PULMONARY VASOMOTOR ACTIVITY

VOLUME I.

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C O N T E N T S

Volume I.

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INTRODUCTION AND OBJECTIVES

In many important respects, the pulmonary circulation is not a lesser circulation, it carries the entire cardiac output and the volume of blood flow through the lungs equals the sum of that through all other organs in the body. During the last two decades the movement away from the standpoint that the pulmonary circulation is largely passive has gathered momentum, and there has been an increasing awareness of the key role played by this circulation in the course and outcome of both congenital and acquired heart disease. Its vasculature contains smooth muscle which receives innervation from the sympathetic and para-sympathetic systems. Under normal conditions in the adult a pressure gradient of only four or five millimetres of mercury is sufficient to transmit some five litres of blood per minute through the circuit. Under many circumstances it can carry up to three times this volume per minute without a comparable change in this pressure gradient (1)(2), yet in some conditions a lesser increase in flow is accompanied by an elevation of the pulmonary arterial pressure and the reasons for this are not always clear. The demonstration of vasoactivity in the lungs of intact animals or in man has proved difficult because of the comparatively small pressure gradients involved and the compliant nature, normally, of the pulmonary vasculature.

The work here presented was carried out with three objectives in view, first, to develop in animals a method of studying pulmonary vasomotor activity which could be applied in clinical practice; second, to determine some of the circumstances under which pulmonary vasomotor activity occurs, and to distinguish between the active and passive components of these responses; and third, to measure the local effects of some drugs and respiratory gases on the pulmonary circulation.

The location of the pulmonary circulation presents specific problems to the investigator of its haemodynamic characteristics. It lies between the two halves of the heart pump and is relatively inaccessible to the conventional methods used in the study of circulatory dynamics. Most of the techniques which have been evaluated and proved in relation to the systemic circulation cannot readily be applied in a study of the pulmonary circuit.

One feature of the pulmonary circulation, however, is advantageous to the investigator. Compared with the systemic circulation, it is a relatively homogeneous system, consisting of numerous identical units arranged in parallel. These units, each made up of a small muscular artery, arterioles, capillary bed, venules and veins, appear to be self-contained and for many purposes each is representative of the whole. The unit referred to is the sector subtended by a catheter 'wedged' in a small

pulmonary artery (3). The principal method used in this study exploits this subdivision of the pulmonary vasculature, and studies in detail active and passive vasomotion as it affects the 'wedge segment'. These results are supplemented by measurements made on the whole pulmonary circulation by more conventional techniques.

Many of the responses of the pulmonary circulation are dictated or modified by extra-vascular factors or by factors outwith the lungs. Recognition and quantitation of these has been a necessary part of the study.

The experimental work was conducted over a period of three years, and the results of several hundred experiments in 155 dogs are presented and discussed, along with references to related work. The experiments are described more or less in the order in which they were done, but some of the earlier results have been amplified with additional information derived from later experiments.

The first three chapters are concerned with the methods employed, the form and interpretation of the records obtained and the relevant anatomy of the pulmonary circulation.

In chapter four, the relationship between the pulmonary arterial wedge pressure and left atrial pressure is explored. The subsequent four chapters deal with the local actions of certain drugs and respiratory gases on the pulmonary vasculature.

Chapter nine is concerned with the consequences of pulmonary embolism, with particular reference to the presence or absence of pulmonary vasoconstriction induced by embolism. Chapter ten describes the local effect of cold on the pulmonary circulation and in chapter eleven the important influences of the airway pressures on flow and pressure in the pulmonary circuit are discussed. Conclusions drawn from the whole study are presented in chapter twelve.

Where appropriate, each chapter is divided into four parts; an introductory paragraph which outlines the objectives; a description of the experimental preparations used; the results of the experiments; and a discussion of these results, along with a review of previous and subsequent publications.

Most of the experimental findings are presented in the text in the form of tables, and in these each animal preparation has been given a number in order to make clear how many experiments were done on each animal. In addition, in those experiments where the pattern or form of the pressure records clarify description, photocopies of the original tracings have been reproduced. These records are contained separately in Volume III.

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The principal experimental method used was devised by Dr. H. J. C. Swan (Division of Surgical Sciences, Mayo Clinic, Rochester) and I am particularly grateful to him for the courtesy he showed me during several visits to his department in 1961.

Some of the experiments could not be done single-handed, and I was assisted in the experiments referred to in Chapters 6, 8 and 10, by residents in training and students in the Department of Cardiovascular Surgery of the University of Chicago. The work was greatly facilitated by a series of laboratory technicians both in the University of Chicago and the Wellcome Research laboratories and I would like to acknowledge their help and patience. The work in the University of Chicago was supported by a grant from the Hartford Foundation and the E. F. Andrews Fellowship. That done in Glasgow, by a grant from the British Heart Foundation.

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CHAPTER 1.

METHODS AND EXPERIMENTAL PREPARATIONS.

Choice of Method:

Many methods of assessing pulmonary vasomotor activity have been described. They range from preparations of isolated perfused animal lungs on the one hand, to studies made during investigative procedures on patients, on the other. Each method offers its own particular advantages, but few have no significant disadvantage. The use of artificial preparations such as isolated perfused lungs introduces deviations from the physiological state (1)(2)(3)(4). Such animal preparations may exhibit bizarre responses (5), or at least responses which are not relevant in clinical practice, or found in other species of animal (6)(7). In deciding upon an experimental method, some compromise had to be reached between highly artificial preparations in which all the known variables can be controlled or measured, and studies in intact, more physiological systems, which are usually less easily controlled.

In the work to be described the pulmonary circulation has been studied in situ, with its innervation intact (except where stated), and in animals whose homeostatic mechanisms were working under as little stress as is compatible with anaesthesia

and the minimum of trauma. The principal method, based upon perfusion of a wedged catheter, was chosen for the further reason that it could be applied in clinical practice with little modification. In this method a segment of lung can be isolated, insofar as its inflow rate is controlled, yet remain in situ with its innervation and morphological relations undisturbed. The principle is accepted that the interpretation of a change in resistance in terms of vasomotor activity is most reliable when blood flow or blood pressure are held constant (8)(9)(10)(11).

The work was carried out on dogs for several reasons. The anatomy and much of the physiology of the canine pulmonary circulation has been described; much of the previous work on pulmonary vasomotion has used dogs, and for purposes of comparison with previous work in the laboratory it seemed appropriate to use this animal.

Choice of Anaesthesia:

All anaesthetic agents modify the responses of experimental animals to some extent (12)(13)(14)(15). The aim in this study was to produce a steady state without undue depression of reflex activity and other homeostatic mechanisms. It was found that too light a state of anaesthesia was as disadvantageous as one that was too profound. In the former, a steady state could not be achieved because changes in systemic vasomotor activity and cardiac rate and output followed extraneous

stimuli such as loud noises in the laboratory, or touching the animal. In the latter, responses were blunted or abolished altogether in some cases.

Chloralose was tried but it proved difficult to use and did not provide a steady state. Johnson (16) showed that in man, ether anaesthesia was associated with an increase in the calculated pulmonary vascular resistance and a similar response was noted when cyclopropane was used (17). Thiopentone, used as a continuous intravenous drip (about 0.2 mg./kg./min.) seemed to offer no advantage over the longer acting pentobarbitone. Pulmonary vasomotion in response to certain drugs has been demonstrated to persist in dogs anaesthetised with pentobarbitone (18).

Pentobarbitone (Nembutal) was the anaesthetic chosen for most of the experiments. No premedication was given. Anaesthesia was induced with a single intravenous dose, 20 to 25 mg./kg., with the addition of one increment after about 30 minutes if the medial palpebral reflex was still present. All the animals were intubated with a cuffed Magill tube. Respiration was spontaneous or controlled and the administered gases were varied according to the requirements of the experiment. In all the open-chest animals and in some of the closed-chest preparations, ventilation was by intermittent positive pressure controlled by a Palmer pump. In these animals the anaesthetic was supplemented with succinylcholine, administered by continuous

intravenous drip in a dose of 4 to 5 mg./kg./hour. The Palmer pump is a constant volume ventilator and an appropriate tidal volume and cycle rate were chosen in the first instance, according to the size of the dog. Subsequent checks of arterial P_{CO_2} were made to confirm that correct ventilatory factors were being used. Latterly a 'Capnograph' (carbon dioxide analyser) was available and was used to monitor the CO_2 percentage in the expired air throughout each experiment. In experiments in which the airway pressures were not recorded continuously, standard factors were used within the following ranges. The respiratory rate was 20 to 26 per minute; tidal volume 200 to 350 ml.; peak inflation pressure 8 to 12 mm.Hg. and the end-expiratory pressure 0 to 3 mm.Hg. Progressive atelectasis is known to develop in the dependent segments of the lungs in anaesthetised dogs (19). This was observed, and it was seen to cause a fall in lung compliance and a consequent rise in inflation pressures. It occurred more rapidly in animals ventilated with 100 per cent oxygen, after the alveolar nitrogen content had been washed out. 'Shunting' of venous blood through these atelectatic areas caused a fall in arterial P_{O_2}. These consequences were avoided by inducing an artificial 'sigh', (i.e. a brief full inflation of the lungs), from time to time.

The Perfused Wedged Catheter: (20)(21)(22)

This was the principal special technique used. It was first described by H.J.C. Swan in 1961 (23), but because an important artefact came to light during the early experiments in this study, it was modified in respect of the perfusate and for use in open-chest preparations.

The method assumes that if a catheter which is 'wedged' in a peripheral pulmonary artery is perfused at a constant flow rate, then the pressure in the catheter can be related to the resistance to flow in the perfused area. The pulmonary arteries are end arteries (24) and the factors which affect the flow of the perfusate from the catheter are the vascular resistance in the perfused segment, the airway pressure in the surrounding lung and the left atrial pressure (fig. 1). In addition, the intra-thoracic pressure and forces due to the elasticity of the lung parenchyma act indirectly on the perfused wedge segment. The segment of pulmonary vascular bed which can be perfused through a wedged catheter can be delineated by angiography and to the naked eye, by perfusing it with the appropriate medium (fig. 2). That there is no other arterial inflow to this segment is shown by the fact that 'dye' will remain, filling the segment, until the wedged catheter is disimpacted. Some dilution of the medium does occur near the left atrium, since the pulmonary veins draining adjacent segments are confluent at that point. (The

important influence of these veins on the interpretation of the results of some experiments is discussed in subsequent chapters.)

Further description of the method will be facilitated by definition of some of the terms used. The physiological symbols, and most of the terms used in the text and tables are those recommended by the Pappenheimer Committee (25). New terms have been devised however, in relation to some of the methods applied in the study, and these are defined below. The initials in parentheses are the abreviations used in the tables of results.

Static Wedge Pressure (St.W.P.): This refers to the pressure measured in a fluid-filled catheter, the tip of which is wedged in a peripheral pulmonary artery. This is the conventional 'pulmonary wedge pressure', or 'pulmonary capillary pressure' (26)(27)(28)(29)(30).

Gross Perfused Wedge Pressure (G.W.P.): This is the pressure measured in a wedged catheter during perfusion of the catheter and the subtended vascular bed. This pressure is evoked by resistance to flow at three sites - the catheter, the vascular bed and the left atrial pressure. The pressure due to catheter resistance was measured by perfusing the catheter alone in air (with its tip at the same level as the transducer), before or after each experiment and is designated (Cath.P.).

Net Perfused Wedge Pressure (N.W.P.): Since the catheter itself offers resistance to flow and contributes to the measured 'gross' perfused wedge pressure, the pressure increment from this source was noted in each experiment. This pressure was subtracted from the recorded gross perfused wedge pressure to give the 'net perfused wedge pressure' for use in calculating resistance in the wedge segment.

Vascular Resistance in the Wedge Segment (R.): This was calculated as follows:-

$$\text{Resistance} = \frac{\text{Net Perfused Wedge Pressure} - \text{Mean Left Atrial Pressure (mm.Hg.)}}{\text{Perfusion Flow Rate (ml./min.)}}$$

Alternatively, in some experiments, the resistance to flow was calculated for that portion of the wedge segment which lay between the catheter tip and the confluence of veins from adjacent segments. This has been referred to as the 'pre-venous resistance', and was derived by the formula:-

$$\text{Pre-venous Resistance} = \frac{\text{Net Perfused Wedge Pressure} - \text{Static Wedge Pressure}}{\text{Perfusion Flow Rate}}$$

Airway Pressure: In this study this refers to the phasic or mean (electrically integrated) pressure measured in the trachea or a main bronchus.

Pressure Measurements:

Pressures were measured with Statham strain gauge transducers (Type P23d and P23e), and recorded on a Grass Polygraph.

The damping properties of different cannulae and lengths of catheter were studied in conjunction with these transducers by using a pump which produced a sine wave of variable frequency (fig. 3), and by bursting a balloon to form a square wave. Suitable catheters were chosen as a result of these studies, and from the recommendations of Hansen (31) and Wood (32). The cannulae used in the left atrium, pulmonary artery and femoral artery were 15 cm. in length and 0.8 mm. bore (Polythene), and they were connected to the transducers by 62 cm. lengths of non-distensible nylon tubing of 1.5 mm. bore. The wedge catheter was usually a No. 7, thin-walled (Lehman) end-aperture cardiac catheter (20 cm. in length, in the open-chest preparations, and 80 cm. in the closed-chest animals). During most of the experiments the recorded pressures were electrically integrated, so as to yield mean pressures. Thus, the only oscillations seen in most of the perfused-wedge pressure records are respiratory in origin. In circumstances in which the time relationship of simultaneous events was being studied, care was taken to ensure that the damping characteristics and time constants of each of the records was identical, because it was found that comparisons between damped and undamped tracings may be fallacious (fig. 4).

The airway pressure was recorded through a wide-bore needle in the trachea or main bronchus, connected to the transducer by non-distensible nylon tubing. The tubing and

transducer, but not the needle, were filled with saline. A few centimetres of the tubing adjacent to the needle were also air-filled. The saline-air interface in the tubing was kept at the same horizontal level as the transducer.

The transducers were calibrated using mercury or saline columns and zero pressure equalled ambient atmospheric pressure. In the earlier experiments, the importance of standardising the position of the transducers with reference to the heart and to each other was not appreciated, but the error was rectified in later experiments. This detail is of basic importance in studies in which the static wedge pressure, pulmonary venous pressure and left atrial pressure are being compared.

Perfusion of the Wedged Catheter:

The Harvard pump* used for this purpose produces a non-pulsatile flow, unaltered by changes in the downstream pressure within the range minus 30 to plus 500 mm.Hg. The perfusion circuit is shown diagrammatically in fig. 5. The perfused wedge pressure was measured through the side arm on the connecting tubing. Two other 3-way taps were interposed in this tubing, so that drugs could be introduced. The volume between these taps was known, so that if the dose of drug was introduced in that volume of saline through one of the taps, with the other open to allow the displacement of a like volume of blood, the

* Harvard Instrument Co., Dover, Massachussetts.

drug could be introduced in a known dose without raising the pressure in the otherwise closed system.

Saline was used as the perfusate in preliminary experiments, but proved unsatisfactory for perfusions lasting more than a few minutes. Histology of wedge segments perfused with saline for longer periods showed perivascular oedema. It was also considered that anoxic changes and possibly vasomotion could occur in a vascular bed perfused with a non-oxygen carrying solution. Therefore, in all the experiments described, autologous blood was used as the perfusate. The dog's own venous blood was used, except in the hyperoxic experiments, and the perfusion syringe was refilled through a cannula in a femoral vein.

The temperature of the perfusate was kept normal by immersing the connecting tube, between the pump and the catheter, in a water bath at 39°C. The perfusion syringe, connectors and catheter system were silicone-coated. Sedimentation of the cellular elements of the blood in the syringe was prevented by using a magnet to agitate a steel ball in the barrel of the syringe.

Flow Measurement:

Complementary data was obtained in some of the open-chest animals by measuring the instantaneous and mean blood flow in a main pulmonary artery.

Flow was measured with a gated square-wave electromagnetic flowmeter* and recorded on a Grass Polygraph. The detector of this flowmeter was applied around the artery in which flow was to be measured. Exposure of a one centimetre length of vessel was necessary and the artery used was the intermediate branch of the right main pulmonary artery to the lower lobes, since this vessel could be exposed with a minimum of trauma (merely the division of pleural reflections). The flowmeter was pre-calibrated by passing blood through a segment of excised artery at a known flow rate.

In some experiments a factor for total pulmonary flow was obtained by multiplying the measured flow to one lobe by four. While the figure gained by this extrapolation will not be precise in absolute terms, it is believed that it will serve in circumstances where changes in flow are being studied, since the distribution of the output of the right ventricle to each of the lobes is approximately equal and relatively constant in a supine animal (33).

Experimental Protocol (Closed-Chest Animals)(Fig. 6)

Twenty four dogs were used in this group. All were adult mongrel dogs of weight between 9 and 15 kg. Puppies and old dogs were not used, and the animals were free from disease as judged by clinical criteria. They were anaesthetized as

* Carolina Medical Electronics, Winston-Salem, N. Carolina.

described above, an endotracheal tube was passed and they were fixed supine on an x-ray screening table. The systemic blood pressure was monitored through a cannula tied into a femoral artery with its tip in the abdominal aorta. A wide-bore cannula (2.0 mm.) was passed into the inferior vena cava, via a femoral vein. This cannula was used for withdrawing blood and as a route for the administration of drugs. A similar wide-bore cannula was introduced into the other femoral artery. Both wide cannulae were connected through taps to a siliconed glass reservoir which contained 5 ml. saline and 1000 I.U. heparin, and mounted so that it could be raised or lowered in relation to the level of the dog. This reservoir was used to withdraw blood (by gravity) and it could be pressurised for the rapid re-infusion of this blood. A Rose-Braunwald transseptal needle (No. 17T), introduced through the right jugular vein, was advanced through the inter-atrial septum until its tip lay in the left atrium. The left atrial pressure was monitored through it. The left jugular vein was also exposed and used to introduce a cardiac catheter. The butt end of this catheter was connected to a Harvard pump and the catheter and pump were primed with autogenous heparinised blood. The pressure in the catheter was recorded through a side arm which led to a pressure transducer. Under fluoroscopic control the catheter was advanced until its tip was 'wedged' in a peripheral pulmonary artery, usually in

a lower lobe. In some animals, a second catheter with a balloon at its tip was passed into the right ventricular outflow tract, so that it could be manipulated into one or other main pulmonary artery. The balloon was filled with radiopaque contrast medium so that its position could be seen on fluoroscopy. Passage of this catheter was facilitated by partially inflating the balloon when it reached the outflow tract of the right ventricle.

Immediately the wedge catheter was impacted, perfusion was started at a slow rate, so that flow through the wedge segment was interrupted for the minimum time. The perfusion rate was increased until the mean 'net perfused wedge pressure' was between 5 and 10 mm.Hg. higher than the left atrial pressure. Perfusion was then continued at this rate and records taken as controls. During the breaks in perfusion necessary for recharging the syringe, the static wedge pressure was recorded. When a steady perfused wedge pressure had been recorded for some ten minutes, the stimulus under study was applied while continuous pressure records were obtained (using a recording paper speed of 0.5 or 1.0 mm./second). After withdrawal of the stimulus, further records were taken to observe return of the pressures to control levels (where this occurred). From ten to fifteen such experimental runs could usually be done on each animal before changes in the control observations indicated

deterioration of the preparation.

In some animals at the end of the series of experiments the chest was opened and the perfused segment of lung was excised for histological study. In three instances the vascular bed of the wedge segment was fixed in situ by perfusing it with a 10 per cent solution of formalin in saline.

Experimental Protocol (Open-chest Animals):(Fig. 7)

This group forms the bulk of the experimental material and one hundred and thirty one dogs were used. The animals were adult mongrel dogs and free of evident pulmonary disease and distemper. Anaesthesia and ventilation (intermittent positive pressure) were used as described above. With the dog in the right anterior oblique position, the right hemithorax was opened through the 5th intercostal space. When complete haemostasis had been secured, the animal was heparinised (3 mg. of heparin per kg. body weight). This dose of heparin was repeated after one hour. The systemic blood pressure was measured through a catheter inserted into a femoral artery. A second cannula (wide-bore) was tied into a femoral vein and joined to the perfusion system through a tap. A fine polythene cannula was advanced into the left atrium through a small pulmonary vein in the middle lobe of the right lung. This cannula was connected to a pressure transducer for the measurement of left atrial pressure. The intra-bronchial pressure was monitored through a needle in the right main bronchus (or

trachea). Before the wedge catheter was introduced, the perfusion syringe in the Harvard pump, the tap system, connectors and catheter were primed with autogenous venous blood, and care was taken to evacuate air-bubbles. In order to avoid interference with the perivascular nerves to the lobe which would contain the wedge segment, the artery to this lobe was not cannulated directly. The wedge catheter (a 20 cm. length of thin-walled, No. 7 Lehman) was introduced centripetally through an artery to the middle lobe, then advanced centrifugally in one of the arteries to the right lower (or sub-cardiac) lobe, until its tip 'wedged'. As soon as the catheter was wedged, perfusion was commenced at a 'physiological' flow rate. Control recordings were then taken and the experiment conducted as described for the closed-chest group.

In each experiment a considerable amount of time was spent in wedging the catheter and great care was taken to ensure that the catheter tip was in fact impacted in a small pulmonary artery. Loomis Bell has studied the position of the 'wedged' catheter tip in patients undergoing routine catheter investigations (34). He delineated the vessels just distal to the catheter tip by angiography and found that the catheter was correctly wedged in only 24 out of 68 cases. His criterion for correct wedging was that the catheter tip be impacted in straight segment of artery which had a common axis with the catheter and was just smaller than it. Study of injection-corrosion specimens and arteriograms

of the pulmonary arteries showed that in the dog, three or four long straight arteries of about 2 mm. luminal diameter are constantly present in the right lower lobes. The catheter was wedged in one of these arteries in most experiments and the following criteria were used as indications of correct wedging.

(1) The 'feel' of the catheter as its tip wedged.

(2) An abrupt transition from pulmonary arterial to 'left atrial' pressure in the catheter.

(3) The appearance on the pressure tracings of larger pressure swings, synchronous with respiration.

(4) In closed-chest animals, the movement of the catheter tip on fluoroscopy.

(5) Recognisable left atrial pressure waves in undamped records throughout the respiratory cycle in both the static and perfused wedge pressure tracings.

(6) One was able to get oxygenated blood to drip from the catheter by gravity if it was correctly wedged. It was not usually possible, however, to withdraw blood with a syringe.

(7) At the end of the experiment, the catheter "snapped back" from the wedge position.

(8) With familiarity with the method, further confirmation of true wedging could be gained when the catheter was perfused from study of the pressure and wave forms.

The foregoing outlines the methods used in this study. Some adaptions and modifications were made to suit the requirements of individual experiments and these are detailed in the chapters concerned.

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CHAPTER 2.

CHARACTERISTICS OF THE PERFUSED WEDGED CATHETER PRESSURE.

Since perfusion of a wedged catheter was a new technique, a series of preliminary studies were carried out to determine the character of the pressure records obtained, to establish such factors as the reproducibility of results under control conditions and the stability of the preparation; and to find and eliminate sources of artefact.

Perhaps the most important prerequisite for the validity of the perfused wedge pressure records was correct wedging of the catheter. The measures taken to ensure this have been described in the previous chapter. It would be relevant to describe here three common sources of error which were encountered in this respect. (1) It was found that the artery in which the catheter tip was wedged could become kinked during certain phases of respiration. This was made evident by the appearance of recurrent extra positive waves in the recorded perfused wedge pressure. These denoted a phasic brief obstruction to perfusion and they usually occurred during expiration (figs. 8 and 9). (2) The catheter could wedge with its tip straddling a bifurcation or adjacent to the point of origin of a branch. In such circumstances the size

of the perfused segment could alter as one or other, or both, of the branches were perfused. This was manifest in the records as an abrupt increase or decrease in perfusion pressure. (3) The third artefact was found to occur under conditions in which the volume of pulmonary blood flow was abruptly increased upstream in the artery within which the catheter was wedged. The consequent distension of the pulmonary arteries could allow disimpaction of the catheter tip, with the consequent reappearance on the recorded tracing of pulmonary arterial pressure waves (fig. 10).

The influence of the airway pressures on the pulmonary circulation is discussed in Chapter 11, but some general comments on the effects of respiration are appropriate here.

