating the great contribution which John McMichael has made to the physiological approach to medicine, to deal with a physiological subject. This paper gives a brief account of the investigations, still somewhat preliminary, which our group has been carrying out into the possible part played by bronchial muscle in airways obstruction.

If increased tone of bronchial muscle contributed to airways obstruction in asthma or chronic bronchitis the tone might be either *static*, that is to say unaltered throughout the respiratory cycle, or *dynamic*, that is to say increasing on expiration. Classically, in the normal animal, there is said to be no increase of tone on expiration, but this might perhaps occur in disease. Our earlier investigations attempted to investigate whether the narrowing of bronchi on expiration was purely passive, reflecting the relaxation of negative intrathoracic pressure, or whether under some conditions there might be an active component in the bronchial muscle (dynamic increase in tone). At present we are carrying the investigation a step further and are attempting to record static increases in tone by measuring the elastance of the bronchial wall.

The measurement of bronchial endomural pressure

In co-operation with Dr D. C. Simpson, of the Department of Medical Physics, Dr A. C. Douglas and Miss Sylvia Merchant, a double-channelled probe was designed carrying a small balloon at its distal end which, at bronchoscopy, was inserted into a basal segmental bronchus, usually coming to rest about 2.5 cm beyond its origin. The balloon was saline-filled and recorded changes in pressure with the respiratory cycle. Air was enabled to pass in and out of the relevant segment by means of the hollow interior of the probe, air escaping into the bronchus by ports proximal to the balloon. A second saline-filled channel measured the intraluminal pressure at the most proximal port.

The variations in bronchial endomural pres-

sure as the bronchus narrowed and widened might, of course, merely reflect changes in intra-thoracic pressure so that it was important to record the latter. This was done by measuring intra-oesophageal pressure excursions at the same time, at first by an open saline-filled polythene tube, later by an air-filled balloon in the classical manner. It is known that oesophageal pressure excursions measured in the supine position in fact overestimate the changes in pleural pressure with respiration.

If the bronchial endomural pressures recorded merely reflected changes in intra-thoracic pressure, which depend on the excursions of pleural pressure, there should be a constant, or at least a systematic, relationship between the oesophageal pressure excursions and those in the bronchial balloon. Because of the buffering effect of the lung it would be expected that the bronchial balloon pressure-excursions would be less than those in the oesophagus. Studies in this Department by Dr Barry Hovell on resected human lungs, suspended in an air-tight jar and subjected to varying negative and positive pressures with simultaneous recording of bronchial endomural pressures, confirmed this theoretical concept. The ratio between the balloon pressure excursions and the oesophageal pressure excursions varied between 0.7 and 0.9. In several experiments Hovell showed, by dissecting away the lung, that the drop in pressure between the pleura and the inner wall of the bronchus was mainly in the bronchial wall itself.

Results in man

(1) *Range of bronchial endomural pressure*

It was found that the endomural bronchial pressure variation with respiration in a patient breathing normally (though under somewhat artificial experimental conditions) varied from about 4 cm H₂O to more than 100 cm H₂O, the higher readings being in very wheezy patients.

(2) Relationship to FEV

Many wheezy patients with low forced expiratory volume had high bronchial balloon pressure excursions, but there were others with relatively little wheeze but with low FEV who had relatively low excursions. These were probably the more emphysematous patients.

(3) High balloon/oesophageal pressure ratios

In a number of wheezy patients the ratio between the bronchial balloon pressure excursions and the oesophageal pressure excursions was greater than unity. This made it very improbable that in these patients the bronchial balloon pressure excursions could have merely reflected pleural pressure change, especially as in the supine position the pleural pressure changes were probably overestimated. Ratios as high as 3:1 were recorded.

(4) Variation after voluntary deep breathing

It was found in a number of patients that after deep breathing there was a change in the ratio between bronchial balloon pressure excursion and oesophageal pressure excursion, suggesting a change in bronchial tone.

(5) Effect of antispasmodics

We have also investigated the effect of adrenaline and aminophylline on the bronchial balloon pressures. The trace of the bronchial balloon pressure excursions has, of course, a wave-like form, with end-expiratory and end-inspiratory peaks. If the patient is breathing in a reasonably static manner a line joining the end-expiratory or end-inspiratory peaks is approximately horizontal. If an antispasmodic relaxed the tone of the bronchial wall one would expect the bronchial balloon to be less firmly grasped at end-expiration and to relax more at end-inspiration. The nett effect would be a gradual drop of the trace. This is in fact what we have found, though there has been some variation in the extent of the drop from patient to patient. In a number of patients there has also been a decrease in the ratio between the intra-bronchial balloon pressure excursions and the oesophageal pressure excursions.