When the catheter tip was correctly wedged, the pressure recorded in it and the dominant waves (in an undamped record) were similar to and synchronous with those recorded through a catheter in left atrium. Superimposed on these high frequency waves, larger slower waves were recorded due to the phasic changes in the intra-thoracic and intra-vascular pressures which accompanied respiration. In closed-chest preparations, when the animal was breathing spontaneously, inspiration was accompanied by an increase in negative pressure within the chest and a fall in the perfused wedge pressure (fig. 11a). In the open-chest animals, ventilation was maintained by intermittent positive pressure and inflation of the lungs was accompanied by a rise in perfused wedge pressure, with

some obliteration of the high frequency waves transmitted from the left heart at peak inflation (fig. 11b). Similar pressure swings in response to ventilation were seen in the static wedge pressures and left atrial pressures, but the damping effect of alveolar inflation was seen only in the former. Since the studies were concerned principally with mean pressures, most of the pressure tracings in subsequent experiments were damped so that the only phasic deflections or waves recorded were those due to changes in airway pressure. A sustained change in the mean airway pressure was associated with an altered resistance to perfusion and experiments to demonstrate this effect of airway pressure on the vascular resistance, as measured in the wedge segment, are discussed in Chapter 11.

The perfusate in the perfused wedge catheter preparation encounters resistance to flow at three levels. (1) In the catheter itself; this is constant and depends on certain criteria such as temperature and viscosity of the perfusate, the size of the catheter and the flow rate. (2) In the vessels of the wedge segment, arteries, capillaries and veins. (3) At the outflow from the wedge segment, i.e. the pressure in the left atrium.

For each flow rate used, the pressure due to the first factor was measured for each experiment and was found to remain constant, provided the temperature and viscosity of the perfusate were unaltered. The left atrial pressure was measured. The

flow rate was known. Thus, the pressure gradient from catheter tip to left atrium could be calculated, and the resistance to flow derived.

In each experiment, when perfusion was commenced through the wedged catheter, the recorded pressure reached a level which remained constant for as long as perfusion was continued at the same rate. The choice of the correct perfusion rate was the subject of several of the preliminary experiments. The aim was to produce a pressure gradient across the vessels of the wedge segment, of between 5 and 15 mm.Hg. It was thought that too low a rate of perfusion might allow spontaneous active closure of some vessels (1)(2), with consequent unpredictable changes in the capacity of the perfused segment and its vascular resistance. On the other hand, rates of perfusion which were too high might damage the segment or at least so stretch the potentially vaso-active vessels as to diminish or prevent their responses. These considerations were studied first by plotting the net wedge pressure against flow, when the latter was increased then decreased in a stepwise fashion (fig. 12).

The pressure/flow relationship in the wedge segment during intermittent positive pressure ventilation and during spontaneous breathing are shown in fig. 13. Such curves obtained by other investigators have demonstrated some degree of qualitative variability (3). Most have had in common a convexity towards

the pressure axis (4)(5)(6)(7)(8), while other workers have produced curves which are convex to the flow axis, both in animals (9) and in man (10)(11)(12)(13). It is clear that the relationship between pressure and flow in the pulmonary circulation varies according to the circumstances under which it is studied and the curves obtained when the pressure is measured in isolated perfused lungs during progressive increments of flow, are not comparable with those obtained in man during unilateral pulmonary occlusion, for example. Further, the quality of the curve will vary depending on the factor chosen to represent pulmonary arterial pressure. This may be absolute pulmonary pressure, pulmonary pressure minus left atrial pressure, or pulmonary pressure minus 'wedge' pressure. In the curves reproduced in fig. 12, the pressure axis represents perfusion pressure minus static wedge pressure, i.e. the pressure gradient across that part of the vascular bed in which flow was known.

That a given flow would consistently evoke a constant pressure for a predictable length of time was fundamental to the value of the method. Many control runs showed that this was true. However, when a low flow was substituted for a high flow, or vice versa, or where perfusion was recommenced after several minutes of no flow, the consequent pressure did not plateau for several seconds (fig. 14). This suggests that during periods of reduced flow, the resistive vessels adapted by reducing their capacity

and on the resumption of a higher flow, some time elapsed before readjustment in tone stabilised, after which the tonus of the vessels remained constant.

An alternative explanation is that the change in pressure represents a change in the number of vessels being perfused. Wearn has shown that not all the pulmonary vessels are necessarily being perfused at any given time (2), and new vessels may be opened up by increased perfusion rate. Our records would favour the former explanation, i.e. that the vessels exhibit some hysteresis in common with other visco-elastic systems.

In experiments where the wedge segment was perfused with an excessively high flow for quite short periods, a progressive increase in pressure was recorded during subsequent perfusion at 'physiological' flow rates. Microscopic examination of a wedge segment where this had occurred showed perivascular oedema. This phenomenon of a climbing pressure in response to a constant 'normal' perfusion rate was also seen in experiments wherein the wedge segment had been subjected to a sudden surge of pressure (such as could result from careless loading of the perfusion pump)(fig. 15).

The Perfused Wedged Catheter in the Closed-Chest Preparations:

In closed-chest animals the wedged catheter was introduced in a conventional manner from a systemic vein (usually the jugular). After several experiments had been done, it was found that the presence of an intra-cardiac loop of catheter introduced specific

characteristics into the pressure records of the perfused wedged catheter and that these constituted a potential source of artefact under certain experimental conditions. Apart from their importance in the planning of this study, the observations made from the pressure records obtained from a trans-cardiac wedged catheter have important applications in clinical practice, and so we digress here to refer to them in some detail. First, the experiments which led to the discovery of the artefact are described.

A preparation using a trans-cardiac wedged catheter was used in experiments designed to assess the response of the pulmonary vascular resistance to a sudden increase in pulmonary blood flow and to a rapid increase or decrease in the circulating blood volume as a whole. An increase in pulmonary flow was induced in one lung by occluding abruptly the contra-lateral main pulmonary artery with an intra-luminal balloon. A wedge segment in the ipse-lateral lung was perfused at a constant rate and so could not share in the passive dilatation which one believed would occur in the rest of this lung when its arterial inflow was approximately doubled. Any change in the perfused wedge pressure would therefore represent an <u>active</u> change in vessel calibre. The records from a representative experiment are shown in fig. 16. From these tracings it can be seen that immediately the balloon in the left main pulmonary artery was inflated, an abrupt drop in

pressure occurred in the perfused wedged catheter in the right lung. Unilateral occlusion of a main pulmonary artery apparently also lowered the static wedge pressure (fig. 17). This was taken into account in calculating the change in pressure gradient across the wedge segment. Apparently, a marked fall in resistance occurred - as calculated from the results of these experiments. This evidence would lead one to conclude that active reflex pulmonary vasodilatation occurred in response to an increase in pulmonary arterial inflow.

A second stimulus studied in the closed-chest experiments was the effect of a rapid increase or decrease of blood volume. The hypothesis which prompted this series of experiments was that the pulmonary vascular bed in its capacity as one of the blood reservoirs of the body might dilate or constrict actively in adaptation to a rapid change in blood volume. It was hoped that this could be demonstrated by using the perfused wedge technique. The blood volume of the experimental animal was acutely depleted by allowing it to bleed through a femoral artery cannula into a reservoir. In each experiment, when this was done, the perfused wedge pressure showed a rapid rise. The control perfusion pressure in the wedged catheter was regained when the same volume of blood was reinfused (fig. 18). Further experiments were carried out, in which the combined effects of changes in blood volume and in the pulmonary arterial inflow were studied.

A summation effect of the two stimuli was seen (fig. 19). The loss of blood volume appeared to be accompanied by pulmonary vasoconstriction; the increase in volume, induced by contra-lateral pulmonary artery occlusion, with pulmonary vasodilatation.

These results, however, were at variance with other more direct observations. Thus the rapid infusion of 250 ml. of blood in the same preparations was usually associated with a rise in pulmonary artery pressure (fig. 20), and even assuming a 100 per cent increase in cardiac output, the fall in pulmonary resistance could not be of the order calculated from the perfused catheter experiments. Further, when the pressure in one main pulmonary artery was monitored while the other was occluded, an abrupt rise in pressure invariably occurred. In the experiment depicted in fig. 21, the pulmonary vascular resistance before occlusion can be written as $R_1 = \frac{12}{Flow}$ and during occlusion as $R_2 = \frac{38}{Flow \times 2}$. This is an over-simplified statement, and the small fall in left atrial pressure which accompanies occlusion of a pulmonary artery is not taken into account. It does show, however, an increase of resistance to the increased flow in the unoccluded lung, contrary to what the perfusion experiments showed.

The character of the pressure changes in the trans-cardiac perfused wedge experiments also gave rise to doubts. The pressure changes seemed to be too abrupt to be explained on a reflex basis.

For these reasons the preparation was re-examined for sources of artefact. Movement of the catheter tip in the wedged position was seen not to occur, but it was noticed that the amplitude of the dominant waves in the static wedge pressure records were increased if the loop of the catheter in the right ventricle was enlarged. This phenomenon became more pronounced when the wedged catheter was perfused (fig. 22).

It was then noted, by watching the cardiac silhouette on fluoroscopy, that both the stimuli used in the foregoing experiments (i.e. alterations of blood volume and occlusion of a pulmonary artery), had a marked effect on the size of the right ventricle. Thus, when a pulmonary artery was abruptly occluded, the right ventricle could be seen to dilate and the amplitude of its movements between systole and diastole increased. Conversely, the rapid withdrawal of blood was accompanied by a reduction in the size of the right ventricle. The rapid infusion of blood (whether by the venous or arterial route) was also followed by enlargement of the right ventricle. These changes in the capacity of the ventricular cavity were accompanied by a corresponding change in the radius of the intra-cardiac loop of catheter. The considerable pressure changes recorded in a conventionally wedged (unperfused) catheter during these manoeuvres are shown in fig. 23. Further evidence pointing to the source of the artefact was gained as follows. A saline-filled catheter, whose tip was occluded

with plasticine, was introduced and advanced to a wedged position (confirmed by subsequent 'snap-back' of the tip on disimpaction). The butt end of this catheter was connected to a pressure transducer in the usual way, a pressure of about 10 mm. was induced using a syringe through a side arm, then this side arm was closed. The pressure recorded in this blind ended catheter could be raised or lowered by the stimuli used in the foregoing experiments.

It was therefore concluded that the changes in perfused wedge pressure observed in response to alterations in blood volume and occlusion of a pulmonary artery were due at least in part to changes in the size of the right ventricle.

Final confirmation of the source of the artefact was gained by repeating the experiments in open-chest preparations, in which the catheter was introduced via a pulmonary artery branch, and did not pursue an intracardiac course. Under these circumstances the small changes in perfused wedge pressure followed those in the left atrium and the calculated vascular resistance in the wedge segment was unaltered in response to these stimuli (fig. 24). Reviewing some of the phasic (undamped) pressure recordings obtained with a trans-cardiac perfused catheter, one believes also that the wave forms (other than respiratory fluctuations) are due largely to the action of the right ventricle on the catheter loop (fig. 25).

These experiments, then, failed in their object of demonstrating pulmonary vasomotion in response to changes in pulmonary blood volume and flow. They did, however, reveal an important limitation in the perfused wedged catheter method, when this method employed a trans-cardiac catheter and when the stimuli applied were accompanied by alterations in the size of the right ventricle, or in its force of contraction.

The experiments also demonstrated that changes in right ventricular action could alter the conventional pulmonary artery wedge pressure, and this finding is of considerable relevance in clinical practice. It means that the pressure changes in a wedged catheter may not be due entirely to changes in the left atrial or pulmonary venous pressures, when the records are made during circumstances which alter cardiac action (such as exercise or the administration of vaso-active drugs).

In summary, the principal characteristic of the perfused wedge catheter, relevant to this study, was that perfusion at a constant flow rate evoked a constant pressure. Some hysteresis was noted when large changes in flow occurred. The pressures recorded through a catheter which pursued a trans-cardiac course were significantly modified by alterations in heart size and action. This observation applied to both perfused and unperfused wedged catheters. Because of this, an open-chest preparation, in which the perfused catheter did not traverse the heart, was used in most of the subsequent experiments.

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CHAPTER 3.

ANATOMY.

A review of the anatomy of the pulmonary vasculature was a necessary preliminary to this study. In particular, the size and character of the vessels perfused by a wedged catheter; the nerve supply of these vessels; and their connections with the bronchial circulation were relevant, and these aspects are described here.

According to the classifications of Brenner (1), Edwards (2), and Bloom (3), the catheters used in this study wedged at about the site of the transition from 'elastic' to 'muscular' pulmonary arteries. Fig. 26 shows photo-micrographs of sections of lung, cut at points peripheral to the tip of a wedged No. 7 catheter. Using Hyland's nomenclature for the pulmonary arteries in the dog, the catheter wedges in a second order artery, and the principal arteries perfused are third order arteries (i.e. those with a lumen of about 1.0 mm.)(4)(5). Injection-corrosion specimens showed that two or three arteries with a lumen diameter of about 2 mm. run a relatively long straight course in the lower lobes of the lung in the dog (6), and the catheter was wedged in one of these arteries in most experiments. The segment perfused by one of these vessels

(and hence the wedged catheter) was conical in shape. The base of the cone measured about 4 cm. and it was 5 cm. in height. Our own dye injection and angiographic studies confirmed the findings of Bolt (7), that these are end arteries.

The muscular pulmonary arteries lie close to and branch with the bronchioles, respiratory bronchioles and alveolar ducts (2), so that it is not surprising to find that changes in airway pressures can influence the resistance to blood flow through these vessels.

Pulmonary arterioles and venules are very similar in structure. They have a single elastic lamina, no muscular media and very little adventitia (1). There is, however, a muscle layer in some of the arterioles for a short segment at their point of origin from the muscular arterial stem (2). The small venules which drain the wedge segment are formed around the respiratory bronchioles. These join to form veins which then leave the airways and, at lobular vein size, become confluent with veins from adjacent segments. This anatomical fact is highly significant with regard to the downstream point of pressure reference in a wedged catheter, and this is considered in the next chapter. The medium sized pulmonary veins contain a little smooth muscle, but still much less than arteries of corresponding size. The presence of functionally significant muscular 'sphincters' at the pulmonary vein-left atrial junction has been described by several workers (8 - 10) and there is an increasing weight of evidence to

show that pulmonary vasomotor activity does occur in certain circumstances (11 - 15). Certainly the left atrial musculature is prolonged along the walls of the large pulmonary veins for 1 or 2 cm., and the presence of baroreceptors has been described here (12). It is important to note, however, that the distribution and quantity of smooth muscle in the pulmonary vessels varies markedly from species to species (16)(17). For instance, it is probable that the 'gnarly' constriction of the small pulmonary arteries which has been observed in rabbits after the administration of nor-adrenaline (18) is related to the fact that a relatively thick muscle layer is present in these vessels.

The Bronchial Arteries:

In contrast to the small pulmonary arteries, the bronchial arteries are provided with a thick muscle coat and this suggests that they are capable of active changes in calibre. Whether or not they affect the haemodynamics of the pulmonary circulation under physiological and experimental conditions has been the subject of much controversy. The presence of significant broncho-pulmonary anastomoses would greatly lessen the value of the perfused wedged catheter technique, since these anastomoses could permit an extra (and unpredictable) inflow of blood into the wedge segment. For this reason, some of the observations made by others on the bronchial arteries and the nature of broncho-pulmonary anastomes are reviewed here.

The bronchial arteries arise from the aorta, from the concave aspect of the arch and upper descending aorta at about the level of the fifth thoracic vertebra. They run to the hilum of each lung, where they form a vascular ring round the main bronchus. From this vascular annulus, two distinct sets of branches arise (19). The 'visceral pleural' arteries are of little interest in the context of this study, they supply the pleura and send branches into the interlobular septa to supply the interstitial tissue of the alveoli. The 'true bronchial arteries' also arise from the annulus and usually two branches travel with, and divide with, each bronchus. These branches are joined like the arcades of the mesenteric arteries to form peribronchial and intra-mural networks along the bronchi (20).

The corresponding bronchial veins (21) arise on the walls of the respiratory bronchioles and run centrally on the bronchi to drain into the pulmonary veins, or directly into the left atrium. They communicate freely with the pulmonary veins en route. The pleuro-hilar veins drain into the azygos or hemi-azygos veins. There is free communication between those bronchial veins which drain into the pulmonary venous circulation and those which drain into the systemic veins.

Broncho-pulmonary Anastomoses:

These are frequently found and are of considerable functional significance in certain diseases of the lungs and in

congenital heart disease (22). Controversy exists as to their significance in the normal lung, however. Verloop (23) described broncho-pulmonary anastomoses in normal lungs in the form of short thick-walled muscular arteries ('apexrarterien'). Harris and Heath also subscribe to the presence of such anastomoses in normal human lungs (24). On the other hand, many workers in careful studies have failed to find evidence of such anastomoses (21, 25 - 29). The evidence to support the contention that the bronchial circulation can exert influence on the pulmonary circulation is haemodynamic and based largely on the work of Daly and his collaborators (30 - 32). It must be noted however that these workers derived their results from highly artificial preparations and their results have not been substantiated by other studies in the dog, in which bronchial flow was measured by

Pulmonary Arterio-Venous Communications:

Pulmonary Arterio-Venous Communications:

Controversy also exists concerning the physiological importance of pulmonary arterio-venous shunts. Thus, Frimmetal (36) has claimed that glass spheres, of between 100 and 180 micron in diameter, could reach the pulmonary veins when injected into the pulmonary artery in dogs, but in similar experiments also in anaesthetised dogs, carried out by Ring and his co-workers, only 6 per cent of micro-spheres of 8 u. in diameter traversed the pulmonary circuit (37). Other recent studies on

the subject which have been reviewed by Fishman (38) lead to the conclusion that pulmonary arterio-venous shunts are not of functional significance in the normal man and dog.

The Nerve Supply to the Pulmonary Vessels: (32, 39 - 41)

We are again indebted to Daly for much detailed information concerning the innervation of the pulmonary vasculature. The presence of both sympathetic and para-sympathetic nerve supply to the small pulmonary vessels (42), and of post-ganglionic sympathetic fibres to pulmonary arterioles, capillaries (43) and veins (44), has been demonstrated, but such observations have not clarified the role of these nerves in the regulation of pulmonary blood flow (38)(42). That they are potentially active has been demonstrated. Daly and his co-workers have adduced evidence to show that stimulation of the upper thoracic sympathetic outflow is followed by pulmonary vasoconstriction in the dog (45 - 47), whereas stimulation of the distal cut end of the vagus seems to evoke a dilator response (42), and Simmons has shown that bilateral cervical vagotomy is associated with an increase in the pulmonary vascular resistance in dogs (48). Daly has emphasised an important function of the bronchial circulation in maintaining the integrity of pulmonary vascular innervation and this observation must be borne in mind in interpreting results obtained from experiments employing isolated lung preparations. On the other hand, intactness of the nerve supply to the lung is

by no means a pre-requisite for pulmonary vasomotion - which can still occur quite dramatically in denervated lungs, both in animals and in man (49).

In summary, the distribution of smooth muscle and autonomic nerves in the pulmonary vasculature would indicate that the vessels which are capable of altering their calibre are the large and small pulmonary arteries and veins and possibly the veno-atrial junctional area. The pulmonary arterioles in man and in the dog are thin-walled, non-muscular structures, compared with corresponding vessels in the systemic circulation. (In the rabbit and cow, these pre-capillary vessels are muscular).

The presence of extra-vascular smooth muscle has been demonstrated by histological techniques, both in the tracheo-bronchial tree and throughout the lung (50)(51). There is no evidence, however, that this reticulum plays any active part in influencing vasomotor activity (38).

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CHAPTER 4.

THE RELATIONSHIP BETWEEN THE PULMONARY ARTERY WEDGE PRESSURE AND THE LEFT ATRIAL PRESSURE.

In 1948 Hellems and his co-workers postulated that the pressure measured in a catheter which had been wedged in a peripheral pulmonary artery represented accurately the pressure in the left atrium (1)(2). Since then, the pulmonary artery wedge pressure has been used extensively in place of the left atrial pressure as one of the factors used to calculate pulmonary vascular resistance. Many published works have added corroborative evidence to Hellems original work (3 - 7). During the last ten years, however, conflicting reports have appeared from time to time concerning the relationship between the two pressures (8 - 11). Besides pointing out the technical difficulties inherent in obtaining a valid 'wedge' pressure (8)(12), reports have differed concerning the pattern of the pressure differential between the wedge pressure and the left atrial pressure, and the mechanisms which might account for it. Murphy (13) concluded that the left atrial pressure was often higher than the wedge pressure, while on the other hand, Luchsinger as the result of a carefully controlled study in man contended that the pulmonary artery wedge pressure was consistently 35 per cent higher than

the left atrial pressure (14). Other workers have noted a positive gradient from the pulmonary artery wedge pressure to the left atrial pressure and have interpreted it as evidence of active venomotion (15 - 17). Certainly the pulmonary veins are embraced by a layer of smooth muscle at their junction with the left atrium (18) and presumably are capable of vasomotion.

In the course of the present study, simultaneous records of the pulmonary artery wedge pressure (static wedge pressure) and the left atrial pressure were taken under many different circumstances, and it became clear early in the study that they were usually not identical and further that their relationship was not constant under changing circulatory conditions. Accordingly, experiments were planned to explore specifically the relationship between the two pressures, and records available from other experiments in this study were reviewed with these factors in mind.

In any comparison of experimental results, careful attention must be paid to the standards of reference used. This principle is particularly important when small pressure differentials such as that between the static wedge and the left atrium are being considered. In Bernstein's study, for instance, the zero point of reference for the wedge pressure was 5 cm. dorsal to the angle of Louis, but was 10 cm. dorsal to this point for the left atrial pressure records (8).

Material and Methods:

The open-chest preparation was used in these experiments and the catheter was introduced in a manner which did not interfere with the local innervation. A second catheter was introduced into the left atrium through a small pulmonary vein. In some animals a third catheter was advanced through the left atrium until its tip lay free within a large pulmonary vein, 3 to 4 cm. from the veno-atrial junction. Pressures were measured through these catheters. Except where stated, the pressure transducers were held at the same level and zero reference was atmospheric pressure. A femoral artery and vein were also cannulated and connected to a reservoir in such a way that blood could be withdrawn or re-infused. In some animals provision was also made to occlude abruptly one main pulmonary artery with a balloon catheter.

In addition, some relevant data from experiments done on closed-chest animals were used, with particular reference to the effects of right ventricular action on the intra-cardiac loop of catheter.

Using the foregoing preparations, the relationship between the static wedge pressure and the left atrial pressure was studied under four experimental conditions:-

(1) During a rapid intra-venous infusion of blood.

(2) During withdrawal of blood from the femoral artery.

(3) During occlusion of the contra-lateral main pulmonary artery.

(4) During acute elevation of the mean left atrial pressure.

(This was induced by causing mitral incompetence.)

In order to minimise any response specifically related to the infusion of 6 per cent Dextran, an exchange transfusion was carried out 30 to 60 minutes before the definitive experiments. 200 ml. of Dextran (6 per cent in 5 per cent Dextrose-water) were infused while an equal volume of blood was removed into a heparinised container.

In a further series of experiments, the relationship between the pressure in a pulmonary vein and that in the left atrium was studied, while the same stimuli were applied.

Results:

In all the preparations used, as long as resting or control conditions prevailed, the relationship between the left atrial pressure and the static wedge pressure remained constant. The latter was the same as, or higher than, the former. The static wedge pressure was never lower than the left atrial pressure. In 65 preparations, in which repeated records of the two pressures were taken, under resting conditions, the static wedge pressure was the same as the left atrial pressure in 11, and was higher in 54. The difference in pressure ranged from 0 to 5 mm.Hg., but was

Table 1.

Dog No.	CONTROL			VOLUME INFUSED	AFTER INFUSION		
	St.W.P.	L.A.P.	ΔP.		St.W.P.	L.A.P.	ΔP.
1	4.0	1.0	3.0	100 ml. in 1 min.	7.0	2.0	5.0
1	4.5	1.0	3.5	"	7.0	2.0	5.0
1	4.0	1.0	3.0	"	7.0	2.5	4.5
2	4.0	2.0	2.0	150 ml. in 1 min.	11.0	7.0	5.0
2	5.0	2.0	3.0	100 ml. in 40 secs.	9.0	4.0	5.0
2	5.0	1.0	4.0	50 ml. in 40 secs.	9.0	2.5	6.5
2	5.5	2.0	3.5	100 ml. in 40 secs.	10.0	4.0	6.0
3	4.0	1.0	3.0	"	12.0	4.0	8.0
3	3.5	1.0	2.5	100 ml. in 1 min.	10.0	3.0	7.0
3	4.0	2.0	2.0	"	11.0	4.0	7.0

The results of experiments to show the effect of a rapid intravenous infusion (of autogenous blood) on the relationship between the static wedge pressure and the left atrial pressure.

constant for each animal under resting conditions.

The effect of intravenous infusions is shown in Table 1 (opposite). When a volume of autogenous blood was infused rapidly, both the static wedge pressure and the left atrial pressure were increased, but the rise in the former was always greater. The pressure differential between the static wedge pressure and left atrial pressure increased during the infusion and remained high during the period of stabilisation which followed. Fig. 27 shows the pattern of change which was common to each of these experiments. After 3 to 5 minutes both pressures returned to control levels. The mean airway pressure was 5.5 mm.Hg. (the significance of this factor is discussed later).

The results of experiments in which blood was withdrawn rapidly are shown in Table 2. In response to this stimulus, both the static wedge and the left atrial pressures fell. In each experiment, however, the fall in the left atrial pressure exceeded the fall in the static wedge pressure. During the ensuing 3 or 4 minutes, while the left atrial pressure returned to near control levels, the static wedge pressure remained reduced, so that the net change when the circulation had stabilised was a reduction in the pressure differential from static wedge to left atrium.

In each of these preparations (after the withdrawal of blood), when blood flow to the lung in which the wedge catheter

Table 2.

Dog No.	CONTROL			BLEED			RECOVERY (5 mins.)		
	St.W.P.	L.A.P.	ΔP.	St.W.P.	L.A.P.	ΔP.	St.W.P.	L.A.P.	ΔP.
4	7.0	5.0	2.0	5.0	1.0	4.0	6.0	5.0	1.0
4	7.5	5.0	2.5	5.0	1.0	4.0	6.5	4.5	2.0
5	10.0	7.5	2.5	6.5	2.5	4.0	8.0	7.0	1.0
5	8.0	7.0	2.0	6.0	2.0	4.0	7.0	6.5	0.5
2	5.0	3.0	2.0	3.5	0	3.5	4.0	3.0	1.0
3	6.0	3.5	2.5	4.0	0	4.0	4.5	3.0	1.5

The results of experiments to show the effect of withdrawal of blood from the systemic circulation on the relationship between the static wedge pressure and the left atrial pressure. The airway pressure was 6 mm.Hg. (mean) in these experiments.

Table 3.

Dog No.	CONTROL (after bleeding)			CONTRA-LATERAL PULMONARY ARTERY OCCLUSION		
	St.W.P.	L.A.P.	ΔP.	St.W.P.	L.A.P.	ΔP.
4	6.5	4.5	2.0	8.0	5.0	3.0
5	7.5	6.5	1.0	8.5	6.0	2.5
2	4.0	3.0	1.0	5.0	3.0	2.0
3	4.5	3.0	1.5	6.0	3.0	3.0

The results of experiments to show the effect of increasing pulmonary blood flow (by occlusion of the contra-lateral pulmonary artery) on the static wedge/left atrial pressure gradient, in animals which had been bled of 150 to 200 ml. The mean airway pressure was 6 mm.Hg. in these experiments. The results shown are the means of three experiments in each animal.

Table 4.

Dog No.	CONTROL			MITRAL INCOMPETENCE		
	St.W.P.	L.A.P.	ΔP.	St.W.P.	L.A.P.	ΔP.
7	12.0	9.5	2.5	16.0	14.0	2.0
7	13.0	11.0	2.0	16.0	14.0	2.0
8	5.0	3.0	2.0	7.0	5.0	2.0
9	8.0	7.0	1.0	10.0	9.0	1.0
9	7.5	6.0	1.5	11.0	9.5	1.5
10	7.0	5.0	2.0	9.0	7.0	2.0

The results of experiments to show the effect of acute mitral incompetence on the relationship between the static wedge pressure and the left atrial pressure. The mean airway pressure in these experiments was 5 mm.Hg.

Table 5.

Dog No.	CONTROL			AFTER INFUSION (250 ml.)		
	P.vein	L.A.P.	Δ P.	P.vein	L.A.P.	Δ P.
11	2.5	2.0	0.5	5.0	2.5	2.5
12	3.0	1.0	2.0	5.5	1.5	4.0
13	5.0	3.0	2.0	6.0	3.0	3.0
14	3.0	1.5	1.5	6.0	2.5	3.5
14	3.5	1.5	2.0	6.0	3.0	3.0
15	7.0	4.0	3.0	9.0	5.5	3.5

The results of experiments to show the consequences of a rapid infusion of autogenous blood on the pressures in a pulmonary vein and in the left atrium.

Table 6.

Dog No.	CONTROL			OCCLUSION OF OPPOSITE PULMONARY ARTERY.		
	P.vein	L.A.P.	Δ P.	P.vein	L.A.P.	Δ P.
11	3.0	2.5	0.5	5.0	1.5	3.5
12	3.0	1.0	2.0	5.5	1.0	4.5
13	5.0	3.5	1.5	6.5	2.5	4.0
14	3.5	1.5	2.0	5.5	1.0	4.5
14	4.0	2.0	2.0	6.0	1.0	5.0
15	7.5	5.0	2.5	8.5	3.5	5.0

The results of experiments to show the effect of increasing pulmonary blood flow (by occlusion of the contra-lateral pulmonary artery) on the pressures in a pulmonary vein and in the left atrium.

lay was increased (by occluding the contra-lateral pulmonary artery), the wedge/left atrial gradient was increased to the control level or greater (Table 3).

The results of experiments to show the relationship between static wedge pressure and left atrial pressure, when the latter was raised in acute mitral incompetence, are shown in Table 4. The valve was rendered incompetent by distorting the anterior cusp with a probe which was introduced through the left atrium. In our preparation it was possible to raise the left atrial pressure by about 35 per cent in this way. In each experiment the static wedge pressure rose by a corresponding amount, so that the pressure differential from static wedge pressure to left atrium remained constant.

Comparison of the pressure measured directly in a small pulmonary vein with the left atrial pressure during rapid infusions also yielded interesting results. They are shown in Table 5. Under control conditions there was a small pressure gradient from the small pulmonary veins to the left atrium. When 100 or 200 ml. of blood were infused rapidly, this gradient was increased in each case. A similar response was seen in those experiments in which pulmonary blood flow was abruptly increased to the lung in which the pulmonary venous pressure was being monitored. Occlusion of one pulmonary artery caused a small fall in left atrial pressure and a rise in pulmonary venous pressure in the

opposite lung, with a net increase in the pulmonary vein/left atrial pressure gradient (Table 6).

Proper placing of the cannulae was difficult in some of these preparations, and some experiments were discontinued for technical reasons. No other pattern of response was seen, however, and the results of all the experiments which were without obvious artefact have been included.

Discussion and Review:

These experiments show: (1) that the mean static wedge pressure is normally higher than the mean left atrial pressure and that the pressure differential remains constant under control conditions; (2) the pressure measured in a pulmonary vein 2 to 4 cm. from the veno-atrial junction is also higher than the left atrial pressure; (3) acute elevation of the left atrial pressure is accompanied by an increase in the static wedge pressure of the same magnitude; (4) the pressure differential between the static wedge and the left atrium is increased by the rapid infusion of blood into a systemic vein and by occlusion of the contra-lateral main pulmonary artery; (5) the pressure differential between a pulmonary vein and the left atrium is increased by the same procedures.

These results call for a re-consideration of what is being measured by the wedged pulmonary artery catheter. This pressure has been regarded as a damped replica of the left atrial pressure.

It has been accepted that a segment of the pulmonary vascular bed - comprising arteries, arterioles, capillaries, venules, veins - between the catheter tip and the left atrium, acts as an extension of the catheter to the latter chamber, so that when the catheter is impacted, flow through the wedge segment ceases and there is a static column of fluid from the pressure transducer to the left atrium. The vessels in the wedge segment are subject to transmural pressures, transmitted from the airways, and may also undergo intrinsic changes in calibre, but these factors should not influence the mean pressure while there is no flow. External compression, or vasoconstriction of the vessels, would only expel some blood into the left atrium and reduce the volume contained in the wedge, it would not alter the 'wedge pressure'.

How then can one explain the pressure gradient from the wedged catheter to the left atrium? The writer believes that one must introduce blood flow at some point in the wedge segment, and that the concept of a static column of fluid from catheter to left atrium is untenable. If fig. 28A is regarded as representative of the tip of a wedged catheter and the vascular bed which it subtends, then blood would flow from the region of higher pressure. Unless this blood was being replaced continuously, the pressure gradient would gradually diminish. In our experiments where the vascular bed of the wedge segment was delineated with dye or radio-opaque medium, we found no evidence to suggest that blood flowed in from

adjacent segments, and this is in keeping with the angiographic studies of others (19). In common with Donald (20), however, we did observe wash-out of the dye from the veins, 2 or 3 cm. from where they joined the left atrium. At this point the veins draining several contiguous segments are confluent, and at this point blood flow does occur in the wedge segment. No flow occurs between this point and the catheter tip upstream, so that a truer representation of the vascular bed in the wedge segment is that shown in fig. 23B. This hypothesis suggests that the pressure gradient is due to the resistance to flow in the juxta-atrial pulmonary veins. Support is given to this concept by the fact that the gradient increased in conditions of increased pulmonary blood flow (whether due to rapid intravenous infusion or to occlusion of the contra-lateral pulmonary artery). Thus, in the pulmonary wedge segment as in any other haemodynamic system, the existence of a pressure gradient other than that due to gravity, implies the presence of flow through a resistive area. Since flow in the wedge segment occurs only in the juxta-atrial veins, this must be the site of resistance.

The contribution of the pulmonary veins to the total pulmonary vascular resistance has been the subject of several studies (16)(17)(21 - 26). In 1949, Haddy observed that the pulmonary venous pressure, measured 2 cm. from the left atrium, increased with the cardiac index (27). Aviado also found a rise

in pulmonary venous pressure when pulmonary blood flow was increased (21), and the same group amplified this study by measuring the pressure-flow relationship in both the intra-pulmonary and extra-pulmonary portions of the pulmonary veins, and showed that the latter contributed a significant proportion of the total resistance to flow (28). Rudolph, in experiments similar to those reported here, also showed that the pulmonary vein / left atrial pressure gradient could be increased by occlusion of the opposite pulmonary artery, and by certain drugs (adrenaline, serotonin)(25). He attributed the increase in gradient to venous constriction. In the light of our experiments and those of Haddy and Avlado, however, Rudolph's results could have been due to the increase in pulmonary flow. We did not see a change in the static wedge / left atrial relationship during the action of adrenaline and serotonin. (See chapter on Drugs.) The doses of these drugs used in our experiments were intended to have a local action only, and did not affect cardiac output in most preparations. It would be in keeping with our findings to suggest that larger doses of the drugs influenced the pressure differential by altering pulmonary blood flow.

Feeley (26) found that the pressure gradient between the small pulmonary veins and the left atrium in dogs averaged 3.6 mm., while the total gradient from pulmonary artery to left atrium

was 10.9 mm. (average), under resting conditions, that is the veins provided at least one third of the resistance to flow in the pulmonary vascular bed. Kuramoto and Rodbard attributed an even greater portion of the total resistance to the veins in some of their experiments (23).

The results from experiments in which pressure is measured in small pulmonary veins must be interpreted with certain reservations. It was our experience that the correct positioning of a fine pulmonary venous catheter was technically difficult. It was found frequently that the catheter would partially wedge, and then measure something approaching the pulmonary arterial pressure. It also seems probable that the presence of a catheter, no matter how fine, in a pulmonary vein will constitute an obstruction to flow and cause a spurious elevation of the measured pulmonary venous pressure. However, due regard to this potential source of artefact was made in the present study, and one believes that the conclusions reached are valid.

There is good evidence then that the pulmonary veins contribute significantly to pulmonary vascular resistance, and there is in addition some experimental evidence to suggest that they are capable of active vasomotion.

Under resting conditions in animals and man, the mean pressure measured in a wedged catheter is higher than the mean left atrial pressure. The finding that the pressure

differential is increased when the pulmonary flow increases - and may be influenced by certain drugs - is of considerable relevance in clinical practice. Unfortunately, confirmation of these findings in man will be technically difficult and the potential artefacts added by the action of the right ventricle on a trans-cardiac catheter (Chapter 2) will make the records difficult to interpret.

The foregoing discussion has been concerned with the relationship between the left atrial pressure, pulmonary venous pressure and the static wedge pressure. The effect of changes in the former factors on the perfused wedge pressure merits separate consideration.

An incidental finding in the experiments reported above, and those in Chapter 7, was that a reduction in the perfused wedge pressure occurred when the left atrial pressure was elevated. This is in keeping with observations in isolated perfused cat lungs (29) and in dog lungs in situ (30)(31), which showed that an increase in left atrial pressure could distend the vessels in the lung and lead to a fall in resistance. The hydraulics of this phenomenon have been demonstrated very clearly by Rodbard (32).

We would conclude that four pressures pertaining to the perfused wedge segment can be measured: (1) the perfused wedge pressure, (2) the static wedge pressure, (3) the pulmonary

venous pressure, and (4) the left atrial pressure. Under control conditions, with perfusion of the segment at a constant rate, these pressures maintain a constant relation to each other with a decrement in pressure from the first to the fourth. This relationship can be altered, however, by changes in blood volume, pulmonary flow, left atrial pressure and airway pressure.

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CHAPTER 5.

THE EFFECTS OF DRUGS.

The pharmacology of the pulmonary circulation has been studied quite extensively and in a review of the subject in 1960, Aviado was able to cite 856 references (1). Yet agreement has not been reached on the effects on the pulmonary vasculature of several commonly used drugs. The detailed evaluation of the purely pulmonary effects of a drug is difficult. Most of the drugs which may be active in the pulmonary circuit affect also the circulation as a whole, and their distant effects often profoundly alter pulmonary haemodynamics by changing such factors as cardiac output, systemic arterial and venous pressure and resistance, pulmonary blood volume and left atrial pressure. These distant effects may exert their influence on the pulmonary circulation directly, reflexly, through hormonal action, or by inducing bronchomotor activity. Separation of the active from the passive components of the pulmonary vascular response to vasoactive drugs can be achieved to some extent by experiments which use isolated perfused lungs, or preparations in which all the variables can be measured or controlled. But this necessitates the use of animal preparations and methods applicable only to animals. However, many of the drugs of potential clinical

interest have different actions in different species (2). Acetylcholine, for example, reduces the pulmonary vascular resistance in man (3)(4), but increases it in the dog (vide infra). Moreover, the action of some drugs varies with the state of the pulmonary vessels, and the proper evaluation of a drug which is expected to show a vasodilator effect can be best carried out on vessels which are already constricted.

In planning a study of the effect of drugs on the pulmonary circulation, one must first define objectives: thus, if the results of the study are to have immediate clinical relevance, it is the total effect of the drug on human subjects which must be considered. If, on the other hand, one is looking for a drug with a specific action, e.g. the ability to reduce pulmonary hypertension, then much preliminary work can be done appropriately on animal preparations.

The aim in this study was to study the strictly local effect of certain drugs on the small pulmonary vessels. The perfused wedged catheter technique was used because it could be applied both in animal experiments and in man, and because by its use, the drug under study could be introduced directly to its site of presumptive action, in a dose small enough to have little or no action when it subsequently reached the heart and systemic circulation.

It has been assumed that the hydraulic equivalent of Ohms Law could be applied with validity to the small circumscribed area of vascular bed, since the substituted values for flow and pressure gradient were measurable with precision.

The method was also used to compare the direct and the secondary effects of the same drug. This was possible with the perfused wedged catheter technique, since a drug which had been introduced into the systemic circulation could not affect the vasculature of the wedge segment directly because the latter was separately perfused with blood which was free of the drug. The only relevant variable which was not measurable in the preparations used was the blood volume of the segment under study.

Materials and Experimental Protocol:

Fifty-seven dogs were used in this section, and more than one hundred experiments were done. In four animals experiments were terminated after technical errors. The animals were anaesthetised with intravenous pentobarbitone, the trachea was intubated and ventilation was controlled by intermittent positive pressure, using a mixture of oxygen and air, containing 30 - 40 per cent oxygen. The open-chest preparation was used, as described in Chapter 1, and the perfusate was autogenous venous blood at 30°C.

The pressures in the wedged catheter and in the left atrium were recorded continuously in each experiment. Other factors,

such as the systemic arterial pressure, the main pulmonary pressure, a static wedge pressure (through another wedged catheter) and the intra-bronchial pressure, were measured where relevant. In some supplementary experiments pulmonary blood flow was also measured with an electro-magnetic flowmeter.

Each experimental run was conducted as follows:

Control records were obtained, then the drug was introduced into the perfusing catheter through taps by causing the displacement of an equal volume of the perfusate. The drug was dissolved in saline and the volume introduced was standardised. The choice of dosage was somewhat empirical and largely determined by preliminary experiments in which various doses were tried. The doses used in the definitive experiments are noted in the results tables. Since the transit time through the length of catheter used in each experiment was known, the time of arrival of the drug at the catheter tip was predictable and could be marked on the records.

Analysis of the Pressure Records:

The method used for recording the response of the perfused wedge pressure to each drug was standardised, and the form of a typical pressure record is shown in fig. 29. This is a foreshortened drawing of the pressure tracing recorded through the wedged catheter. Seven sections of the tracing can be defined as follows:-

(1) The static wedge pressure, i.e. the "pulmonary capillary" pressure. The catheter is not being perfused at this time.

(2) The perfused wedge pressure. The catheter is being perfused at a constant flow rate and this is the control pressure for this experiment.

(3) Perfusion has been interrupted briefly to allow introduction of the drug into the catheter.

(4) Perfusion has been restarted, and this segment represents transit of the drug through the catheter from the point of introduction to the catheter tip. The pressure is slightly lower than the control pressure because of a reduction in the viscosity of the perfusate in the catheter, which has now been diluted by the drug and its saline vehicle.

(5) The arrow marks the point of arrival of the drug at the wedge segment.

(6) In this segment, a change in pressure is recorded (if the drug produced a change in resistance to flow). In the example shown, the record would be interpreted as evidence of vasoconstriction.

(7) Perfusion has been stopped and the pressure here is the static wedge pressure (pulmonary capillary pressure) measured during activity of the drug.

In the case of short acting drugs, continued perfusion of the wedge segment was accompanied by a return of the wedge pressure to control levels. In these animals, the experiment could be repeated several times.

The recording paper speed was 0.5 mm./sec. unless stated otherwise, and the grid markings are 5 mm. apart in the tracings which are reproduced.

The following drugs were studied in this way:

Adrenaline.

Nor-adrenaline.

Tolazoline (Priscol).

5-hydroxytryptamine (Serotonin).

Iso-propyl-noradrenaline (Isuprel).

Acetylcholine.

Theophylline-ethylenediamine (Aminophylline).

Metaraminol (Aramine).

Since saline was the common vehicle, the effect of saline alone was studied first.

Results:

The findings for each drug studied are presented as follows: There is first a description of specific adaptations of the method to suit the requirements of the experiment. The results of the experiments are then detailed in tabular form with a photograph of a representative record to show the pattern of the response.

In setting up some of these experiments, the pressure transducers were mounted vertically one above the other instead of horizontally at the same level. Consequently, some of the pressure relationships (e.g. between static wedge and left atrium) are relative and not absolute. However, the position of the transducers was constant for each experiment, and so the results derived from the measurement of changes in pressure are valid. For each drug, conclusions are drawn and discussed along with a review of other relevant work on the subject.

The Effect of the Saline Vehicle:

In the experiments where the effect of a single dose of a drug was studied, it was introduced into the wedge segment as bolus, using saline as the vehicle. The admixture of the bolus of saline with the blood perfusate, by causing a reduction in the viscosity of the latter, altered the relationship between pressure and flow in the catheter and in the perfused segment. Since this effect per se could modify the records of experiments where drugs were introduced, several recordings were taken to demonstrate and quantitate the effect of a bolus of saline on the perfused wedge pressure tracings. An example is shown in fig. 30. The record shows a dip in the perfused wedge pressure tracing which corresponds with the passage of the saline through the wedge segment. The first 17 mm. of the perfused wedge pressure record represents transit of the saline through the catheter. This is

Table 7.

Dog No.	Flow ml./min.	Cath P	CONTROL					DOSE	ADRENALINE				
			St.W.P.	L.A.P.	G.W.P.	N.W.P.	R	mg.	St.W.P.	L.A.P.	G.W.P.	N.W.P.	R
18	0.76	7	5.0	4.0	28	13	10.5	.001	5.0	4.0	50	43	50.0
8	0.76	7	5.0	5.0	21	14	9.2	.001	7.0	5.0	44	37	39.0
19	2.0	1	2.0	2.0	14	13	5.5	.0005	2.0	2.0	27	26	12.0
20	2.0	1	2.5	4.0	13	12	4.75	.0005	2.5	4.0	23	22	9.75
20	0.76	5	4.0	4.0	14	9	6.29	.0007	4.0	4.0	25	20	21.2
21	0.76	5	1.0	2.0	12	7	7.9	.0007	1.0	2.0	23	18	22.4
21	2.0	1	1.0	3.0	14	13	6.0	.0005	1.0	3.0	27	26	12.5
22	2.0	5	4.0	2.0	20	15	5.5	.0007	4.0	2.0	41	36	16.0
22	2.0	5	4.0	2.0	19	14	5.0	.0007	4.0	2.0	39	34	15.0

The results of experiments to show the local effect of adrenaline on the perfused wedge segment. Cath.P = the pressure evoked by perfusion of the catheter alone in air; St.W.P. = static wedge pressure; L.A.P. = left atrial pressure; G.W.P = gross wedge pressure; N.W.P. = net wedge pressure; R = vascular resistance in the wedge segment (N.W.P. minus St.W.P., divided by flow).

followed by a sharp fall in pressure with a slower rise to a plateau which is about 0.5 mm. higher than at the beginning of the record - because at the end point both the catheter and wedge segment were again being perfused with whole blood.

Adrenaline: Material and Protocol.

The local effect of adrenaline on the perfused segment was studied in 9 experiments in 5 dogs. In each experiment the dose of adrenaline was introduced in 0.3 ml. saline into the perfusion catheter, while a continuous record of the perfused wedge pressure was recorded. In two further experiments in 2 dogs, the effect of adrenaline was studied in a wedge segment which had been perfused previously with tolazoline.

Results: (Table 7)

When adrenaline in a single dose of 0.001 mg. was introduced into the wedge segment, a marked rise in the perfused wedge pressure occurred (fig. 31). No change occurred in the left atrial pressure or in the static wedge pressure - whether measured in the same wedge segment; in an adjacent wedge segment, or directly through a catheter in the left atrium. The local pressor effect of adrenaline lasted for some 15 - 20 minutes. There was no change in the intra-bronchial pressure during these experiments (fig. 32).

From the table (7), it can be seen that the effect of adrenaline was to increase the resistance to blood flow in the

wedge segment from two to five fold. The degree of change in resistance was related directly to the dose used, but the relationship was not linear.

When adrenaline was given after perfusion of the wedge segment with tolazoline (0.17 mg.), its constrictor effect was greatly attenuated. The results of these experiments are shown in Table 14 (facing page 92). The results described later in this section show further that tolazoline, when introduced into the wedge segment after adrenaline, was capable of greatly reducing a pressor response to the latter (Table 13, facing page 91).

Discussion:

The question of whether the pulmonary vessels respond to autonomic stimuli and to circulating adrenaline has been investigated extensively in several species of animal and in man. In 1898, Velich showed that the infusion of adrenal extracts could produce a rise in pressure in the pulmonary artery (5). The studies of Daly and his collaborators have demonstrated the sympathetic innervation of the pulmonary vasculature (Chapter 3), and these workers have shown that electrical stimulation of the upper thoracic sympathetic chain usually causes pulmonary vasoconstriction in the dog (6)(7)(8). Wearn has noted that the local application of adrenaline to the cat lung was associated first with constriction, then dilatation of the vessels (9), and a similar biphasic response was noted by

Irwin in rabbits (10). Nisell found that adrenaline caused dilatation of arterioles in isolated lung preparations in the cat, but postulated that the bronchodilator action of adrenaline might cause a fall in resistance to blood flow through the lungs (11). In the dog, Hamilton (12) found no increase in pulmonary vascular resistance in response to adrenaline. But in dog lungs, perfused by a pump, Aviado concluded that adrenaline was productive of vasoconstriction (13). In a carefully controlled study also in dogs, Fesley et al. reported a reduction in total pulmonary vascular resistance with adrenaline with a concomitant increase in pulmonary blood volume (14).