As the concept of increase in dynamic tone is not in agreement with classical teaching one must be a little hesitant in accepting it in these patients. We have seen raised balloon/oesophageal ratios when we were measuring the intra-oesophageal pressure either by an open tube or by the classical air-filled balloon. The only possibility of a technical artefact would be if we were underestimating the oesophageal pressure

excursions. In fact all the evidence suggests that measurement in the supine position overestimates rather than underestimates these excursions. It would also be a little surprising if these errors only tended to be made in wheezy patients. Nevertheless, one must still have a slight element of doubt until other evidence can be adduced. We hope we may obtain collateral evidence by a new technique of measuring bronchial elastance which will be briefly dealt with in the next section.

Measurement of bronchial elastance

The elastance or compliance of the bronchial wall must depend, at least partly, on the tone of the bronchial muscle. If there is increase in static tone the elastance of the bronchial wall should increase. With Dr Ross McHardy and Miss Sylvia Merchant we have devised a technique to measure elastance. We use the same type of intra-bronchial balloon already described. The principle is to add very small quanta of fluid to the balloon system, thus pushing the balloon outwards against the bronchial wall. The rise in pressure produced by the added fluid is measured and is determined by the elastance of the balloon itself and of the bronchial wall against which it is pressed, with a possible component from the surrounding lung. The pressure system is very volume-sensitive so that the fluid additions are in the microlitre range. By using a micrometer syringe with a vernier scale it is possible to add such quantities with accuracy. Experiments have shown that, within the relevant range, the pressure/volume relationships both in the balloon, and in the balloon in a bronchus, lie on a straight line. By subtracting the elastance of the balloon from that of the combined balloon-bronchial system the elastance of the bronchus can be calculated.

After a series of preliminary experiments we measured the elastance of bronchi in freshly resected sheep's lungs. The lungs were suspended in a jar in the same way as described above for Dr Hovell's experiments with human lungs. Measurements were made with the pressure in the airtight jar at atmospheric, -20 and -40 cmH₂O. Measurements on the lungs from six sheep were made on a Latin Square design, three measurements at each pressure being recorded in random order so as to be able to estimate independently the effects of pressure, of time since resection and of differences between sheep. Finally, with each lung, the lung was cut away from the bronchus and the measurement repeated so as to determine what contribution to elastance was made by the lung surrounding

the bronchus. The lungs and bronchi from most of the sheep have subsequently been examined by Dr Brian Heard of the Department of Pathology.

Results

(1) Preliminary analysis at the time of writing suggests that there is a certain variability in the results from sheep to sheep but that the readings are little influenced by the degree of negative pressure to which the lung is subjected or by the time since resection (the experiments are always performed within 2 hr of death). In five out of six sheep only slight contribution to elastance seemed to be made by the surrounding lung. The elastance of the bronchi (in the lung) varied from 0.9 to 3.5 cmH₂O/ μ l.

(2) Observations have also been made on several patients. Most of these were undergoing routine diagnostic bronchoscopy because of haemoptysis or suspected carcinoma. They did not have an important degree of wheeze or airways obstruction. The results have not yet been fully analysed but the figures for bronchial elastance are so far within a range similar to that in sheep.

It should be possible by this technique to measure bronchial elastance both on inspiration and on expiration and in this way not only to calculate static tone and its variation in disease, but also to measure the effect of antispasmodics and to confirm or refute our previous finding of increase in dynamic tone with expiration in some wheezy patients.

The formation of collaterals

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OBSTRUCTION of an artery supplying part of a vital organ like the heart or brain may lead to infarction of the tissue which it supplies but sometimes vascular obstruction is silent. Symptomless occlusion of one internal carotid artery or a major division of the coronary tree is by no means uncommon.

Large collateral vessels by-passing obstructed arteries are a common finding. Everyone is familiar with the skeins of tortuous vessels seen on an arteriogram of a patient with obstruction of the superficial femoral artery in the leg. The processes by which collaterals form are obviously of importance and yet very little is known about them.

Recently experimental work on vascular obstruction in the retinal circulation of various animal species including pigs and monkeys has given a new insight into the mechanisms of formation of collaterals.

Method of study

The retinal blood vessels are uniquely accessible to repeated study. The evolution of vascular changes at the same site can be studied over a period varying from hours to months and at the end of the experiment the precise area can be located for histological examination.

Colour photographs of the retina give only limited information about circulatory changes. However, use of colour filters and injections of sodium fluorescein dye through a catheter positioned in the carotid artery make it possible to visualize all orders of vessel size down to and including the capillaries. When this technique is combined with ciné photography it is possible to measure the velocity of flow in retinal arterioles.

Vascular obstruction can be produced by several means but the most convenient is the intra-carotid injection (Ashton & Henkind, 1965) of glass microspheres which produce a sudden and localized occlusion of a branch retinal arteriole.

Circulatory changes following acute vascular obstruction

The retinal circulation has no arcades or bridges between one arteriole and another. The vessels are end-arterioles and it might be predicted that obstruction of such a vessel would lead to complete cessation of flow within its vascular territory. Surprisingly, this is not so. Immediately following arteriolar obstruction by glass emboli the blood column in the obstructed artery becomes darker in colour, but flow con-