In human subjects, infusions of adrenaline have been shown to increase pulmonary flow, pulmonary pressure and pulmonary wedge pressure (15)(16). The calculated resistance did not change in a consistent fashion in Fowler's studies, while Witham found that adrenaline increased resistance in normal subjects, but lowered it in cases with pre-existing pulmonary hypertension. Thus, although several authors have noted an increase in pulmonary pressure consequent on the infusion of adrenaline (16 - 19), the drug also causes an increase in pulmonary flow (18)(20)(21), and according to some studies an increase in wedge pressure (17)(22)(23), pulmonary venous pressure (24) and pulmonary blood volume (14)(25). Harris concluded recently that adrenaline was without significant effect on the pulmonary vascular resistance

in the intact animal or man (26).

Our own results are not necessarily at variance with these varied conclusions. Our experiments were concerned with the local effect of adrenaline directly on the pulmonary vasculature, and the results presented show that it does have a powerful constrictor effect in circumstances where the vessels studied were protected from a change in flow or an elevation of left atrial pressure. Our findings are in agreement with the work of Alcock (27) and Aviado (1), who also used preparations in which the systemic or cardiac effects of the drug were eliminated or modified. The distinction between the local and overall effects of adrenaline on the pulmonary circulation were recently considered and studied by Peeley (14), who concluded that while adrenaline increased the "stiffness" of the pulmonary vessels, this effect was opposed by an increase in the transmural pressure, so that distension predominated and was accompanied by a consequent increase in pulmonary blood volume and a fall in total pulmonary vascular resistance. This fundamental concept of the net effect of a drug depending on the sum of two or more opposing forces was postulated by Wiggers in 1909 (28). The significance of these observations in clinical practice is that although circulating adrenaline may not demonstrably elevate the calculated pulmonary vascular resistance, an increase in right ventricular work may be necessary to overcome the local

constrictor effect of the drug on the pulmonary vessels.

Nor-adrenaline: Material and Protocol.

The same experimental plan was adopted as for adrenaline. In 6 experiments in 4 dogs, a dose of nor-adrenaline was introduced into the perfusion catheter and the consequent changes in the perfused wedge pressure were recorded. In two further experiments in 2 dogs, the effect of tolazoline on the response to nor-adrenaline was studied, and in 2 other animals, the dose of nor-adrenaline was introduced after the wedge segment had been perfused with blood containing tolazoline.

In order to confirm that the effects observed following perfusion of the wedge segment with a dose of nor-adrenaline were locally mediated, the preparation was modified in further experiments in which nor-adrenaline was infused intravenously at a controlled rate, while the wedge segment was perfused with previously drawn blood which did not contain nor-adrenaline. The rate of intravenous infusion of the drug was adjusted so as to sustain a rise of mean systemic blood pressure to a level of about 30 per cent above the control level (4 experiments in 2 dogs). The mean pulmonary pressure (measured through a catheter in the main pulmonary artery) was also monitored in these experiments.

Results:

The qualitative effect of nor-adrenaline introduced directly into the vessels of the wedge segment was similar to

Table 8.

Dog No.	Flow ml./min.	Cath F	CONTROL					DOSE mg.	NOR-ADRENALINE				
			St.V.P.	L.A.P.	C.V.P.	R.V.P.	R		St.V.P.	L.A.P.	C.V.P.	R.V.P.	R
23	2	4	3.0	2.0	15.0	11.0	4.0	.0007	3.0	2.0	25.0	21.0	9.0
23	2	4	3.0	2.0	14.0	10.0	3.5	.0015	3.0	2.0	23.0	19.0	8.0
24	2	4	2.0	2.0	17.5	13.5	5.75	.0007	2.0	2.0	29.0	25.0	11.5
24	2	4	2.0	2.0	18.0	14.0	6.0	.0015	2.0	2.0	31.5	27.5	12.75
25	2	4	1.0	2.0	13.0	9.0	4.0	.0015	1.0	2.0	17.0	13.0	6.0
26	2	4	2.5	3.0	15.0	11.5	4.5	.0015	2.5	3.0	25.5	21.5	9.5

Results of experiments to demonstrate the local effect of nor-adrenaline on the perfused wedge segment.

Table 9.

Dog No.	Flow ml./min.	CONTROL							NOR-ADRENALINE (by systemic vein)						
		Syst. P.	Pulm. P.	St.W.P.	L.A.P	G.W.P	H.W.P	R	Syst. P.	Pulm. P.	St.W.P	L.A.P	G.W.P	H.W.P	R
27	2	110	18	5.0	4.0	18.0	14.0	4.5	155	22	4.0	3.0	17.0	13.0	4.5
27	2	105	19	5.0	4.0	19.0	15.0	5.0	155	22	4.0	3.0	19.0	14.0	5.0
28	2	120	14	6.0	4.0	18.0	14.0	4.0	165	17	5.0	3.5	17.0	13.0	4.0
25	2	90	13	5.0	4.0	16.0	12.0	3.5	145	15	4.0	3.0	15.0	11.0	3.5

Results of experiments to show the effect of nor-adrenaline, administered into the systemic circulation, on some parameters of the pulmonary circulation.

Syst.P = mean systemic arterial pressure; Pulm.P = mean pulmonary arterial pressure; other symbols are as for Table 7. The Cath.P = 4 mm. in each experiment.

that of adrenaline (Table 8). The drug caused a sustained (20 - 30 minutes) rise in the perfused wedge pressure and hence in the calculated resistance. No change occurred in either the static wedge pressure or the left atrial pressure. When a dose of tolazoline was subsequently introduced into the wedge segment, the perfused wedge pressure returned to the control level (see Table 12). In the two animals wherein the wedge segment had been dosed previously with tolazoline, nor-adrenaline had a much reduced effect; the perfused wedge pressure rose by only 1.0 mm. and the calculated resistance increased by only 14 per cent. The results obtained when nor-adrenaline was infused into a systemic vein are shown in Table 9. A rise in systemic arterial pressure was noted (the infusion was adjusted so as to maintain this pressure at the raised level). At the same time, the mean pulmonary arterial pressure rose while the left atrial pressure and static wedge pressure fell slightly. The net perfused wedge pressure, minus the static wedge pressure, however was unchanged, (the gross perfused wedge pressure reflected the small fall in left atrial pressure).

Discussion:

As with adrenaline, the effect of nor-adrenaline on the pulmonary circulation in the intact animal preparation or in man, is compounded of its local effect plus its effects on the systemic circulation and its inotropic effect on cardiac action (29).

Studies in patients with a left-to-right shunt through a ventricular septal defect have shown that the systemic action of the drug is dominant, in that the shunt was increased in a left-to-right direction in response to an infusion of nor-adrenaline (30). Most workers have found that intravenous infusions of nor-adrenaline in the intact dog and man cause a rise in the pulmonary arterial pressure (17 - 19)(31)(32), but among the more detailed investigations concerning resistance, results are conflicting. Thus Fowler (31) found that the wedge pressure and pulmonary pressure both rose, with no increase in pulmonary flow and no change in the calculated pulmonary vascular resistance. While Patel (32), studying 18 normal subjects, found a variable change in pulmonary flow and an increased vascular resistance. In dogs, Hellems found either a decrease or no change in the pulmonary vascular resistance in response to nor-adrenaline (33), whereas in a perfused dog lung preparation Horst (34) and Patel (35) found an increase in resistance.

Our results show that the local action of nor-adrenaline on the pulmonary vessels is constrictor when the blood flow to the area under study is held constant. In the experiments in which the drug was infused into a systemic vein, the left atrial and static wedge pressures fell. These results disagree with those of Feeley (14), who found a marked rise in left atrial pressure under similar experimental conditions. Because of

this rise in left atrial pressure in Feeley's experiments, the pressure gradient across the lungs was little changed and the calculated resistance was variable. Our failure to cause a rise in left atrial pressure in some experiments may be attributed to the small doses used. Support is given to Feeley's observations on the effect of larger doses by the work of Shadle (36) and Kushner (37), who have shown that one of the effects of adrenaline and nor-adrenaline is to elevate the left ventricular end-diastolic pressure and hence the left atrial pressure.

Tolazoline: Material and Protocol.

Twenty-four experiments were done on 19 dogs. The open-chest preparation was also used for these experiments and the drug was introduced into the wedge segment as a single bolus in some and as a continuous perfusion lasting some eight or nine minutes in others. Its effects were studied on the normal wedge segment and on segments which had been perfused previously with adrenaline and nor-adrenaline.

The extent to which it modified the response to adrenaline, nor-adrenaline, serotonin and a raised alveolar P_{CO_2} was recorded when these stimuli were applied subsequently to a segment which had been perfused with tolazoline.

In two animals, pulmonary blood flow and pressure were measured during the systemic infusion of tolazoline, in order to assess the overall effect of this drug on the circulation.

Table 10.

Dog No.	Flow ml/min	Cath P.	CONTROL					DOSE mg.	TOLAZOLINE				
			St.W.P	L.A.P	G.W.P	N.W.P	R		St.W.P	L.A.P	G.W.P	N.W.P	R
29	2	4	0.5	0.5	16.0	12.0	5.75	0.5	0.75	0.5	16.5	12.5	5.8
29	2	4	0.5	0.5	18.5	14.5	7.0	0.5	0.5	0.5	18.5	14.5	7.0
29	2	4	1.0	1.0	17.0	13.0	6.0	0.5	1.0	1.0	17.0	13.0	6.0
30	2	7	4.0	2.0	21.0	14.0	5.0	1.0	4.0	2.5	21.0	14.0	5.0
30	2	7	5.0	3.0	23.0	16.0	5.5	1.0	5.0	3.0	23.0	16.0	5.5

The results of experiments to show the local effect of Tolazoline on the perfused wedge segment.

Table 11.

Dog No.	Flow ml/min	Cath P.	CONTROL					DOSE MG.	TOLAZOLINE (after 5 minutes)				
			St.W.P	L.A.P	G.W.P	M.W.P	R		St.W.P	L.A.P	G.W.P	M.W.P	R
31	2	5	3.0	1.0	18.0	13.0	5.0	0.01	3.0	1.0	18.0	13.0	5.0
32	2	1	5.0	4.0	20.0	19.0	7.0	0.05	5.0	4.0	20.0	19.0	7.0
33	2	1	2.0	4.0	10.5	9.5	3.75	0.05	2.0	4.5	11.0	10.0	4.0
34	2	1	2.0	4.0	12.0	11.0	4.5	0.10	2.5	5.0	11.0	10.0	3.75
35	2	5	6.0	6.0	16.0	11.0	2.5	0.50	10.0	10.0	20.0	15.0	2.5
36	2	4	5.0	3.0	19.0	15.0	4.5	0.05	6.0	4.0	17.0	13.0	3.5
37	2	4	2.0	1.0	14.0	10.0	4.0	0.05	2.0	1.0	14.0	10.0	4.0

The local effect of a continous infusion of tolazoline into the vessels of the perfused wedge segment.

Results:

When a single bolus of tolazoline was introduced into the wedge segment, no effect attributable to the drug was observed (Table 10). No change in the perfused wedge pressure occurred other than that due to the diluent effect of the saline vehicle, despite the use of relatively large doses (0.5 mg. and 1.0 mg.). The records from one experiment are shown in fig. 33.

In 7 experiments in 7 dogs, doses of tolazoline were given as a continuous infusion through the wedged catheter over a period of several minutes; 0.5 mg., 2.5 mg., 5.0 mg., or 25 mg. of the drug were added to 50 ml. of blood and this was used as the perfusate. (Four of these dogs were used in subsequent experiments.) The results are tabulated opposite (Table 11). The net perfused wedge pressure did not change significantly in six of the seven experiments. In one it fell and this could have been due to the mechanical effect of a rise in the downstream pressure as discussed in Chapter 4, since the relatively large dose of tolazoline used was associated with a rise in the left atrial pressure.

When still larger doses of tolazoline were infused (30 mg. total dose), profound circulatory changes occurred. In the experiment illustrated in fig. 34, the main pulmonary pressure and blood flow to the right lower lobe were monitored in addition to the perfused wedge pressure and left atrial pressure.

Table 12.

Dog No.	Flow ml/min	Cath P.	CONTROL St.W P.	L.A. P.	G.W. P.	N.W. P.	R	DOSE mg.	NOR-ADRENALINE St.W P.	L.A. P.	G.W. P.	N.W. P.	R	DOSE mg.	TOLAZOLINE St.W P.	L.A. P.	G.W. P.	N.W. P.	R
25	2	4	1.0	2.0	13.0	9.0	4.0	.0015	1.0	2.0	17.0	13.0	6.0	.016	1.0	2.0	12.0	8.0	3.
26	2	4	2.5	3.0	15.5	11.5	4.5	.0015	2.5	3.0	25.0	21.5	9.5	.016	2.5	3.0	15.0	11.0	4.

Results showing the effect of tolazoline on the pressor response of the perfused wedge segment to nor-adrenaline.

Table 13.

Dog No.	Flow ml/min	Cath P.	CONTROL St.W P.	L.A. P.	G.W. P.	N.W. P.	R	DOSE mg.	ADRENALINE St.W P.	L.A. P.	G.W. P.	N.W. P.	R	DOSE mg.	TOLAZOLINE St.W P.	L.A. P.	G.W. P.	N.W. P.	R
21	2	1	1.0	3.0	14.0	13.0	6.0	.0005	1.0	3.0	27.0	26.0	12.5	.016	1.0	3.0	15.5	14.5	6.
22	2	5	4.0	2.0	19.0	14.0	5.0	.0007	4.0	2.0	29.0	34.0	15.0	.016	4.0	2.0	23.0	18.0	7.

Results showing the effect of tolazoline on the pressor response of the perfused wedge segment to adrenaline.

The most marked change occurred in the pulmonary flow, which fell at first, then increased to 150 per cent of the control level during the next few minutes. This increase in flow was maintained until records were stopped 45 minutes later. This effect was confirmed in another animal. Tolazoline in a dose of 2.5 mg./kg. caused a 50 per cent increase in pulmonary blood flow.

The effect of tolazoline on vessels previously constricted by other agents is shown in Tables 12 and 13. The experiments described earlier in this section have shown that the resistance to perfusion in the wedge segment could be increased by the local action of adrenaline and nor-adrenaline. The subsequent local action of tolazoline is described here.

In two experiments in two animals, vasoconstriction, as evidenced by a sustained rise in the perfused wedge pressure, was produced by introducing 0.0005 mg. adrenaline into the catheter as a single dose. Subsequent perfusion with tolazoline added to the perfusate was accompanied by a reduction in the perfused wedge pressure to near control levels.

In another two animals the same procedure was followed, using nor-adrenaline as the constrictor agent. Subsequent perfusion with tolazoline again reduced the perfused wedge pressure to control levels. The relevant part of the records from such an experiment is shown in fig. 35.

Table 14.

Dog No.	Flow ml/min	Cath P.	CONTROL (after Tolazoline)					DOSE	ADRENALINE				
			St.W.P	L.A.P	G.W.P	H.W.P	R	mg.	St.W.P	L.A.P	G.W.P	H.W.P	R
31	2	5	3.0	1.0	18.0	13.0	5.0	.001	3.0	1.0	20.0	15.0	6.0
32	2	1	5.0	4.0	20.0	19.0	7.0	.001	5.0	4.0	21.0	20.0	7.5
								mg.	NOR-ADRENALINE				
27	2	4	6.0	4.5	18.0	14.0	4.0	.0015	6.0	4.5	19.5	15.5	4.75
34	2	1	2.5	5.0	11.0	10.0	3.75	.0015	2.5	5.0	12.0	11.0	4.25
								ug.	SEROTONIN				
36	2	4	6.0	4.0	17.0	13.0	3.5	.15	6.0	4.0	22.0	18.0	6.0
37	2	4	2.0	1.0	14.0	10.0	4.0	.15	2.0	1.0	27.0	23.0	10.5
								%	CARBON DIOXIDE				
33	2	1	2.0	4.5	11.0	10.0	4.0	10%	2.0	4.5	13.0	12.0	5.0
35	2	5	10.0	10.0	20.0	15.0	2.5	10%	10.0	10.0	22.5	17.5	3.75

The results of experiments to show the local effects of adrenaline, nor-adrenaline, serotonin and carbon dioxide after pre-treatment of the wedge segment with tolazoline.

The effect of pre-treatment of the wedge segment with tolazoline is shown in Table 14. In these experiments, the segment under study was first perfused with blood containing tolazoline (0.05 mg./ml; total dose 0.75 mg.) and the effect of a subsequent single dose of adrenaline, nor-adrenaline, serotonin, or elevation of the alveolar P_{CO_2} was then recorded in separate experiments.

Adrenaline and nor-adrenaline: the constrictor response to a single bolus of each of these agents was markedly attenuated (4 experiments in 4 animals - Fig. 36, 37).

Serotonin: The introduction of serotonin into the wedge segment was still associated with a marked rise in the perfused wedge pressure, despite pre-treatment with tolazoline. The increase in calculated resistance due to serotonin was not so great as in untreated segments, but an insufficient number of experiments were done to permit of conclusions on a quantitative basis.

Carbon dioxide: Elsewhere in this study (Chapter 6) it will be shown that an increase in alveolar P_{CO_2} caused a rise in perfused wedge pressure. Prior perfusion of the wedge segment with tolazoline did not modify this response (2 experiments in 2 dogs). (See fig. 38.)

Discussion:

A drug which could selectively reduce the pulmonary

arterial pressure would be of great value in the therapy of many cases of heart disease, both congenital and acquired, and a natural focus for the efforts of many investigators has been the sympathetic olytic agents and in particular tolazoline (38 - 43). Malmagyi suggested that sympathetic activity might play a part in the aetiology of pulmonary hypertension (44) and there is anatomical and experimental evidence that stimulation of the sympathetic innervation of the pulmonary vasculature is associated with elevation of the pulmonary pressure (8). Our own studies have shown that adrenaline and nor-adrenaline have a marked local constrictor action on the pulmonary vessels.

Some authors have found that tolazoline effectively lowers the pulmonary arterial pressure where this is raised in cases of congenital (41) and acquired heart disease (42)(43) and primary pulmonary hypertension (38)(39). On the other hand, Yu (46) found it of little value in the latter condition, and Rudolph (47) found it to be of no benefit in patients with primary pulmonary hypertension, nor in patients with pulmonary hypertension secondary to congenital shunts. McKinnon (48), in 4 cases of mitral stenosis, found that both pulmonary flow and pressure rose somewhat after the administration of tolazoline. Several reasons can be offered to explain these conflicting findings: some of the authors did not measure the wedge pressure or the left atrial pressure; the use of the Fick method to determine cardiac output

during a changing state is questionable (particularly in the study reported by Grover (41), who estimated oxygen uptake from the body surface area); some of the pulmonary pathology treated may have reached a state of irreversibility and in other cases the pulmonary hypertension may have been due in part to an excessive pulmonary flow.

In our experiments, we used dogs with normal pulmonary vasculature and we studied only the effect of tolazoline as an antagonist to adrenergic drugs, and so the results can hardly be related to those reviewed above, obtained in patients with cardio-pulmonary disease. Our results do show, however, that tolazoline can reduce and prevent the pulmonary constrictor effects of adrenaline and nor-adrenaline. This suggests that the drug would be of value in those states where vasoconstriction is considered to be mediated through locally released or circulating catecholamines (49)(50), such as after cardio-pulmonary bypass.

The fact that tolazoline did not modify the constrictor action of raised alveolar P_{CO_2} is further evidence that this local response to carbon dioxide is not mediated through the release of these catecholamines.

The increase in pulmonary blood flow which followed the infusion of large doses of tolazoline was probably a consequence of its actions on the systemic circulation with an increased

Table 15.

Dog No.	Flow ml/min	Cath P.	CONTROL					DOSE ug.	SEROTONIN				
			St.W.P	L.A.P	C.W.P	M.W.P	R		St.W.P	L.A.P	C.W.P	M.W.P	R
38	2	1	0	4.0	8.0	7.0	3.5	0.25	0	4.0	16.0	15.0	7.5
38	2	1	0	4.0	11.0	10.0	5.0	0.25	0	4.0	20.0	19.0	9.5
39	2	1	5.0	4.0	13.0	12.0	3.5	0.15	5.0	4.0	20.0	19.0	7.0
39	2	1	4.5	4.0	14.0	13.0	4.2	0.33	4.5	4.0	26.0	25.0	10.25

The results of experiments to show the effect of serotonin on the vessels of the wedge segment. The drug was introduced directly into wedged catheter.

Table 16.

Dog No.	CONTROL				SEROTONIN (by systemic vein)			
	Syst. P.	P.A.P	C.W.P	L.A.P	Syst. P.	P.A.P	C.W.P	L.A.P
40	170	12.0	19.0	3.0	180	15.0	19.0	3.5
40	155	15.0	20.0	5.0	160	17.5	20.5	5.0
41	160	17.0	23.0	2.0	170	20.0	23.0	2.5
42	125	14.0	18.0	5.0	140	20.0	18.0	6.0

The results of experiments to show the effects of a continuous infusion of serotonin into a systemic vein.

cardiac output.

Serotonin: Material and Protocol.

Four dogs were used, and the experiments followed the same pattern as has been described for the previous drugs. Two experiments were done on each animal. In four experiments, serotonin was introduced directly into the perfused wedge segment. In the other four, it was given as a continuous intravenous infusion, while the wedge segment was perfused with venous blood (without serotonin). In the latter experiments the main pulmonary pressure and systemic blood pressure were also recorded.

Results:

These are shown in Tables 15 and 16. The local effect of serotonin on the pulmonary vasculature was constrictor; the response of the perfused wedge pressure was very similar to that obtained when adrenaline was infused. The calculated resistance was increased by more than 100 per cent and the effect lasted for 40 to 50 minutes (fig. 39). Previous perfusion of the segment with tolazoline did not modify the pattern of response. When serotonin was administered systemically by the intravenous route, while the perfusate in the wedge segment contained none, no change in the net perfused wedge pressure occurred. The systemic blood pressure and left atrial pressure rose to a small extent, the pulmonary pressure to a greater extent. These changes were accompanied by an increase in heart rate.

Discussion and Review:

That serotonin is a potent constrictor of pulmonary vessels in the dog has been amply documented (15)(34)(51 - 60). Reid (59) first noted that the intravenous injection of this drug was followed rapidly by a rise in pulmonary arterial pressure, and it has been claimed that serotonin is the only substance which acts on the pulmonary circulation in doses insufficient to influence the systemic circulation (60).

Controversy still exists, however, as to its mode of action, although most studies indicate that the drug acts locally on the pulmonary vessels (34)(52)(54). Some have implicated bronchoconstriction as a contributory factor in the response (61 - 63), but Borst (34) found no change in airway pressure during pulmonary vasoconstriction induced by serotonin. Duteil and Aviado (64) have suggested that the pressor response is augmented by an increase in pulmonary blood flow mediated through the sympathetic nervous system, but in Vitolo's studies the pulmonary hypertensive effect of the drug was not modified by bilateral adrenalectomy or the administration of hexamethonium (52). Braun (65) also implicated a reflex action as an important part of the effects of serotonin on both the systemic and pulmonary circulations. He injected serotonin into the descending aorta and observed two discrete periods of elevation of the systemic arterial pressure. A rise in the pulmonary arterial pressure

accompanied the second (larger) rise in systemic pressure and he attributed this to the action of serotonin on the aortic and carotid chemoreceptors. Constriction of the pulmonary veins by serotonin has also been suggested by the results of some studies (55)(65 - 68).

Our studies have added little information. They confirm that serotonin is a most potent constrictor of the pulmonary vessels in the dog, and that its point of action is local.

We did not find an increase in the static wedge/left atrial pressure gradient, and this suggests that no constriction of the large pulmonary veins occurred.

In common with some other drugs, the effect of serotonin in man appears to differ entirely from its effect in dogs. Harris showed that an infusion of serotonin into the pulmonary artery in normal subjects was without effect on the pulmonary pressure (69)(70).

Iso-propyl-nor-adrenaline (Isuprel).

Material and Protocol.

Two groups of experiments were done to study the effects of Isuprel. In one (seven experiments, three dogs) the drug was introduced in small dosage directly into the wedge segment through the perfused wedged catheter. In the other group (four experiments, two dogs) the drug in a dose of 0.1 ug.,

Table 17.

Dog No.	Flow ml/min	Cath P.	CONTROL					DOSE µg.	ISUPREL				
			St.W.P	L.A.P	C.W.P	M.W.P	R		St.W.P	L.A.P	C.W.P	M.W.P	R
43	2	5	1.0	1.0	16.0	11.0	5.0	.0005	1.0	1.0	16.0	11.0	5.0
43	2	5	1.0	1.0	16.0	11.0	5.0	.003	1.0	1.0	15.0	10.0	4.5
43	2	5	1.0	1.0	16.0	11.0	5.0	.040	1.0	1.0	15.5	10.5	4.7
44	2	5	4.0	3.0	19.0	14.0	5.0	.005	4.0	3.0	18.0	13.0	4.5
44	2	5	4.0	3.0	19.0	14.0	5.0	.005	4.0	3.0	18.0	13.0	4.5
45	2	5	5.0	3.0	23.0	18.0	6.5	.040	5.0	3.0	21.5	16.5	5.7
45	2	5	5.0	3.0	24.0	19.0	7.0	.005	5.0	3.0	23.0	18.0	6.5

The results of experiments to show the local effect of a single dose of Isuprel on the perfused wedge segment.

was given intravenously in order that the summation of its effects on the circulation might be observed in so far as they affected the pulmonary circulation. In this second group, records were taken of pulmonary blood flow, the mean pulmonary pressure and the mean left atrial pressure.

Results:

When small doses of Isuprel (0.04 - 0.0006 ug.) were introduced into the perfused wedge segment only, a fall in the calculated resistance was noted in six out of seven experiments (Table 17). The resistance did not change with the smallest dose used (0.0006 ug.). The static wedge pressure and left atrial pressure were unaffected (fig. 40).

The effect of Isuprel was small, but consistent. It is of interest to compare consecutive tracings taken to contrast the effect of Isuprel with that of a similar volume of saline. These are shown in fig. 41. They show that whereas the perfused wedge pressure returns to a level which is higher than the control level after saline has passed through the wedge (because the perfusate is then more viscous), the perfused wedge pressure plateaus at a lower level after Isuprel, and so the calculated resistance has fallen.

In the second group of experiments, to study the overall effect of the drug, the injection of Isuprel (0.1 ug.) into the femoral vein was followed by quite marked changes in pulmonary

Table 18.

DOG No.	CONTROL				ISUPREL (0.1 µg.)(I-V)			
	L.A.P	Pulm Flow	P.A.P	R	L.A.P	Pulm Flow	P.A.P	R
46	5.5	1.20	23.0	14.6	5.5	1.52	29.0	15.5
47	3.0	1.24	19.0	12.9	2.5	1.48	27.5	16.9
48	5.5	1.28	24.0	14.5	5.5	1.62	28.4	14.2
49	3.0	1.30	20.0	13.1	3.0	1.72	25.0	12.8

The results of experiments to show the effect of Isuprel (administered systemically) on the pulmonary circulation.
R = total pulmonary vascular resistance, calculated as $\frac{P.A.P - L.A.P}{Flow}$

flow and pressure (Table 18). However, they were of a transient nature and the factors measured returned to control levels in four minutes. In the experiment illustrated in fig. 42, the changes were maximal at 60 seconds, and it can be seen that both pulmonary flow and pressure rose, while the left atrial pressure fell briefly.

Discussion and Review:

In 1957, Aviado ascribed a new property to the drug Isuprel, when he noted that it dilated pulmonary vessels (13). His findings were largely in agreement with the previous work of Hebb (71). The drug and its analogues have been used clinically for some time as bronchodilators, indeed Harris has recently suggested that the reduction in mean pulmonary pressure which accompanies its use in patients with emphysema (72) may be due to its action on the bronchioles (73). Several workers have shown that it does increase pulmonary blood flow in normal man (74); in congestive heart failure (75); in complete heart block (76) and in cases of severe pulmonary hypertension (77). Evidence has not been adduced, however, to demonstrate an active dilator effect on the pulmonary vessels, as distinct from the passive dilatation which would accompany an increase in pulmonary flow. It has been argued that the increase in pulmonary flow which is a dominant effect of Isuprel (77)(78) could per se account for the fall in pulmonary vascular resistance which some authors have

observed (79). However, the early study of Hebb and Konzett (71), using an isolated perfused canine lung preparation, suggested that the drug actively dilated the pulmonary vascular bed and this conclusion was reached more recently by Hyman (80) using dogs, and by Milnor and his collaborators in man (81). The latter group of workers made further studies on the effects of Isuprel, using dogs (14). With an animal preparation, more detailed measurement is possible, and in common with others they noted an increase in cardiac output, a rise in pulmonary pressure, and a small fall in left atrial pressure. In addition they found a rise in the gradient from a small pulmonary vein to the left atrium and an increase in lung volume. The calculated pulmonary vascular resistances (both from the main pulmonary artery to a pulmonary vein, and from a pulmonary vein to the left atrium) fell. But in view of the large increase in pulmonary flow which occurred, their conclusion that the change in resistance was due to active vasomotion is open to question.

The finding of a pressure gradient between the small pulmonary veins and the left atrium was of great interest. The measurements of Feeley and his co-workers (14) suggested that about one third of the pulmonary vascular resistance resides in the veins. That the pulmonary veins and veno-atrial junction play a significant part in determining pulmonary vascular resistance has been suggested in several studies. These have

been discussed in the previous chapter, along with an assessment of the methods used to measure the pressure gradient from the small pulmonary veins to the left atrium.

Our own studies demonstrate that the direct local effect of Isuprel is to reduce pulmonary vascular resistance at some point between the wedged catheter tip and the left atrium. They do not permit conclusions as to what vessels were affected. However, the experiments in which the drug was administered systemically show that its effect on cardiac output greatly overshadows its small local effect on the pulmonary vessels.

Acetylcholine: Material and Protocol.

This drug is rapidly destroyed in the circulation and so several experiments could be carried out successively in the one animal. Seven definitive experiments were done in two dogs. The open-chest preparation was used, and the acetylcholine was introduced only into the perfused wedged catheter. In two animals who received larger doses, pulmonary flow was also measured. This drug was not studied extensively, however, because some of its actions in the dog differ so greatly from those in man.

Results:

In the experiments in which the dose of acetylcholine was small, the perfused wedge pressure rose and the left atrial pressure fell slightly (fig. 43). With larger doses, the same

local effect was observed but more marked effects occurred when the drug reached the left heart (or coronary circulation)(fig. 44). The heart rate slowed and then ventricular asystole occurred; the systemic arterial pressure fell precipitately and the left atrial pressure rose. When the left atrial pressure rose, the perfused wedge pressure fell.

Discussion and Review:

These results show that acetylcholine, in minute doses, acts locally on the pulmonary vessels in dogs to produce vasoconstriction. This action has been noted by several workers (1)(82 -84), who used less direct methods and has been confirmed recently by Loomis Bell, who also used the perfused wedge technique (85).

In the present experiments, the subsequent fall in vascular resistance in the wedge segment which accompanied the bradycardia and asystole, is probably a passive consequence of the rise in left atrial pressure which occurred at that time.

Some workers have described a fall in pulmonary arterial pressure in animal preparations (24)(84)(86), but only in circumstances where bradycardia occurred.

The local effect of acetylcholine on the pulmonary circulation in man is dilator (3), and this effect has been demonstrated in normal people (4)(87), and in those with pulmonary hypertension due to congenital heart disease (88) and mitral

stenosis (89)(90). The latter authors have also noted, however, that an infusion of acetylcholine is accompanied by a fall in the arterial oxygen saturation in some patients with mitral stenosis. This observation has prompted several studies concerning the effect of acetylcholine on the distribution of blood flow in the lungs and its effect on local ventilation/perfusion relationships. These effects have been reviewed by Harris (91). They are not germane to this study, however, and are not discussed further here.

Aminophylline: Material and Protocol.

The effects of this drug were studied in an effort to distinguish its locally-mediated pulmonary vasomotor actions from its bronchomotor effects.

The open-chest preparation was used in five dogs. (Two of these were used in the serotonin experiments.) The factors measured were the static and perfused wedge pressures, the left atrial pressure and the intra-bronchial pressure. Ventilation was maintained at a constant rate and volume. In each experiment aminophylline (in a single bolus of 0.42 mg.) in saline was introduced directly into the perfused wedged catheter. In four of the experiments, the perfusate contained 0.25 ug. serotonin/ml.

Some actions of this drug in the human were also studied and the results of these observations (made in 8 patients undergoing thoracotomy) are included. In these patients, blood

Table 19.

Dog No.	Flow ml/min.	CONTROL					AMINOPHYLLINE				
		St.W.P	L.A.P	G.W.P	M.W.P	R	St.W.P	L.A.P	G.W.P	M.W.P	R
51	2	2.0	0.5	22.0	17.0	7.5	2.0	0.5	18.0	13.0	5.5
51	2	2.0	0.5	21.0	16.0	7.0	2.0	0.5	18.0	13.0	5.5
52	2	4.0	3.0	20.0	15.0	5.5	4.0	3.0	17.0	12.0	4.0
52	2	4.0	2.5	20.0	15.0	5.5	4.0	2.5	17.5	12.5	4.25

The local effect of aminophylline (0.42 mg.) on the perfused wedge segment. (Cath. P. = 5 mm.Hg.)

Table 20.

Dog No.	Flow ml/min.	SEROTONIN (in perfusate)				AMINOPHYLLINE			
		St.W.P.	L.A.P.	M.W.P.	R	St.W.P.	L.A.P.	M.W.P.	R
40	2	5.0	4.0	23.0	9.0	5.0	4.0	15.0	5.0
40	2	5.0	4.0	22.0	8.5	6.0	4.0	13.0	3.5
41	2	1.0	1.0	19.0	9.0	1.0	1.0	13.0	6.0
41	2	1.0	1.0	20.0	9.5	1.0	1.0	11.0	5.0

The local effect of aminophylline in the wedge segment. The perfusate contained a trace of serotonin.

Table 21.

Patient	CONTROL					AMINOPHYLLINE				
	Flow	P.A.P.	L.A.P.	P.	R	Flow	P.A.P.	L.A.P.	P.	R
J.L.	5.0	15	13	2	0.40	6.2	19	15	4	0.65
J.P.	3.2	21	17	4	1.25	3.7	18	14	4	1.10
C.H.	6.2	21	17	4	0.64	7.0	18	14	4	0.57
M.McD.	4.2	21	14	7	1.70	5.1	25	16	9	1.70
E.T.	3.5	22	18	4	1.14	4.0	21	15	6	1.50
I.R.	2.9	18	16	2	0.65	3.2	17	15	2	0.62
K.O.	5.4	24	16	8	1.50	6.0	23	15	8	1.30
E.S.	3.6	12	8	4	1.10	3.8	11	7	4	1.05

The effect (after 5 minutes) of an intra-venous dose of aminophylline (0.25 G.) in man, on pulmonary flow (litres/minute); mean pressure in the pulmonary artery (P.A.P.), and left atrium (L.A.P.); and the calculated pulmonary vascular resistance. Measurements made in 8 patients during thoracotomy for mitral valvotomy.

flow in the main pulmonary artery was measured continuously during the administration of 0.25 gm. of aminophylline intravenously. Flow was measured with an electromagnetic flowmeter. The mean pressures in the pulmonary artery and left atrium were also recorded.

Results:

These are detailed in Tables 19, 20 and 21. In the perfused wedge segment, aminophylline consistently reduced the calculated vascular resistance by a small amount. In the segments where previous treatment with serotonin had induced constriction, aminophylline caused a relatively greater reduction in the perfused wedge pressure and thence the resistance (fig. 45). No change was observed in the left atrial pressure or the intra-bronchial pressure in these experiments.

In the human studies, a rapid intravenous injection of 0.25 Gm. aminophylline produced a marked increase in pulmonary blood flow (up to 60 per cent) and an initial fall in the pulmonary artery to left atrium pressure gradient. This effect was transient however, and five minutes after the injection, while pulmonary flow remained about 20 per cent greater than the control value, the calculated pulmonary vascular resistance was not significantly altered (fig. 46).

Discussion and Review:

The object of the animal experiments was to assess the

local effect of aminophylline on the pulmonary vascular bed. It is recognised, however, that the rather imprecise technique of measuring the total intra-bronchial pressure during constant volume ventilation would probably not detect a localised change in bronchial tone, and although the bronchial vessels would not receive any significant dose of the drug, the terminal bronchioles which receive their blood supply from the pulmonary vasculature could be affected. In this respect, then the evidence for a direct vasodilator action of aminophylline is not conclusive.

The apparent dilator effect of aminophylline in the segments previously constricted by serotonin is interesting. Again, one cannot tell whether this is a vascular effect or due to local bronchodilatation. The fall in perfusion pressure, however, began to occur precisely at the point on the records where the dose of the drug reached the catheter tip, and this is suggestive of a local vascular effect. Other authors have ascribed a pulmonary vasodilator action to aminophylline (1)(92), but most of these studies were done on patients, and a dilator action was inferred from measurement of the pulmonary and left atrial pressures, (or wedge pressure) and the cardiac output. The latter factor increased in these studies. In a group of cases with mitral stenosis studied by Storstein (93), the pulmonary pressure fell without a change in pulmonary flow or

Table 22.

Dog No.	Flow ml/min.	CONTROL					ARAMINE					
		St.W.P	L.A.P	G.W.P	H.W.P	R	Dose mg.	St.W.P	L.A.P	G.W.P	H.W.P	R
53	2	8.0	7.0	28.0	21.0	6.5	0.02	8.0	7.0	34.0	27.0	9.5
53	2	9.0	7.0	30.0	25.0	7.0	0.02	8.0	7.0	35.0	28.0	10.0
54	2	5.0	2.0	19.0	12.0	3.5	0.02	5.0	2.0	23.0	16.0	5.5
54	2	3.0	2.0	23.0	16.0	5.5	0.02	3.0	2.5	28.0	21.0	9.0

The results of experiments to show the local effect of a single dose (0.02 mg.) of Aramine on the perfused wedge segment. (Cath.P. = 7 mm.)

Table 23.

Dog No.	Dose mg.	CONTROL				ARAMINE (5 minutes)			
		P.A.P.	P.Flow	L.A.P.	R	P.A.P.	P.Flow	L.A.P.	R
56	1.0	25	1.4	6.25	13.4	27	1.46	6.25	14.2
56	1.0	26	1.44	6.5	13.5	28	1.48	6.5	14.5
57	1.0	18	1.16	3.0	12.9	21	1.22	3.0	14.7

Changes in pulmonary flow, pulmonary arterial pressure, left atrial pressure and total pulmonary vascular resistance (R) after the intra-venous administration of Aramine.

wedge pressure. Our own measurements in patients, demonstrated a marked increase in pulmonary blood flow, but no significant change in the calculated vascular resistance.

Aramine:

Aramine (metaraminol) is a vasopressor agent which is widely used in the emergency treatment of hypotension, but its effect on the pulmonary circulation is not well documented. The perfused wedge method was used to assess its local pulmonary effects, and in supplementary experiments, the drug was administered through a systemic vein while pulmonary flow and pressure were recorded, in an effort to delineate its overall effect.

Using the perfused wedge method, four experiments were done in three dogs. The standard open-chest preparation was used. Control records were taken, then 0.02 mg. Aramine in saline was introduced into the catheter and further records were taken while perfusion of the wedge segment was continued. In another two animals, the right hemithorax was opened and catheters inserted to measure pulmonary arterial pressure and left atrial pressure. A flowmeter probe was applied around the intermediate artery to the right lower lobe. While continuous records were taken, Aramine (1.0 mg.) was injected into a femoral vein.

Results:

These are detailed in Tables 22 and 23. In the perfused

wedge experiments, arrival of the drug at the catheter tip was followed by a rise in the perfused wedge pressure (fig. 47) in each case. The calculated resistance was increased by more than 40 per cent.

In the second group of experiments, the single dose of Aramine given intravenously produced a small sustained rise in the pulmonary arterial pressure and a smaller increase in flow. No change in left atrial pressure was recorded (fig. 48). The calculated vascular resistance was increased in each experiment.

Discussion and Review:

Little has been published about the pulmonary vascular effects of Aramine, although its actions on other vascular beds are well documented (94)(95).

Livesay showed that the intravenous infusion of Aramine almost doubled the pulmonary arterial pressure in normal subjects without significantly altering pulmonary flow (96). He therefore attributed a vasoconstrictor action to the drug. Harris and Heath suggested that a rise in left atrial pressure could be a contributory factor in this pulmonary hypertensive effect (73).

In our experiments, when Aramine was introduced directly into the wedge segment, a constrictor effect was seen. This was less marked in the second group of experiments in which blood flow to the area studied could alter. The left atrial pressure was

unchanged in our preparations. We would conclude that Arginine has a local constriction effect on the pulmonary vessels, but in the intact animal its systemic administration is also associated with an increase in cardiac output, so that it caused an increase in both flow and pressure in the pulmonary circulation, with a small net increase in pulmonary vascular resistance.

In concluding this section concerned with the actions of drugs on the pulmonary vasculature, two related points merit re-emphasis. The results of these experiments have demonstrated the sensitivity of the perfused wedge method in the detection of small or weak changes in pulmonary vascular resistance, which are locally mediated. When the perfused method was used, in each instance where vaso-activity appeared, the records were unequivocal. By contrast, in the experiments in which flow was allowed to vary and the resistance changes were calculated from measurements of flow and the pressure gradient, the conclusions were less clear and the separate effects of the drug more difficult to distinguish.

The latter results imply again that local pulmonary vascular responses are weak and are easily swamped by more powerful haemodynamic changes elsewhere - in particular, changes in cardiac output.

It must be recognised, however, that while the doses of the various drugs studied were small compared with a systemic

dose, the amount and concentration of the drugs were probably relatively high in the limited segment of vascular bed which they perfused.

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PULMONARY VASOMOTOR ACTIVITY

VOLUME II.

CONTENTS.

CHAPTER 6.

THE EFFECT OF CARBON DIOXIDE.

Hypercapnia in its acute or chronic form occurs in many clinical situations, and its effects on the cardiovascular system are profound. The response of the pulmonary vasculature to elevated tensions of carbon dioxide in the alveoli is presented in this section. The perfused wedge technique was used to allow differentiation of the local influences of CO_2 from those due to reflex or hormonal action, or mediated through changes in blood flow.

Material and Methods:

In seven animals, using the open-chest preparation, recordings of the perfused wedge pressures were taken while alveolar hypercapnia was induced by ventilation with 8 per cent carbon dioxide (in 30 per cent oxygen / 62 per cent nitrogen). In four dogs, the bronchus to the lobe containing the wedge segment was separately intubated, in order that the lobe under study could be ventilated selectively with a gas mixture which differed from that given to the rest of the lungs. In one dog, the lobe containing the wedge segment was denervated. This was done by dissecting and dividing the adventitial coats of the bronchus and vessels. The denuded areas were then painted with an aqueous

solution of phenol (1 in 15). In two experiments, tolazoline (0.05 mg./ml.) was added to the perfusate. In two experiments the bronchus serving the wedge segment was occluded temporarily, ventilation with 8 per cent carbon dioxide was started, and pressures were recorded before and after release of this bronchus. In two experiments the pressure gradient from a small pulmonary vein to the left atrium was monitored, in addition to the standard measurements. For this purpose a fine polythene cannula was introduced into a pulmonary vein from the left atrium and advanced until its tip lay 3 cm. peripheral to the veno-atrial junction. In all the experiments using the perfused wedge method, the perfusate was autogenous venous blood, which was withdrawn before the alveolar carbon dioxide tension was raised.

Systemic arterial pH was measured in 11 experiments, at the time of recording the pressure changes.

When more than one experiment was done on the same animal, a short period of hyperventilation was used to eliminate the carbon dioxide which might have accumulated from the previous run.

The airway pressure was monitored through a wide-bore needle in the right main bronchus in most of the experiments.

Four supplementary experiments were done to record the effect of hypercapnia on pulmonary blood flow and pressure, left atrial pressure and static wedge pressure. Blood flow to the

Table 24.

Preparation	Dog No.	Flow	Cath P.	CONTROL						HYPERCAPNIA					
				St.W.P.	L.A.P	G.W.P	M.W.P	R	Art. pH	St.W.P	L.A.P	G.W.P	M.W.P	R	Art. pH
Hypercapnic mixture to both lungs	58	2.0	1.0	1.0	1.0	11.0	10.0	4.5	7.30	1.0	1.0	12.0	11.0	5.0	7.28
	59	2.0	1.0	2.0	1.0	13.0	12.0	5.0	7.35	2.0	1.0	15.0	14.0	6.0	7.34
	59	2.0	1.0	2.0	1.0	13.0	12.0	5.0	7.31	2.0	1.0	15.0	14.0	6.0	7.24
	60	2.0	1.0	0.5	0.5	14.0	13.0	6.25	7.41	0.5	0.5	15.5	14.5	7.0	7.38
	60	0.76	2.5	0.5	0.5	9.0	6.5	7.9	-	0.5	0.5	10.5	8.0	10.0	-
	60	0.76	2.5	0.5	0.5	8.0	5.5	6.6	7.30	0.5	0.5	10.0	7.5	9.2	7.26
	61	2.0	1.0	2.0	0.5	11.0	10.0	4.0	7.45	2.0	0.5	12.5	11.5	4.75	7.40
	62	2.0	1.0	3.0	2.0	10.0	9.0	3.0	7.37	3.0	2.0	11.5	10.5	3.75	7.29
	63	2.0	1.0	5.0	4.0	16.0	15.0	5.0	7.39	5.0	4.0	18.0	17.0	6.0	7.31
	64	2.0	1.0	3.0	3.0	19.0	18.0	7.5	7.34	3.0	3.0	22.0	21.0	9.0	7.28
Hypercapnic mixture to lobe containing wedge segment	65	0.76	2.5	0.5	0.5	8.0	5.5		7.37	0.5	0.5	10.0	7.5		7.38
	65	0.76	2.5	0.5	0.5	8.0	5.5		-	0.5	0.5	10.0	7.5		-
	66	2.0	1.0	2.0	1.5	11.5	10.5	4.25	7.34	2.0	1.5	13.0	12.0	5.0	7.34
	66	2.0	1.0	2.0	1.5	11.0	10.0	4.0	-	2.0	1.5	12.5	11.5	4.75	-
O_2 to lobe containing wedge segment	67	2.0	1.0	2.5	2.0	11.0	10.0	3.75	7.37	2.5	2.0	11.5	10.5	4.0	7.35
	67	2.0	1.0	2.5	2.0	11.0	10.0	3.75	7.35	2.5	2.0	11.0	10.0	3.75	7.34
CO_2 mixture to rest.	68	2.0	1.0	2.0	2.0	10.0	9.0	3.5	7.40	2.0	2.5	10.0	9.0	3.5	7.38
	68	2.0	1.0	2.0	2.0	10.0	9.0	3.5	7.38	2.0	2.0	10.0	9.0	3.5	7.32
Tolazoline in perfusate	33	2.0	1.0	2.0	4.5	11.0	10.0	4.0	-	2.0	4.5	13.0	12.0	5.0	-
	35	2.0	5.0	10.0	10.0	20.0	15.0	2.5	-	10.0	10.0	22.5	17.5	3.75	-
Bronchial occlusion.	66	2.0	1.0	2.0	1.0	11.0	10.0	4.0	-	2.0	1.5	12.5	11.5	4.75	-
	66	2.0	1.0	2.0	1.0	11.0	10.0	4.0	-	2.0	1.0	12.5	11.5	4.75	-
Denervated lobe.	69	2.0	1.0	3.0	1.0	13.5	12.5	4.75	-	3.0	1.0	15.0	14.0	5.5	-
	69	2.0	1.0	3.0	1.0	15.0	14.0	5.5	-	3.0	1.0	17.5	16.5	6.75	-

The results of experiments designed to show the local effect of ventilation with 8 per cent carbon dioxide on the vessels of the perfused wedge segment. $\left(R \text{ (in wedge)} = \frac{M.W.P. - St.W.P.}{Flow}\right)$

right lower lobe was monitored with an electro-magnetic flowmeter.

Results:

These are detailed in Tables 24 and 25.

When the standard open-chest preparation was used, the substitution of 8 per cent CO_2 in oxygen and nitrogen as the gas mixture caused a rise in the perfused wedge pressure in each of eleven experiments in four dogs. Representative records are shown in figs. 49 and 50. The perfused wedge pressure began to rise a few seconds after ventilation with CO_2 was started, and fell again when the CO_2 was discontinued. No change in the static wedge pressure or the left atrial pressure occurred.

In the preparations in which a lobar bronchus was separately intubated, selective ventilation of that lobe with 8 per cent CO_2, while the remainder of the lung continued to receive a gas mixture without CO_2 (30 per cent O_2 / 70 per cent N_2) caused a similar rise in the perfused wedge pressure (Fig. 51). Ventilation of the lungs with 8 per cent CO_2, with the selective delivery of the oxygen/nitrogen mixture to the wedge segment, was not accompanied by a rise in perfused wedge pressure.

In the experiments in which the bronchus to the right lower lobe was occluded before CO_2 ventilation was commenced, no change in the perfused wedge pressure occurred, until the bronchus was released (fig. 52).

Table 25.

Dog No.	CONTROL					10% CO_2 FOR 30 SECONDS					10% CO_2 FOR 3 MINUTES				
	P.A.P	St.W.P	L.A.P	Flow	R	P.A.P	St.W.P	L.A.P	Flow	R	P.A.P	St.W.P	L.A.P	Flow	R
70	20.0	7.0	6.0	1.48	9.45	21.0	8.0	7.0	1.22	11.5	26.0	8.5	7.5	2.14	9.1
70	20.0	7.0	6.0	1.5	9.34	22.0	7.0	6.0	1.2	13.3	25.0	8.0	7.0	1.92	9.4
71	14.0	3.0	2.0	1.28	9.4	17.0	3.0	2.0	1.16	12.9	19.0	4.0	3.0	1.86	8.6
71	13.0	3.0	2.0	1.24	8.9	17.0	3.0	2.0	1.08	13.9	20.0	4.0	3.0	1.8	9.45

The effect of ventilation of the lungs with a gas mixture containing 10 per cent carbon dioxide on the pulmonary blood flow, pressure and resistance (R).
(R = P.A.P minus L.A.P, divided by flow.)

Where the lobe containing the segment under study had been denervated, the response to hypercapnia followed the same pattern.

The addition of tolazoline to the perfusate did not modify the response to hypercapnia (fig. 38).

No change in the relationship between the pulmonary venous pressure and the left atrial pressure was seen during the hypercapnic stimulus (fig. 53).

No change in airway pressure was recorded in these experiments.

In the experiments in which pulmonary blood flow was measured, the pattern was similar in each experiment, both flow and the mean pulmonary arterial pressure altered about ten seconds after ventilation with the hypercapnic mixture started (fig. 54). The mean pulmonary pressure was increased while the flow was decreased, so that the calculated resistance was increased. With continued ventilation (with 10 per cent carbon dioxide), the pulmonary pressure continued to increase, but flow increased to a proportionately greater extent, so that after 3 minutes the calculated resistance was less than the control values. Both the static wedge pressure and left atrial pressure were raised by this degree of hypercapnia, but their relationship to each other remained constant. No change in the gradient from static wedge to left atrium occurred.

Table 26.

Authors (Reference)	Subject or Preparation	Effect Observed (P.V.R.)
Bean (5), Bjurstedt (6), Borst (7), Duke (8)(9), Logaras (10), Manfredi (11)(12) Weil (13), Von Euler (14)	Perfused dog lungs	Increased
Peters (15)	Perfused dog lungs	Decreased
Ketchan (4)	Perfused rat lungs	Increased
Duke (16), Hyde (17), Nissell (18)	Perfused cat lungs	Increased
Nissell (19)	Perfused cat lungs CO_2 in perfusate	Decreased
Wearn (20)	Microscopy of cat lungs	No change
Hebb (21)	Perfused monkey lungs	Increased
Daly (22), Fishman (23) Harvey (24)	Human (emphysema)	Increased
Paul (25)	Human (mitral stenosis)	Increased
Fishman (26)	Human (emphysema)	No change
Frank (27), Stroud (28), Westcott (29)	Human	Variable
Shepherd (30)	Human (C.H.D.)	Variable

The effect of carbon dioxide on the pulmonary vascular resistance (P.V.R.) noted by other workers.

Discussion and Review:

The observed effects of carbon dioxide on the pulmonary circulation depend on the experimental preparation used. An acute change in arterial P_{CO_2} produces significant changes in heart action, cardiac output and in the systemic circulation (1 - 3) and these summate with local pulmonary effects to produce changes in the pulmonary circulation.

Since Ketchem (4) in 1912 showed that an increase in the carbon dioxide content of his perfusate caused an elevation in the pulmonary pressure in the perfused rat lung, many studies of the action of carbon dioxide on the pulmonary vasculature have been published (4 - 30)(Table 26). A review of these studies leads to the conclusion that a raised intra-alveolar carbon dioxide tension is regularly followed by pulmonary vascular constriction in isolated animal lungs. Most workers (with a few exceptions (20)(31), also found evidence of pulmonary vaso-constriction in more physiological preparations. But the more 'intact' the preparation, the more variables and indirect effects interact to make interpretation difficult. Thus, in the human subject, the local effect of acute hypercapnia on the pulmonary circulation is uncertain and its mode of action remains controversial. There is agreement that an abrupt increase in the alveolar P_{CO_2} induces or aggravates pulmonary hypertension in human subjects with emphysema (22 - 24); with mitral valve

disease (25); and with congenital heart disease (30). The cardiac output was variably increased, however, in each of these studies and Fishman (26) concluded that the observed rise in pulmonary pressure was due to an increase in pulmonary blood flow. He found no increase in pulmonary vascular resistance. Among those studies in which an increase in pulmonary vascular resistance was found, several mechanisms have been suggested to account for it, and both the pre-capillary and post-capillary vessels have been named as the site of vasomotion. The picture is further complicated by the fact that CO_2 affects bronchial tone, and Peters (15) has suggested that broncho-constriction could account for an increase in resistance to blood flow. Sochzer, on the other hand, believed that the constrictor response was vascular, and implicated catecholamines as the probable mediators (3).

Further information has come from the observation that hypercapnia increased the pulmonary diffusing capacity of the lungs (as measured by the carbon monoxide breath holding technique)(7)(17)(31). This fact coupled with measurements of the pulmonary blood volume during acute elevation of the alveolar CO_2 content, has led to re-examination of the suggestion made by Nissell in 1951, that hypercapnia causes pulmonary venous constriction (32). Hyde (17) using isolated cat lungs, perfused first in an antegrade and then in a retrograde fashion, has shown

that an elevated CO_2 tension can cause both arterial and venous constriction in the pulmonary vessels, but that an increase in the carbon monoxide diffusing capacity occurs only when the capillary and post-capillary vascular bed is exposed to raised CO_2 tensions. This work is in accord with those studies which have shown an increase in pulmonary blood volume in response to hypercapnia. These observations are not irreconcilible with Nisseli's work (19) in which he found that a raised CO_2 tension in his perfusate caused dilatation of vessels in the perfused cat lung, whereas increased alveolar P_{CO_2} caused constriction (18). Nisseli concluded that hypercapnia dilated pulmonary arteries and constricted pulmonary veins or venules.

In another study in which hypercapnic blood was used to perfuse the lungs, an increase in pulmonary vascular resistance was noted (5), but the site of vasoconstriction was not postulated.

The results of the present study permit the following conclusions. The local effect of a raised alveolar P_{CO_2} in the dog is vasoconstriction. The effect is mediated by a direct local action and is independent of reflex nervous pathways. It was not modified by a sympatheticolytic agent. There was no evidence in these experiments of a pulmonary venous throttle action, as suggested by Aviado (33). There was no evidence of broncho-constriction. In the 'whole' animal, the constrictor response dominates only for a brief period, after which a rise in cardiac

output overrides the local effect to produce a dilatation of the pulmonary vessels which is probably passive. These observations are largely in accord with previous and subsequent studies, provided the differences in the experimental preparations are taken into account. Thus, in those experiments where pulmonary flow and left atrial pressure were held constant, hypercapnia caused an increase in pulmonary vascular resistance.

The precise mechanism of the action of CO_2 on the pulmonary vessels remains obscure. A similar pressor response to CO_2 has been described in the renal vessels (34). Release of catecholamines has been suggested (3)(35). The present study did not investigate all the catecholamines, but does exclude adrenaline and nor-adrenaline as the local mediators.

One important consequence of ventilation with 8 per cent carbon dioxide is the rapid development of a 'respiratory' acidosis, and the effects of the resultant fall in the pH of the blood perfusing systemic chemoreceptors and perfusing the pulmonary vessels must be considered. Bjurstedt has shown that a reduction in the pH of the arterial and mixed venous blood occurred within one minute of adding 10 per cent carbon dioxide to the gas mixture in artificially ventilated dogs. The fall in pH was accompanied by a rise in the pulmonary arterial pressure, and the authors concluded that this was due to an increase in pulmonary vascular resistance (6). Although their method of estimating pulmonary

blood flow is open to criticism, (they used the method of Liljestrand and Zander (36); pulse pressure, divided by mean blood pressure, equals stroke volume) their conclusions seem valid.

From our own studies we would exclude reflex effects due to carbon dioxide or a lowered arterial pH, which are mediated through systemic chemoreceptors, because the pressor response was limited to the segment in which the alveolar P_{CO_2} was raised. The effect may have been due to a local reduction in pH however.

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CHAPTER 7.

THE EFFECT OF ACUTE HYPOXIA.

It seems reasonable on teleological grounds to expect to find homeostatic mechanisms in the lungs which control the exposure of venous blood to alveolar oxygen, and in 1946, Von Euler and Liljestrand propounded the concept that a local mechanism could direct venous blood away from poorly ventilated areas towards well ventilated portions of the lung. They based this hypothesis on their studies on the influence of inspired gases on the pulmonary arterial pressure in animal preparations (1). In the following year workers with Andre Cournand demonstrated that hypoxia caused elevation of the pulmonary pressure in man (2). Very many investigations have been carried out subsequently at experimental and clinical levels, on the effects of hypoxia on the circulation (3). There are still, however, several areas of disagreement, and it has become clear that there are marked species differences in the responses to hypoxia. Careful consideration of the experimental preparations used, must be exercised in the interpretation of the results obtained (4 - 7). Nevertheless, most of the basic facts concerning the effects of hypoxia on the pulmonary vasculature have been derived from animal experiments (1) (8 - 15), and the writer considered that new information could

be gained by application of the perfused wedge technique to the problems, and so the following experiments were carried out.

Material and Methods:

Two groups of experiments were done. (1) The first was designed to yield information about the effects of breathing low oxygen mixtures on pulmonary blood flow, mean pulmonary arterial pressure, mean left atrial pressure and systemic pressure, in open-chest dogs using a standard anaesthetic technique. (2) The same anaesthesia and hypoxic gas mixtures were used in a second group of experiments in order that some comparisons could be made. In this group, the perfused wedged catheter technique was used and a more precise assessment of changes in vascular resistance was made under conditions of controlled blood flow.

First Group.

Ten dogs were used. They were anaesthetised with pentobarbitone, spontaneous respiratory movements were suspended with succinylcholine and intermittent positive pressure ventilation was maintained using a Palmer pump. The right hemithorax was opened through the 5th intercostal space and the tidal volume and respiratory frequency were adjusted to maintain an expired CO_2 level of 5 to 6 per cent and adequate inflation of the lungs. The end-expiratory pressure was usually 1 cm. of water. The systemic arterial pressure was monitored through

a cannula introduced through the right femoral artery into the aorta. The adjacent femoral vein was cannulated for the withdrawal of blood and as a route for a slow intravenous infusion of succinylcholine. Small pulmonary arterial and venous branches in the right middle lobe were cannulated and the catheters so positioned to enable measurement of the main pulmonary arterial pressure and left atrial pressure respectively. The pulmonary artery to the right lower lobes was mobilised by dividing the folds of the mediastinal pleura which overlie it. Care was taken to minimise handling of this vessel, to avoid damage to vasomotor nerves. The probe of an electro-magnetic flowmeter was applied round this artery.

With the preparation thus set up, control records were taken while the animal was ventilated with 30 per cent oxygen in nitrogen. The gas mixture was then changed to one containing 8 per cent oxygen, while continuous records were taken. After stabilisation of the factors, the gas mixture was again changed to 5 per cent or, in a few experiments, 3 per cent oxygen, and further records were taken.

Second Group.

Ten animals were used, and the same open-chest preparation was employed. A catheter was wedged in a right lower lobe. This catheter was introduced through a branch of the right middle lobe as described in Chapter 1. The left atrial pressure was

Table 27.

Dog No.	CONTROL (30% O_2)						8% OXYGEN						5% OXYGEN					
	P.A.P	L.A.P	ΔP	Pulm. Flow L.	R	Mean Syst P.	P.A.P	L.A.P	ΔP	Pulm. Flow L.	R	Mean Syst P.	P.A.P	L.A.P	ΔP	Pulm. Flow L.	R	Mean Syst P.
72	13.5	7.0	6.0	2.72	2.2	145	16.0	7.0	9.0	3.35	2.7	155	18.0	7.0	11.0	4.0	2.75	150
72	12.5	7.0	5.5	1.78	3.1	155	16.0	7.5	8.5	3.36	2.5	170	17.5	7.5	10.0	4.32	2.31	175
72	11.0	5.0	6.0	2.0	3.0	150	15.0	5.5	9.5	2.76	3.4	155	20.0	8.0	12.0	3.76	3.19	145
73	13.5	8.0	5.5	2.4	2.2	160	15.5	8.0	7.5	3.98	2.2	165	17.0	8.0	9.0	4.8	1.87	135
74	14.0	6.0	8.0	1.78	4.5	115	21.0	4.5	16.5	3.08	5.35	135	25.0	4.0	21.0	3.96	5.3	140
75	14.5	4.0	10.5	2.42	4.3	125	20.0	4.0	16.0	3.18	5.03	135	23.0	3.5	19.5	4.18	4.66	140
76	14.0	5.0	9.0	1.7	5.3	160	19.0	4.0	15.0	2.40	6.25	180	21.5	4.0	17.5	3.1	5.64	180
77	16.0	8.0	8.0	1.8	4.4	170	21.0	7.0	14.0	2.40	5.83	185	25.0	7.5	17.5	3.28	5.33	150
78	15.0	7.0	8.0	2.0	4.0	160	19.5	6.5	13.0	2.88	4.5	175	22.5	7.5	15.0	3.78	3.96	165
79	12.0	4.0	8.0	2.08	3.9	120	15.0	4.0	13.0	2.60	5.0	155	18.0	4.0	14.0	3.46	4.04	160

Shows the effects of ventilation with hypoxic mixtures on the pulmonary circulation. The factors measured were pulmonary arterial pressure, left atrial pressure, pulmonary blood flow and the systemic arterial pressure. R = calculated total pulmonary vascular resistance (see text).

monitored in the usual way. In two animals, a second catheter was advanced through the left atrium into a pulmonary vein until its tip lay free 2 or 3 cm. from the veno-atrial junction. Fine polythene catheters were used for this purpose (O.D. 0.7 mm.) (I.D. 0.5 mm.). In two dogs, the bronchus serving the right lower lobes was separately cannulated and appropriate connections were made to allow selective ventilation of this lobe. The dogs were ventilated with 30 per cent oxygen / 70 per cent nitrogen for the control records, the mixture was then changed to 8 per cent oxygen / 95 per cent nitrogen for several minutes and to 5 per cent oxygen / 95 per cent nitrogen for a further 2 or 3 minutes.

The intra-bronchial pressure was monitored in some experiments in each group.

Results:

Group I. (Table 27)

The pattern of change in the pulmonary artery pressure and pulmonary flow was similar in each experiment. Under control conditions the mean pulmonary artery pressure was 13.6 mm. (S.D.± 1.5); when the respiratory gas mixture was changed to 8 per cent oxygen / 95 per cent nitrogen it rose to 17.8 mm. (S.D.± 2.5) and after 5 per cent oxygen to 20.8mm (S.D.± 3.1). Pulmonary flow also increased, from a control level of 2.1 Litres, to 3.0 L. with 8 per cent oxygen, and 3.9 L. with 5 per cent

oxygen.

The response of the left atrial pressure to hypoxia was more variable. In general terms it fell with the lesser degrees of hypoxia, then rose as hypoxia continued or became more severe. The mean systemic pressure was slightly raised by the hypoxic stimuli used in these experiments. After 3 or 4 minutes of 5 per cent oxygen, however, it would fall, as cardiac failure occurred. This fall in systemic pressure occurred at the same time as left atrial pressure rose. The figure to express pulmonary vascular resistance was derived by dividing the pressure differential from main pulmonary artery to left atrium by the pulmonary flow. (The latter factor was obtained by multiplying the measured flow to the right lower lobes by four.) The pulmonary vascular resistance was increased by the hypoxic stimulus in eight of the ten experiments in this group. The increase was significant in five of these. The relationship between flow and pressure during the two degrees of hypoxic stimulus are shown in fig. 55.

Group II.

(a) Changes in Perfused Wedge Pressure. (Tables 28 and 29)

Ventilation with a gas mixture containing 8 per cent oxygen was followed by a fall in the perfusion pressure in each technically successful experiment. Resistance in the wedge segment was calculated as pressure gradient from the catheter

Table 28.

Dog No.	Flow	30% OXYGEN				8% OXYGEN			
		St.W.P	L.A.P	N.W.P	R	St.W.P	L.A.P	N.W.P	R
80	15.3	5.0	1.0	17.0	1.05	5.0	1.0	15.0	0.92
80	15.3	5.0	1.0	18.0	1.11	5.5	1.0	16.0	0.98
81	7.6	10.0	6.0	20.0	1.84	-	7.0	17.0	1.32
81	7.6	10.0	6.0	20.0	1.84	12.0	7.0	17.0	1.32
81	7.6	10.0	6.0	20.0	1.84	12.0	8.0	17.0	1.18
82	2.0	5.0	3.0	9.0	3.0	3.0	1.0	6.0	2.5
82	2.0	4.0	2.0	9.5	3.25	4.0	1.5	6.0	2.25
82	2.0	5.0	3.0	9.0	3.0	3.0	1.0	6.5	2.75
83	2.0	5.0	4.0	12.0	4.0	6.0	4.0	11.0	3.5
83	2.0	5.0	4.0	12.0	4.0	5.0	4.0	10.0	3.0
83	2.0	5.5	4.0	13.0	4.5	5.0	4.0	11.0	3.5

The results of experiments to show the effect of hypoxic ventilation (8% oxygen) on the vascular resistance in the pre-venous part of the perfused wedge segment. $\left(R = \frac{N.W.P - St.W.P}{Flow}\right)$

Table 29.

Dog No.	Flow	30% OXYGEN				5% OXYGEN			
		St.W.P	L.A.P	E.W.P	R	St.W.P	L.A.P	E.W.P	R
80	15.3	5.0	2.0	15.0	0.85	12.0	8.0	19.0	0.72
80	15.3	5.0	2.0	14.0	0.78	12.0	8.0	19.0	0.72
81	15.3	5.0	1.0	17.0	1.05	8.0	5.0	18.0	0.85
82	7.6	6.0	5.0	14.0	1.18	6.0	5.0	11.0	0.79
83	7.6	5.0	4.0	18.0	1.84	10.0	8.0	20.0	1.58
84	2.0	3.0	2.0	11.0	4.5	7.0	5.0	11.0	3.0
84	2.0	3.0	2.0	11.0	4.5	5.0	3.0	10.0	3.5

The results of experiments to show the effect of hypoxic ventilation (5% oxygen) on the vascular resistance in the pre-venous part of the perfused wedge segment. $\left(R = \frac{E.W.P - St.W.P}{Flow}\right)$

Table 30.

Dog No.	Flow ml/min.	30% OXYGEN				3% OXYGEN (locally)			
		St.W.P	L.A.P	E.W.P	R	St.W.P	L.A.P	E.W.P	R
85	2	4.0	2.5	19.0	7.5	4.0	2.5	17.0	6.5
85	2	4.0	2.5	19.0	7.5	4.0	2.5	17.0	6.5
86	2	3.0	1.0	13.0	5.0	3.0	1.0	11.0	4.0
86	2	3.0	1.0	15.0	6.0	3.0	1.0	14.0	5.5

The results of experiments to show the changes in the vascular resistance in the wedge segment during selective ventilation of that segment with 3% oxygen and ventilation of the rest of the lungs with 30% oxygen.

Table 31.

Dog No.	Flow ml/min	30% OXYGEN				3% OXYGEN (to lungs)			
		St.W.P	L.A.P	W.W.P	R	St.W.P	L.A.P	W.W.P	R
85	2	3.0	1.0	13.0	5.0	6.0	4.0	16.0	5.0
85	2	3.0	1.0	14.0	5.5	6.0	4.5	15.5	4.75
85	2	3.0	1.5	13.0	5.0	7.0	5.0	16.0	4.5
86	2	4.0	1.5	18.0	7.0	7.0	5.5	20.0	6.5
86	2	4.0	2.5	18.0	7.0	8.0	5.5	22.0	7.0

The results of experiments to show the vascular resistance in the wedge segment, during ventilation of the lungs with 3% oxygen and separate ventilation of the wedge segment with 30% oxygen.

tip (W.W.P.) to the static wedge pressure, divided by the flow. In each experiment, hypoxia caused a fall in this resistance value. The alternative formula:- perfusion pressure, minus left atrial pressure, divided by flow, was not applied because it was assumed that an unknown increment of flow might occur through pulmonary venous anastomoses in the downstream section of the wedge segment.

When the gas mixture contained only 5 per cent oxygen, the recorded (absolute) perfused wedge pressure was usually raised above the control levels, but the pressure gradient from the perfusion pressure to the static wedge pressure was still reduced because the static wedge pressure was raised to a greater extent, and so the calculated pre-venous resistance fell, as with lesser degrees of hypoxia.

Tables 30 and 31 show the results of those experiments in which the lobe containing the perfused wedged catheter was separately ventilated. A reduction in resistance occurred consistently only when the lobe received the hypoxic mixture. When the hypoxic mixture was given to the rest of the lung and the segment being studied got 30 per cent oxygen, no change in resistance was observed. Under the latter circumstances, severe degrees of hypoxia caused an elevation of all the pressures, but there was no change in the pressure gradient across the wedge segment and therefore no change in pre-venous resistance.

Table 32.

Dog No.	30% OXYGEN					3% OXYGEN				
	St.W.P	P.V.P	L.A.P	ΔP_1	ΔP_2	St.W.P	P.V.P	L.A.P	ΔP_1	ΔP_2
87	5.0	5.0	3.0	0	2.0	11.0	11.0	8.0	0	3.0
87	5.0	5.0	4.0	0	1.0	10.5	10.0	7.0	0.5	3.0
87	5.0	5.0	4.0	0	1.0	12.0	12.0	10.0	0	2.0
88	3.0	2.0	2.0	1.0	0	6.0	4.0	4.0	2.0	0
88	3.0	2.0	2.0	1.0	0	5.0	3.0	2.5	2.0	0.5
88	4.0	3.5	3.0	0.5	0.5	6.0	5.0	3.5	1.0	1.5

Table 32 shows the effect of acute hypoxia on the pressure gradients between the static wedge pressure and pulmonary venous pressure (ΔP_1); and the pulmonary venous pressure and left atrial pressure (ΔP_2).

(b) Changes in the Static Wedge Pressure, Venous Pressure and Left Atrial Pressure.

These factors were raised by the severer degree of hypoxic ventilation. Since they have an important bearing on the analysis of the results, they have been tabulated separately (Table 32). The change in the differential from static wedge pressure to pulmonary venous pressure was not significant. The gradient from pulmonary vein to left atrium, however, was significantly increased in four out of the six experiments done.

Further information concerning the pattern of the response to hypoxia was gained from a study of the records from individual experiments.

Figure 56 illustrates most clearly the usual changes observed. The perfused wedge pressure fell after ventilation with 8 per cent oxygen had been continued for one minute. With more severe degrees of hypoxia, the absolute perfused wedge pressure rose, but the static wedge pressure and left atrial pressure were also raised and to a greater extent, so that the pressure differential was still reduced (fig. 57). This effect on the perfused wedge pressure of a rise in left atrial pressure during acute hypoxia is well shown in fig. 58. In this record, the perfused wedge pressure fell initially but then rose as the left atrial pressure increased. Figure 59 is representative of several experiments which showed that the reduction in perfused

wedge pressure could occur without any change in either static wedge pressure or left atrial pressure, when lesser degrees of hypoxia were used. The tracings in fig. 60, a and b, are reproduced because they contrast the effects of hypoxia and hypercapnia on the perfused wedge pressure and vascular resistance. The records are of two experiments conducted consecutively on the same preparation. They show quite clearly that the perfusion pressure (with a constant flow rate) fell with hypoxia and rose with hypercapnia.

Discussion and Review:

The most noteworthy new finding in these experiments was that hypoxia apparently caused vasodilatation in the pre-venous part of the perfused wedge segment.

It is clear, however, that hypoxia causes changes in many factors pertaining to the pulmonary circulation and that these changes are intimately related, not only to each other, but also to changes which are occurring at the same time in the systemic circulation. It will clarify discussion if each factor is first considered separately, then the manner in which each interacts to produce the observed effects will be discussed. The factors reviewed are:- pulmonary arterial pressure and pulmonary blood flow; the static wedge pressure, pulmonary venous pressure and left atrial pressure; pulmonary blood volume and the several moieties of pulmonary vascular resistance.

Pulmonary Arterial Pressure: In all of our preparations, the pulmonary arterial pressure rose in response to hypoxia. The rise began within thirty seconds after the introduction of the hypoxic mixture to the ventilator, and a maximum pressure was reached in one or two minutes (fig. 61). A similar rate of reaction in 'narcotized' dogs was reported by Beard (16) when the stimulus was anoxia (nitrogen breathing), and in unanaesthetised dogs, Nahas (8) found that the pulmonary pressure began to rise in twenty seconds and continued to rise over five minutes, with similar degrees of hypoxia. With less hypoxic mixtures, both the time of onset and degree of pressor response was delayed and diminished (3)(7), but within a fairly wide range the extent of the rise in pulmonary pressure seemed to be related to the severity of the hypoxia (17). In the more 'artificial' preparations, however, the response was delayed, even for hours (9)(18)(19), or absent altogether (20).

Although the observed response varies greatly and depends on one or more of the following - species, anaesthesia, intactness or otherwise of the preparation, severity of the hypoxic stimulus and how it is induced, duration of the stimulus and experimental method used - we would conclude from our own experiments and this review that acute hypoxia invariably causes an early and significant elevation of the pulmonary pressure in the dog under conditions of light pentobarbitone anaesthesia and thoracotomy. Studies in

man have also shown that acute hypoxia is similarly followed by a rise in the pulmonary pressure (2)(6)(21 - 24).

Pulmonary Blood Flow: Our results showed that an increase in pulmonary blood flow occurred in response to hypoxia, and that this increase in flow more or less paralleled the rate of rise in pulmonary pressure. The degree of increase in flow was directly (but not linearly) related to the severity of the hypoxia, up to the point where cardiac failure became evident. With intolerable levels of acute hypoxia, cardiac output (after a brief rise) does indeed fall (25)(26), presumably because of impaired myocardial contractility (27).

Our findings are in accord with those of most workers who have measured cardiac output or pulmonary blood flow during hypoxia (6)(7)(8)(23)(25)(28)(29). In the few studies in which cardiac output was reported as unchanged (30) or decreased (4)(31), the Fick principle was applied to measure blood flow, and it can be argued that the criteria necessary to obtain valid results with this method in a changing state were not observed (6)(32 - 35). Our results differ from those of many authorities in that we did not always find an increase in total pulmonary vascular resistance, as calculated from measurement of flow and pressure gradient from pulmonary artery to left atrium.

The fact that pulmonary flow increased in response to bilateral alveolar hypoxia has an important bearing on the analysis

of our pressure records. As we have discussed in Chapter 4, the wedged catheter blocks flow into the wedge segment only as far downstream as the point where veins from adjacent segments join the veins draining the wedge segment. During hypoxic ventilation, the flow through those veins will probably be increased and may alter the pressure ratios in this segment of the vascular bed (vide infra).

Static Wedge, Pulmonary Venous and Left Atrial Pressure:

These pressures are appropriately considered together, since hypoxia had the same qualitative effect on all three. The changes were somewhat variable, but in general moderate hypoxia was associated with a fall in these pressures, while severe hypoxia was followed by a rise. In most experiments, this rise was progressive and was an indication of left ventricular failure. Other workers who have measured the left atrial pressure in anaesthetised dogs in this context report similar changes (7)(31)(36). In unanaesthetised dogs, Thilenius (37) also noted a fall in left atrial pressure when the alveolar P_{O_2} was reduced to 40 mm.Hg. Nahas, however, found no change in similar preparations (8). No change in left atrial pressure occurred in isolated lung preparations subjected to acute hypoxia (18)(38).

In human subjects, the pulmonary 'wedge' pressure has been measured during moderate hypoxia and most authors have reported that there was no change (22)(30)(39)(40).

Our studies have led us to believe that three factors could cause a rise in wedge pressure under the circumstances of these experiments. It could follow passively a rise in left atrial pressure; it could be raised by an increased pulmonary venous flow; and it could be raised by venoconstriction at the pulmonary vein - left atrial junctional area.

In several of our preparations which were exposed to severe hypoxia, the static wedge pressure rose more than the left atrial pressure. Rivera-Estrada and his collaborators have also noted this phenomenon and attributed it to venoconstriction, or to the activity of localised venous sphincters (41). We do not have direct evidence to refute this, but believe that the increase in wedge/left atrial gradient could be explained more simply on a basis of increased pulmonary venous flow.

Pulmonary Blood Volume: The possibility of a shift of blood volume to or from the pulmonary circulation during hypoxia must be considered. If the capacity of the pulmonary vascular bed changed during hypoxic ventilation, then comparisons of the pressure/flow relationships at that time with control curves made previously could be misleading (42). The finding of an increased pulmonary blood volume could per se be evidence of vasomotion. On the other hand, the pulmonary vessels are readily distensible and passive overfilling would be a more probable explanation for this finding. In 1928, Daly showed that an increase in pulmonary

blood flow is generally followed by an increase in pulmonary blood volume (43), and this work has been substantiated more recently by the studies of Ochsner (44) and Witham (45). This apparently passive distension of the pulmonary vessels is associated with a decrease in the calculated pulmonary vascular resistance (46 - 49).

Unfortunately, changes in pulmonary blood volume are difficult to measure with precision in the intact animal or man. Nisell used isolated cat lung preparations to show that an increase in volume did occur during hypoxia (50). But previous work, using a similar preparation, had not demonstrated this (9).

In man, using indirect methods to measure the 'central blood volume', several workers have found no shift of blood during hypoxia (22)(24)(51), and in the intact anaesthetised dog, Stroud and Conn also found no change (52). Aviado, on the other hand, has found an increase in the volume of an isolated lobe in the dog in response to hypoxia (53).

These conflicting results perhaps only serve to emphasise that the adaptations to hypoxia differ in the intact animal or man, from those in isolated lung preparations. The studies by Fritts and his collaborators using the Cotton tester board (54) seem to offer good evidence that no significant change in pulmonary blood volume occurs in human subjects, subjected to moderate degrees of acute hypoxia (24). The effect in dogs seems to depend on the

type of preparation used. Pulmonary blood volume was not measured in our experiments.

The Pulmonary Blood Pressure/Flow Relationship: Fishman and Cournand and their collaborators have used pressure/flow curves to provide evidence of active pulmonary vasoconstriction in response to hypoxia (3)(23), in that a shift of the curve to show an excessive increase in pressure for an increase in flow implied an active increase in resistance. However, as mentioned in Chapter 2, it is difficult to obtain 'control' pressure/flow curves in man or in intact animals, without introducing potential artefacts. All the manoeuvres which are commonly employed to increase pulmonary blood flow in intact subjects (exercise (23)(55), inotropic drugs, intravenous infusions, unilateral pulmonary artery occlusion (56)), are associated with circulatory readjustments of a significant degree.

Because the increase of pulmonary blood flow which occurs with hypoxia complicates the interpretation of results, an alternative approach has been to maintain a constant rate of flow and to measure the pressure gradient across the pulmonary vascular bed, on the grounds that calculations of resistance are more valid in circumstances where either flow or pressure is held constant (46)(57). This principle was applied in the perfused wedge experiments in this study.

Pulmonary Vascular Resistance: It is in the effect of hypoxia

on this parameter that the results of the present study are difficult to reconcile with much of the previously published work. Experiments on preparations ranging from isolated perfused lungs to unanaesthetised animals and observations on normal and diseased human lungs, have led most reviewers to conclude that hypoxia does indeed induce active vaso-constriction (3)(17)(58)(59), and the corollary that oxygen breathing can decrease the pulmonary vascular resistance in some conditions where the latter was elevated (60)(61). The most convincing evidence has derived from those experiments in which the distribution of pulmonary flow was studied during the induction of unilateral hypoxia. Dirken and Heemstra demonstrated that vasoconstriction occurred in a single lung when it was rendered hypoxic (62), and although earlier experiments with unilateral hypoxia yielded negative results (63 - 65), subsequent work employing more precise measurement and selective ventilation of the lungs has shown that unilateral hypoxia can be associated with a shift of blood flow to the other lung (66 - 70). Even these studies, however, are not altogether conclusive. The stimulus used by Rahn (69) was pure nitrogen, administered to one lung. Himmelstein and Courmand had to reduce the oxygen concentration to 4 to 6 per cent before a shift in blood flow occurred (70).

Work on dogs on the effects of hypoxia has also yielded equivocal results. Aviado found no change or a fall in the

perfusion pressure in lungs perfused at a fixed flow rate (53), while others, including Aviado in subsequent experiments, have described a rise in the perfusion pressure while flow was held constant (12)(18)(71). In experiments in which a lobe was perfused in situ, with control of both inflow and outflow, variable results were obtained (72). Several other studies have added evidence that alveolar hypoxia may not cause vasoconstriction (7) (73 - 76). These studies emphasise that the effects of hypoxia are pleomorphic and that one or other effect may dominate in any given preparation.

The results obtained from our preparations permit only of conclusions concerning the effect of severe hypoxia on the pulmonary circulation of the dog, under conditions of barbiturate anaesthesia and thoracotomy. The effects observed cannot be related to observations on human subjects subjected to moderate hypoxia, but, taken in conjunction with other work on dogs, they do offer some insight into the intrinsic mechanisms of the pulmonary circulation.

Our most significant finding was that both the absolute perfusion pressure, and the pressure gradient from catheter to static wedge pressure fell in response to acute hypoxia, and we will consider the possible explanations for this.

Several authors have noted that elevation of the left atrial pressure or pulmonary venous pressure can cause a reduction

in pulmonary vascular resistance. This phenomenon has been noted in other experiments in this study, and it seems possible that the increased pulmonary flow which accompanies hypoxia could, by discharging more blood through veins which are confluent with the veins of the wedge segment, distend these veins and the vessels upstream and so lower resistance in the wedge segment. However, the results of the experiments in which one lobe was selectively ventilated show that the fall in perfusion pressure occurred only when the segment under study was exposed to the hypoxic mixture. Ventilation of the rest of the lung with this mixture would increase flow to a greater extent, but was not associated with a fall in resistance in the wedge segment. Therefore, the results of the present study indicate that acute alveolar hypoxia is associated with a fall in resistance to flow in the pre-venous section of the pulmonary vascular bed, and that this fall is not merely the consequence of a rise in pulmonary venous or left atrial pressure, but appears to be due to a local response of the vessels.

Rivera-Estrada, in experiments on dogs, noted an increase in the pulmonary wedge pressure in the presence of an unchanged left atrial pressure, in response to 5 to 10 per cent oxygen (41). He postulated pulmonary venoconstriction, but did not measure flow. In the light of our studies and others, the increase in pressure gradient could have been due to

increased flow through confluent veins.

Hypoxic ventilation of both lungs was followed by an increase in the pressure gradient between a pulmonary vein and the left atrium, and we attribute this to the increase in flow through this segment. The gradient from static wedge pressure to left atrial pressure increased in some experiments, but to a less significant extent, and it was unchanged in others. This observation suggests that some of the pressures recorded in the pulmonary veins were falsely high. The presence of a catheter in a small pulmonary vein will obstruct flow to some extent and could cause a spurious pressure differential between vein and atrium.

The Dalys' and others have drawn attention to two potential roles which the bronchial arteries might play in the haemodynamic effects of hypoxia. Daly emphasised the changes in response which occurred in those preparations in which the bronchial circulation was not perfused (77)(78), since the integrity of the local innervation depends on blood supply from the bronchial arteries (79) and since bronchial flow may contribute to the response. In some of their experiments, the Dalys' (80) attributed an apparent fall in pulmonary resistance to passive changes in the bronchial circulation.

In our preparations, we would expect an increase of bronchial flow as a consequence of systemic hypertension, and

this would raise the pressure differential between the perfused wedge pressure and the static wedge pressure, or left atrial pressure (assuming bronchial-pulmonary anastomoses here). This, however, did not occur. The evidence that the bronchial circulation is under reflex control from the carotid baroreceptors and chemoreceptors (78), and may undergo reflex vasomotion in response to hypoxic stimuli, further complicates the situation.

Reflex effects on the pulmonary vessels themselves during hypoxia have been considered by several workers. Aviado and his collaborators ventilated an innervated lobe independently with oxygen and the rest of the lung with a 5 to 10 per cent oxygen mixture, and found pulmonary vasoconstriction in the former, which they concluded was due in part to hypoxic stimulation of carotid and aortic chemoreceptors (71). The methodology of this work has been criticised by Daly (78). Daly's studies, however, using his "vasosensory controlled perfused living animal preparation", also showed that stimulation of the carotid body chemoreceptors could cause reflex constriction in the pulmonary vascular bed. Stimulation of carotid sinus baroreceptors on the other hand caused a reduction in pulmonary vascular resistance in Daly's preparations (80). It must be pointed out, however, that these preparations too were highly artificial, and that it required a pressure increase of about 100 mm.Hg. in the carotid sinus to cause a consistent fall in pulmonary vascular resistance.

In summary, the results of the present study show that acute alveolar hypoxia causes a fall in the vascular resistance in a segment of the pulmonary circulation perfused at a constant rate, in situ. It seems to be a local response, in that it appeared only when the segment under study received the anoxic gas mixture. The response was seen under circumstances in which bronchial flow was probably not altered and we found no evidence to implicate broncho-pulmonary shunts.

This section also showed that a further fall in resistance followed elevation of the left atrial or pulmonary venous pressure. The haemodynamic basis for this phenomenon (also referred to in other sections), has been described by Rodbard et al. (81).

These experiments with hypoxia supplement those described in Chapter 4, in showing that an increase in pulmonary blood flow can cause a rise in the pressure gradient between the static wedge pressure and the left atrial pressure.

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CHAPTER 8.

THE EFFECT OF PULMONARY ARTERIAL HYPEROXIA.*

The therapeutic possibilities of oxygen therapy under hyperbaric conditions have excited growing interest in the past few years (1)(2), and have provided the impetus for investigations into the physiological (or pathological) consequences of hyperoxygenation (3). There is evidence that one effect of supra-normal levels of arterial oxygen tension is to cause constriction in the vascular beds of some organs. This effect has been noted in the renal circulation by Aber et al. (4) and in the cerebral circulation by Jacobson (5) and others (6).

In this section, the results are described of experiments to show the effect of perfusion of the pulmonary wedge segment with hyperoxic blood.

Material and Methods:

The closed-chest preparation was used in most of these experiments. Respiratory paralysis was secured with succinylcholine and ventilation was maintained by intermittent positive pressure with room air. The animals were prepared as described in Chapter 1 and each experiment was conducted as follows.

* Part of this section has been published in the Proceedings of the Second International Congress on Hyperbaric Oxygenation. (Reference 2)

Table 33.

Dog No.	Flow ml/min	CONTROL					ARTERIAL					HYPEROXIC				
		P_{O2}	St.W.P	L.A.P	W.W.P	R	P_{O2}	St.W.P	L.A.P	W.W.P	R	P_{O2}	St.W.P	L.A.P	W.W.P	R
89	2.0	47	4.25	-	15.25	5.6	-	4.0	-	-	-	410	4.0	-	18.0	7.0
89	2.0	45	4.0	-	14.0	5.0	85	4.0	-	15.0	5.5	420	4.0	-	16.5	6.3
90	4.94	48	5.0	3.0	28.2	4.7	-	5.0	3.0	-	-	355	5.0	3.0	28.5	4.75
90	4.94	39	5.0	3.0	27.0	4.4	80	5.0	3.0	30.5	5.2	470	5.0	3.0	43.0	7.7
90	4.94	33	5.0	3.0	29.2	4.9	-	5.0	3.0	-	-	480	5.0	3.0	54.5	10.0
91	4.94	45	5.0	-	24.0	3.8	-	-	-	-	-	405	5.0	-	35.0	6.0
92	2.0	37	7.0	-	12.5	2.7	81	7.0	-	14.5	3.7	430	7.0	-	15.5	4.2
92	2.0	36	7.0	-	13.5	3.25	83	7.0	-	15.0	4.0	450	7.0	-	14.5	3.8
93	2.0	42	3.0	2.0	10.0	3.5	90	3.0	2.0	11.5	4.3	390	3.0	2.0	13.5	5.2
93	2.0	40	3.0	2.0	11.25	4.1	87	3.0	2.0	12.5	4.8	405	3.0	2.0	14.5	5.8

Changes in pressures and resistance in the wedge segment after perfusion with arterial and hyperoxic blood. The control readings are the average of four periods of perfusion.

As soon as the catheter was wedged, perfusion with the dog's own venous blood was commenced and control pressures were recorded. The perfusion syringe was then refilled, first with arterial blood, then with hyperoxic blood and the pressures evoked by the same perfusion rate recorded. The hyperoxic blood was prepared by putting 30 ml. of arterial blood into a polyvinyl bag which had been flushed with oxygen. The bag was then rotated slowly in a water-bath at 38°C. In 5 or 6 minutes this blood had a P_{O_2} of more than 300 mm.Hg.

Resistance in the wedge segment was calculated as the

$$\frac{\text{Net perfused wedge pressure - static wedge pressure (mm.Hg.)}}{\text{Perfusion flow rate (ml./min.)}}$$

The oxygen tension in samples of the blood used for perfusion was measured for each experiment.

In three experiments the left atrial pressure was also recorded through a trans-septal needle (Ross-Braunwald).

The temperature of the perfusate was maintained at 38°C.

Results:

These are detailed in Table 33 (opposite).

The pattern of change was the same in nine out of the ten experiments. In each, perfusion of the wedge segment with hyperoxic blood was accompanied by a rise in perfusion pressure which reached a plateau in about 30 seconds, and remained elevated for as long as perfusion with hyperoxic blood continued. Subsequent replacement of the hyperoxic blood with venous blood

was followed by a fall in the perfused wedge pressure to control levels (fig. 62). No change occurred in the static wedge pressure or left atrial pressure, where this was measured. The changes in calculated resistance are shown in fig. 63.

Discussion and Review:

There are a few reports in the literature concerning the effects of perfusion of the pulmonary circulation with arterial blood. As an incidental observation, Aviado and his collaborators noted that an elevation of the oxygen content of the blood in the pulmonary artery could cause vasoconstriction (7) and the same observation has been made by Boake et al. (8). Moulder and his colleagues used a pump oxygenator to supply oxygenated blood to the pulmonary artery and they found a significant rise in the pulmonary vascular resistance (9)(10).

In our preparation, only the vessels in the wedge segment were exposed to the hyperoxic blood and the response suggests a local constrictor action. Carrier has shown that the calibre of isolated perfused arteries increases or decreases in parallel with the oxygen tension of the perfusate (11). The same team had previously studied the effect of the pH of the perfusate under similar circumstances and they concluded that the oxygen tension had the greater effect on vessel calibre (12).

If the human pulmonary vasculature reacts to arterial or hyperoxic blood like that of the dog, these findings would have

an important bearing on the development of pulmonary vascular changes in patients with congenital heart disease involving left to right shunts (13 - 15). A constrictor response in the pulmonary vascular bed might also play a part in the aetiology of the pulmonary pathology which has been found in animals and man following exposure to hyperbaric oxygen (16).

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CHAPTER 9.

PULMONARY EMBOLISM.

The impaction of a pulmonary embolus is attended by profound changes in the pulmonary and systemic circulations and in the pattern of pulmonary ventilation, and these have been the subject of many investigations. Some workers have maintained that mechanical blockage of the pulmonary arterial tree can account for the effects observed (1 - 8). However, clinical experience and experimental work have shown that the consequences of pulmonary embolism are not always directly related to the size of the embolus or the extent of the subsequent infarct (9). It seems probable that factors other than simple obstruction are involved in causing the pulmonary hypertension, systemic hypotension, tachypnoea, fall in lung compliance and other manifestations which follow the impaction of an embolus. Several theories have been advanced to explain these and chief among them is that pulmonary embolism induces reflex pulmonary vasoconstriction (10)(11), mediated by reflex nervous influences (10)(13 - 16), or hormonal action (17 - 20), or a combined neurohormonal action (21 - 23).

Many experiments have been reported to support or to disprove the vasoconstriction theory and these are discussed

below. An argument frequently used to discount the occurrence of vasoconstriction in association with pulmonary embolism is based on the absence of generalised pulmonary hypertension following embolisation of one lobe, as in Daley's experiments in 1951 (24). Malmagyi has agreed that this work implies that local embolisation does not cause generalised vasoconstriction in the lungs, but draws comparisons with situations in the systemic circulation where localised emboli also fail to cause generalised constriction (25).

We have used the perfused wedge method in experiments which can be regarded as the corollary of those of Daley and Bing. In our preparation, evidence of vasoconstriction was looked for in the small perfused wedge segment during embolisation of the remainder of the pulmonary vascular bed. Emboli were not introduced into the perfused wedge segment.

Material and Methods:

The open-chest preparation was used in six dogs. Respiratory paralysis was secured with succinylcholine and respiration was maintained with a constant volume ventilator. Through a right thoracotomy, cannulae were placed as follows. (1) In the main pulmonary artery, in order to monitor the pulmonary arterial pressure. (2) In the left atrium to monitor pressure in that chamber. (3) A short length of No. 7 cardiac catheter was wedged in a branch of the artery to the right

lower lobes. This was perfused at a constant flow rate with autogenous venous blood. The pressure in the perfused wedged catheter was monitored. (4) A cannula in the femoral artery was used to monitor systemic blood pressure and for sampling. (5) A cannula was introduced into the inferior vena cava through a femoral vein and the perfusion syringe was primed and refilled from this source. In four experiments the airway pressure was also recorded through a needle in a main bronchus.

Emboli were introduced through a second cannula in the main pulmonary artery (inserted through the outflow tract of the right ventricle). They were glass beads of 500 micron diameter; six grams were suspended in 6 per cent Dextran solution and this dose was injected in three moieties.

After the second or third injection of emboli, the wedge perfusion syringe was recharged with autogenous venous blood so that a circulating hormonal agent (if any) would be introduced into the segment under study.

Results:

These are tabulated in Tables 34 and 35.

After the cannulae were in place, pressure recordings were taken over a period of 30 minutes, during which no spontaneous variations occurred. 2 gm. of glass beads in Dextran were then injected into the main pulmonary artery. The mean pulmonary arterial pressure rose some 25 per cent; no change occurred in

Table 34.

Dog No.	CONTROL					EMBOLI I					II					III				
	St.W P.	L.A P.	R.W. P.	P.A P.	Mean syst B.P.	St.W P.	L.A P.	R.W P.	P.A P.	Mean syst B.P.	St.W P.	L.A P.	R.W P.	P.A P.	Mean syst B.P.	St.W P.	L.A P.	R.W P.	P.A P.	Mean syst B.P.
94	5	4	6	14	135	5	4	6	18	118	5	4	6	30	132	4.5	4	7	43	93
95	7	5	11	15	120	8.5	6.5	10	25	96	7	5	11	33	114	7	5	11	50	70
96	8	5	9	19	128	8	5	9	23	120	8	5	9	40	120	8	5	9	57	76
97	4	2	12	13	125	4	2	12	17	110	4	2	12	32	120	4	2.5	11.5	40	85
98	3	2	11	15	115	3	2	11	20	105	3	2	11	30	115	3	2	11	39	100
99	7	6	13	12	155	7	6	13	15	113	7	6	12.5	28	160	7	6	12.5	36	140

The results of experiments to show the effect of pulmonary emboli on the pressures in the pulmonary circulation, wedge segment and systemic circulation.

Table 35.

Dog No.	INTRA-BRONCHIAL PRESSURES (mm.Hg.)							
	CONTROL		EMBOLI I		II		III	
	Peak	Mean	Peak	Mean	Peak	Mean	Peak	Mean
96	15	8	15	8	16	8	17	9
97	13	7	13	7	13.5	7	14	7
98	13	7	13	7	15	7.5	16	8
99	18	8	18	8	19	8	21	9

Results of experiments to show the effect of pulmonary emboli on the airway pressures, during controlled positive pressure ventilation with a constant tidal volume.

the perfused wedge pressure. A further 2 gm. of beads were injected and the mean pulmonary pressure became further elevated to about double the control level. No change occurred in the perfused wedge pressure. The third injection of glass beads raised the pulmonary arterial pressure to between 40 and 50 mm.Hg. At this time, the perfused wedge pressure was 1 mm. above the control value in four experiments and unchanged in two. Thepattern of change in the pressures in the perfused wedge and in the main pulmonary artery is shown in fig. 64.

No significant change occurred in the static wedge or left atrial pressure, except in one experiment in which impaction of the second dose of emboli was followed by a bradycardia which lasted for several minutes. In the experiments in which the airway pressure was measured, it was increased with the third increment of emboli. The mean intrabronchial pressure rose slightly, but the peak inflation pressure altered more significantly (Table 35). The systemic blood pressure fell briefly with the first dose of emboli, and was little changed until the third dose, which was followed by a more sustained systemic hypotension in 4 dogs.

Discussion and Review:

Within the confines of our experimental preparation, miliary embolisation with glass beads was not associated with vasoconstriction in the small segment which was free of emboli

and the results are in agreement with previous studies which have favoured mechanical blockage as the explanation for the haemodynamic changes of pulmonary embolism.

Similar experiments have since been carried out by Daily (26) with the same findings. In addition, Daily noted that stimulation of the distal portion of the sympathetic chain sectioned at T1 - T2, could cause a pressor response in the perfused wedge segment, under the circumstances of these experiments. He concluded, therefore, that reflex sympathetic vasoconstriction did not accompany pulmonary embolisation.

The use of glass micro-spheres as emboli is open to criticism, in that it does not simulate the conditions which obtain when acute massive pulmonary embolism occurs in clinical practice. This criticism applies to many studies in which a variety of emboli have been used: glass beads (1), lead pellets (27), starch granules (28), lycopodium spores (12), Penrose drains (29), barium sulphate (2), fibrin (30), and several others (3)(4)(13)(22). Better simulation was obtained by those workers who used radio-opaque clots as described by Allison (31), or thrombus prepared by Chandler's method (32). Parmley used such emboli in a well controlled study (9), and concluded that vasospasm did play an important role. He noted that the pressure measured in tertiary branches of the pulmonary arteries rose abruptly at the moment of impaction of an embolus in the proximal

primary arteries. In other words, he postulated that reflex vasoconstriction occurred in the vessels distal to the site of occlusion. It must be pointed out, however, that such a mechanism would not raise the proximal main pulmonary arterial pressure, nor interfere with pulmonary blood flow to any greater extent than would the primary mechanical block.

Hyland considered that the response might depend on the type of vessel blocked by the embolus. He used graded emboli (of polystyrene, glass and clot) in order to block selectively various sizes of pulmonary arteries, and concluded that mechanical blockage rather than vasoconstriction is the mechanism by which pulmonary hypertension is produced by emboli which occlude pulmonary arterial (as opposed to arteriolar) vessels (33).

How much of the pulmonary vascular bed must be occluded to cause an increase in the mean pulmonary arterial pressure is a relevant question. In 1923, Haggart demonstrated (with a screw clamp on the pulmonary artery in cats) that 52 per cent to 66 per cent of the main pulmonary artery could be occluded without haemodynamic change (34). Moore and Bingor confirmed this finding, using the same method (35). Several subsequent studies have agreed that at least half of the pulmonary vascular bed must be obstructed before significant pulmonary hypertension can be caused by mechanical blockage (27)(36 - 38), and this evidence in animals has been substantiated by clinical

observations. (39) Care must be taken, however, to distinguish between the effects of slow or chronic occlusion of the pulmonary vascular bed and sudden abrupt occlusion. Our own experience in dogs was that abrupt occlusion of one pulmonary artery could raise the pressure markedly in the other - by as much as 100 per cent in some animals.

The lodgement of a pulmonary embolus causes changes in the airway pressures and lung compliance in addition to its haemodynamic effects. We noted an increase in the lung inflation pressure under circumstances where the tidal volume was held constant. Singh has described this same effect after pulmonary gas emboli in animals (40), and Boyer observed a phasic change in the intra-pleural pressure in those breathing spontaneously (41). These findings relate to other studies in which lung compliance was measured. Most authors have found that pulmonary embolism is associated with a significant fall in lung compliance (20) (25)(42), and there is experimental and clinical evidence to indicate that this is due to widespread broncho-constriction (25) (43 - 45). Whether the broncho-constriction is due to a local reflex, a humoral agent or some other mechanism remains obscure. Severinghaus claimed that it was due to under-perfusion, because he was able to reduce it by the administration of one or two per cent carbon dioxide (46).

Systemic arterial desaturation has been noted to follow

pulmonary embolisation in clinical observations and in some experiments. According to the work of Robin and his collaborators and Niden, this arterial hypoxaemia is not abolished by breathing 100 per cent oxygen (47)(23). It cannot, therefore, be due to impairment of the pulmonary diffusing capacity as was suggested by Williams (6). That it could be due to the opening up of pulmonary arterio-venous communications was suggested by Niden, who showed that glass beads of up to 420 microns in size could be recovered from the pulmonary venous outflow following their injection into the right ventricle. Subsequent observers, however, have failed to find evidence of functionally significant arterio-venous shunts operating after pulmonary embolism.

The release of a humoral agent as a contributing factor in the responses to pulmonary embolism has been claimed by several workers. Halmagyi and his collaborators used a cross-circulation preparation in sheep to demonstrate that blood from a donor which had been subjected to pulmonary embolism, could produce a rise in the pulmonary arterial pressure and a fall in the compliance of the lungs in the recipient animal. However, the evidence for the presence of a circulating humoral agent in these experiments was convincing only when a barium sulphate suspension was used as the embolising agent; when blood clots were used in the same preparation, equivocal results were

obtained (20). In the 1950's and early 1960's, serotonin was regarded by many workers as the agent responsible for some of the effects of pulmonary embolism (15)(17)(19)(20)(45)(48 - 51). However, subsequent work by Malmagyi, in which he showed that a serotonin antagonist (lysergic acid butanolamide) did not modify the haemodynamic and respiratory changes, suggests that serotonin does not play an important role. Histamine has also been implicated in the pathology of pulmonary embolism (18) but again only in response to miliary embolism with barium sulphate. The many potential fallacies in drawing conclusions with regard to 'hormonal' responses, particularly in translating such animal studies to the human, have been emphasised by Nemir (52).

In considering the reflex pathways which could play a part in the consequences of pulmonary embolism, some have implicated the vagus (15)(16), and others the sympathetic (10)(13)(14), but there has not been clear evidence to indicate that either is involved and Daily's work would seem to exclude sympathetic reflexes in this context. The fact that various neuroplegic procedures in experimental animals can modify the response to pulmonary embolism does not necessarily mean that they normally play a part in the intact animal or man.

The fall in systemic blood pressure which followed embolisation in our preparation, has been noted by most workers and occurs in the clinical situation (4)(53). A simple

explanation would be that it is due to a fall in cardiac output, but we did not measure this factor, nor systemic resistance and cannot therefore derive any conclusions on this point. Some have suggested that the systemic hypotension may arise through a reflex from receptors in the pulmonary veins or left atrium (16)(54 - 56). We found no consistent change of pressure in these chambers and cannot attribute the systemic hypotension to this mechanism.

As a result of his studies Parmley (9) favoured a reflex mechanism to account for the fall in systemic pressure because of the abrupt pattern of its onset, its transient nature and its reversibility even when severe, but the site of initiation of the reflex was not clear.

Several authors have demonstrated the existence of baroreceptors in the main pulmonary artery and its bifurcation (16)(57 - 60) and some of these studies have demonstrated that distension of the main pulmonary arteries is accompanied by systemic vasoconstriction (59)(60). Aviado (16) and Daly (54), on the other hand, believed that stimulation of these receptors would cause systemic vasodilatation (and account for the hypotension). Other stretch reflexes which influence the systemic circulation were described in the lung itself by Salisbury and his collaborators (61). The findings of Osorio's group, that distension of the large pulmonary arteries could

cause distal pulmonary hypertension through a 'pulmo-pulmonary' reflex (58), is in accord with Parmley's findings (9). It suggests again that large emboli which block larger pulmonary arteries may be associated with distal vasoconstriction. Thus, the presence of pressure sensitive areas in the lungs and main pulmonary arteries seems to be established, but their homeostatic role and participation in the sequelae of pulmonary embolism remains the subject of controversy.

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CHAPTER 10.

THE EFFECT OF COLD PERFUSION.

Applications of partial and total body cooling in clinical practice have called for studies on the effect of cold perfusion on the vasculature of various organs. The effects of cold perfusion on the systemic circulation have been investigated in some detail (1 - 4), and the subject was reviewed by Lewis in 1961 (5). By contrast, little work has been done concerning the local effects which changes in the temperature of the blood may have on the pulmonary circulation. Goetz (6) used a method of separate perfusion of the pulmonary and systemic circulations by means of two extracorporeal pumps. He found that perfusion of the pulmonary circulation with hypothermic oxygenated blood was associated with a rise in pulmonary blood pressure and a simultaneous fall in systemic pressure, and he postulated both a local and a reflex effect of cold blood on the pulmonary circulation (7).

In most perfusion preparations, if attention is not paid to maintenance of the correct temperature of the perfusate, deterioration of the preparation results, or at least, anomalous results are obtained, and in earlier experiments in the present study, when the characteristics of perfused wedge catheter

pressure records were being recognised, it was noted that in some experiments a progressive rise in perfused wedge pressure occurred shortly after the start of perfusion. In later experiments, when the temperature of the perfusate was maintained at 38°C., this phenomenon did not occur. These observations suggested either that perfusion of the wedge segment with cold perfusate caused vasoconstriction, or that reduction of the temperature of the perfusate was associated with an increase in its viscosity and a consequent increase in pressure at a constant flow rate. The following experiments were done to test the first hypothesis and to assess the significance of a change in viscosity.

Material and Methods:

(1) The usual apparatus for perfusion of a catheter and measurement of the pressure in it was set up. A 20 cm. catheter was used, and most of the length of the connecting tube was immersed in a water bath. The catheter was then perfused with its tip in air, at the same level as the transducer. This was done with the water bath temperature at 38°C. and then at 20°C. First blood, then saline were used as the perfusate. The pressures and corresponding flows were recorded at the two temperatures.

(2) Using the open-chest animal preparation, a catheter was wedged, perfused with blood at 38°C., and control pressure records taken. While perfusion was continued at the same rate,

Table 36.

Dog No.	Perfusate	Flow	Cath P	CONTROL (37°C)					COLD PERFUSION (20°C)				
				St.W.P	L.A.P	G.W.P	N.W.P	R	St.W.P	L.A.P	G.W.P	N.W.P	R
100	Saline	3.98	4.5	6.0	4.0	20.0	15.5	2.89	6.0	4.0	24.0	19.5	3.89
100	Blood	2.0	7.0	6.0	4.0	22.0	15.0	5.5	6.0	4.0	27.0	20.0	8.0
100	Blood	2.0	7.0	7.0	5.0	26.0	19.0	7.0	7.0	5.0	30.0	23.0	9.0
101	Saline	3.98	4.5	4.0	3.0	16.5	12.0	2.26	4.0	3.0	20.5	16.0	3.27
101	Blood	2.0	7.0	4.0	3.0	21.0	14.0	5.5	4.0	3.0	26.0	19.0	8.0
101	Blood	2.0	7.0	4.0	3.0	19.0	12.0	4.5	4.0	3.0	23.5	16.5	6.75

The results of experiments to show the effect of a reduction in the temperature of the perfusate on the pressures and resistance in the perfused wedge segment.

$$\left(R = \frac{N.W.P - St.W.P}{Flow}\right)$$

the perfusate was cooled (as it passed through a water bath at 20°C.) and pressure records were taken again.

(3) This experiment was repeated, using saline as the perfusate.

Results:

(1) When the catheter was perfused in air at a constant rate, no change in pressure occurred when the temperature of the perfusate was dropped from 37° to 20°C. This was true for both blood and saline.

(2) The results of the animal experiments are tabulated in Table 36 (opposite). They show that a reduction in the temperature of the perfusate (whether it was blood or saline), was associated with a rise in the calculated vascular resistance in the wedge segment.

Discussion:

The rise in perfused wedge pressure which accompanied reduction of the temperature of the perfusate could be due to change in viscosity or vascular constriction. In our studies, when the catheter alone was perfused -- no rise in perfusion pressure was seen. Therefore, the change in viscosity associated with a temperature drop from 37° to 20°C. had no appreciable effect as measured by impedance to flow through the catheter. The viscosity of saline is unaltered by temperature changes within the range used here, yet cold saline perfusion of the wedge segment also caused a rise in pressure. These results show then that

cold perfusion of the vascular bed in the wedge segment caused vasoconstriction.

The effect would appear to be locally mediated, and this is in accord with the observations of Goetz, who found that sympatholytic agents, atropine, and vagal section did not modify the pressor effect of cold perfusion in the pulmonary circulation (7).

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CHAPTER 11.

THE INFLUENCE OF THE AIRWAY PRESSURES.

This part of the study is concerned with the manner in which changes in the airway pressure and intra-thoracic pressure may influence blood flow and vascular pressures in the pulmonary circulation.

The inter-relationship between the airway and the intra-vascular pressures is complex. The entire pulmonary circulation lies within the thorax and is subject to phasic swings in pressure from negative to positive, and since the small pulmonary vessels are related intimately to the air passages, throughout much of their course, they are subject to distortion by them (1). The pressure changes which obtain within the thorax during both spontaneous and artificial ventilation affect not only the vessels within the parenchyma of the lungs, but also the rate and volume of blood flow which enters and leaves the pulmonary circulation. During spontaneous breathing, in inspiration, the pressure gradient between the extra-thoracic great veins and the right atrium is increased, this augments venous return to the heart and increases the stroke volume of the right ventricle. Conversely, positive pressure inflation of the lungs impedes venous return, by diminishing this gradient (2 - 7), and by

Table 37.

PREPARATION	VENTILATION	FACTORS MEASURED
Closed chest	Spontaneous	Perfused wedge pressure Static wedge pressure Intra-oesophageal pressure Systemic arterial pressure
Closed chest	Intermittent positive pressure	Perfused wedge pressure Static wedge pressure Intra-tracheal pressure Systemic arterial pressure
Open chest	Intermittent positive pressure	Pulmonary arterial pressure Left atrial pressure Pulmonary blood flow (to one lobe) Intra-bronchial pressure
Open chest	Intermittent positive pressure	Perfused wedge pressure Left atrial pressure Intra-bronchial pressure
Open chest	Intermittent positive pressure + local bronchial occlusion.	Perfused wedge pressure Left atrial pressure Intra-bronchial pressure

The preparations used and factors measured in the experiments designed to investigate the influence of airway pressures on the pulmonary circulation.

direct compression of the great veins and chambers of the right heart (8 - 11). Furthermore, when the lungs fill with air, there is evidence that blood is displaced out of them causing a measurable increase in left atrial filling and left ventricular stroke volume (vide infra). Thus, ventilation is probably associated with phasic changes in the volume of blood contained in the lungs (12)(13).

Methods:

Because several inter-related factors were involved, more than one experimental preparation was used. In each preparation some variables were controlled and the others measured. The preparations used and the factors measured are summarised in Table 37 (opposite).

Observations were made in twenty seven dogs.

In the closed-chest animals, blood flow to the segment under study was controlled and delivered through a wedged catheter. The left atrial pressure was measured through a Ross-Braunwald needle introduced transseptally into the left atrium; and the intra-thoracic pressure was recorded through an open ended catheter in the oesophagus. In some of the open-chest animals, a wedged catheter and a left atrial cannula were introduced as described in Chapter 1. In other open-chest animals, blood flow to the right lower lobes was recorded (using an electro-magnetic flowmeter), while the pressure in the main pulmonary

artery was measured through a catheter introduced centrally from a peripheral arterial branch. The left atrial pressure was also measured in these animals. In the open-chest animals, ventilation was maintained with a variable volume respiratory pump and the mean airway pressure was varied by altering the stroke volume and the end expiratory pressure.

Results and Interpretation of the Records:

(1) Closed-chest preparations with spontaneous respiration.

The records in this group showed that the mean pulmonary pressure, left atrial pressure and intra-thoracic pressure all fell with inspiration and rose with expiration. Since instantaneous pulmonary flow was not measured, no conclusions about changes in resistance could be drawn other than the obvious one that the swings in intra-thoracic pressure were reflected to some extent in the intra-vascular compartments. The systemic arterial pressure on the other hand showed a rise during each inspiratory phase.

In the experiments in this group in which the perfused wedge method was used, flow was controlled and known in the segment in which perfusion pressure was measured, i.e. the influence of ventilation on such variables as venous return and right ventricular output were avoided and changes in vascular resistance (in the wedge segment) could be inferred from changes in the perfusion pressure.

The observations in this group can be presented most clearly by referring in the first instance to the tracings from one experiment. In the record shown in fig. 65, the intra-thoracic pressure dipped to minus 20 mm.Hg. with each inspiration. (The extent of the normal negative pressure swing was exaggerated by intubating the trachea with a rather narrow tube.) The perfused wedge pressure showed a synchronous fall with inspiration and a rise during the expiratory pause. The catheter in this experiment was perfused at a constant rate (3.88 ml./min.) and the pressure evoked by perfusion of the catheter alone was 15 mm.Hg., so the net pressure in the vessels of the perfused segment was 40 - 15 mm. = 25 mm. during expiration; and 30 - 15 mm. = 15 mm. during inspiration. The extra-vascular pressures during expiration and inspiration were 3 mm. and minus 20 mm. respectively. The left atrial pressure was 0 during inspiration and 4 mm.Hg. in expiration.

These figures may be interpreted in more than one way. The intra-vascular pressures, as measured, indicate that resistance to blood flow decreased during inspiration, on the grounds that the pressure gradient across the wedge segment which was 21 mm. during expiration, fell to 15 mm. in inspiration, while the flow remained constant. But these pressures measured through the wedged catheter are compounded of the pressure evoked by the resistance to blood flow through the

vascular bed, plus that fraction of the intra-thoracic pressure which is transmitted through the vessel wall (fig. 66). The same consideration applies to the left atrial pressure. But what proportion of the extra-vascular pressure is transmitted across the vessel wall or left atrial wall is not yet known (14)(15)(16). There is evidence that more is transmitted through the former than the latter, since the inspiratory dips in a static wedge pressure tracing are 3 or 4 times greater than those recorded from the left atrium. This last observation can be partly explained by postulating an increase of blood flow into the left atrium during inspiration. That this does occur is shown by the phasic upswings in systemic pressure which accompany inspiration (fig. 67). If the systemic resistance remained constant, these changes in pressure imply an increased output from the left ventricle during inspiration and this must be preceeded by increased filling of the left atrium and left ventricle.

Returning to the transmural pressure concept, if one assumes that one third of the intra-thoracic pressure changes are transmitted through the left atrial wall, and that two thirds are transmitted through the much thinner vascular walls, then in the experiment in fig. 65, the net intra-vascular pressures would be 15 - (-13) = 28 in inspiration and 25 - (+2) = 23 in expiration; while the corresponding left atrial pressures would be 6.5 mm.

and 3 mm., and the pressure gradients for the calculation of resistance are 21.5 mm. (inspiration) and 20 mm. (expiration). Since flow was held constant, this alternative interpretation of the figures suggests that inflation of the lungs during spontaneous breathing is associated with a very small increase in pulmonary vascular resistance.

(2) Closed-chest, with intermittent positive pressure ventilation.

As one would anticipate, the records of the pulmonary artery pressure, left atrial pressure and intra-bronchial pressure during intermittent positive pressure ventilation showed a phasic rise and fall which accompanied inflation and deflation of the lungs respectively, i.e. the pressures moved in the opposite direction to those with spontaneous breathing. However, the swings in the systemic arterial pressure occurred in the same phase as those seen in the spontaneously breathing animals, in that systemic pressure rose during inflation of the lungs and this is interpreted as being further evidence of increased left atrial filling during this part of the respiratory cycle (whether ventilation is spontaneous or by positive pressure).

It is noteworthy that the rise in pulmonary pressure which accompanied inflation was considerably greater than the rise in left atrial pressure, that is the pressure gradient across the lungs was increased by positive pressure inflation (fig. 68). Flow was not measured, but it has been shown by

others that this factor is reduced by lung inflation (by reduction of venous inflow and by direct pressure on the right heart). Therefore we can conclude that positive pressure inflation of the lungs brings about a significant increase in pulmonary vascular resistance. The records obtained from the perfused wedge experiments in this group added complimentary information, in that flow was held constant and known. In those experiments, since flow was not reduced during inflation, an even greater rise in pressure gradient occurred (fig. 69).

As with spontaneous ventilation, the intra-thoracic pressure changes during intermittent positive pressure ventilation will be transmitted across the vessel (and atrial) walls to some extent, and will contribute to the elevations in the pressures recorded. However, it is probable that the principal effect of positive extra-vascular pressures will be mechanical compression of the vessels, and the conclusion that the vascular resistance to flow rises is still valid.

In the spontaneously breathing preparations, it has been noted that airway pressure changes were reflected more clearly in the static wedge pressure records than in the left atrial pressures. Corroborative findings were obtained in this group of closed-chest animals ventilated by intermittent positive pressure. Fig. 70 illustrates the greater influence of rises in airway pressure on the static wedge pressure than on the

Table 28.

Dog No.	Mean Intra-Bronchial Pressure mm.Hg.	Pulmonary Vascular Resistance Units
102	6.0	4.4
	7.5	5.5
	9.5	5.8
	10.0	7.2
	11.0	8.0
	13.5	8.5
103	3.0	4.0
	4.5	4.5
	6.0	5.0
	7.5	5.5
	10.0	6.5
	12.0	8.0
104	3.0	4.5
	4.0	5.0
	6.0	6.0
	7.0	6.5
	8.0	6.75
	10.0	8.0
	12.5	10.0
105	3.0	4.85
	4.0	5.5
	5.0	6.0
	6.5	6.5
	9.0	7.5
	12.0	9.5
106	3.0	5.5
	5.0	6.5
	6.0	7.0
	8.0	8.0
	9.5	8.5
	10.5	9.0
	12.0	10.5
107	3.0	6.5
	4.0	6.8
	5.0	7.0
	6.0	7.4
	8.0	7.6
	9.0	8.4
	12.0	10.1

The relationship between the airway pressure and the total pulmonary vascular resistance during intermittent positive pressure ventilation. Pulmonary vascular resistance = (Pulmonary pressure minus left atrial pressure) divided by flow.

left atrial pressure.

(3) Open-chest preparations. (Intermittent positive pressure ventilation.)

Three types of experimental set-up were used:-

(a) Blood flow and pressure were measured in the pulmonary artery to the right lower lobes while the inflation pressure was varied. The left atrial pressure was also recorded.

(b) In this preparation the perfused wedge catheter was used, and the perfused wedge pressure, left atrial pressure and airway pressure were recorded.

(c) In this preparation the effect of varying periods of bronchial occlusion on the perfused wedge pressure were studied.

Table 38 shows the results obtained from group (a) experiments and the pattern of an experimental run is illustrated in fig. 71. They show that high inflation pressures were associated with a small increase in the mean pulmonary artery pressure and a marked reduction in pulmonary flow. The principal change in the left atrial pressure record, with high inflation pressures, was an increase in the amplitude of the phasic swings due to ventilation, the mean pressure was not significantly altered.

The pulmonary vascular resistance calculated from the results of these experiments has been plotted against the mean airway pressure in fig. 72. The resistance units were calculated

Table 39.

Dog No.	Airway	N.W.P	L.A.P	R
108	2.0	7.0	1.0	3.0
	4.0	7.5	1.0	3.25
	5.5	8.0	1.0	3.5
	7.5	8.5	1.0	3.75
	9.0	9.0	1.0	4.0
109	2.0	7.25	3.0	2.12
	3.5	8.0	3.0	2.5
	4.5	8.5	3.0	2.75
	5.5	9.0	3.0	3.0
	6.5	9.5	3.25	3.75
	8.5	10.5	3.5	3.5
110	2.5	8.5	4.0	2.25
	3.0	8.75	4.0	2.37
	4.0	9.25	4.0	2.62
	5.5	10.0	4.0	3.0
	7.0	10.5	4.0	3.25
	9.0	11.0	4.5	3.25
111	2.0	8.0	2.0	3.0
	3.5	8.5	2.0	3.25
	5.5	9.25	2.0	3.62
	7.0	10.0	2.0	4.0
	8.5	10.5	2.0	4.25
112	2.0	9.0	2.0	3.5
	3.0	9.5	2.0	3.75
	4.0	10.0	2.0	4.0
	5.0	10.5	2.0	4.25
	6.5	11.25	2.0	4.62
	9.0	12.0	3.0	4.5
113	3.0	10.5	4.0	3.25
	4.5	11.0	4.0	3.5
	6.0	12.0	4.0	4.0
	9.0	12.5	4.0	4.25

The relationship between the airway pressures and the resistance in the wedge segment during intermittent positive pressure ventilation. Resistance = (Net perfused wedge pressure minus left atrial pressure) divided by flow. Flow through the wedge segment was 2.0 ml./minute.

conventionally as follows:

$$\frac{\text{Mean pulmonary arterial pressure - left atrial pressure (mm.Hg)} \times 100}{\text{Pulmonary blood flow (mls./min.)}}$$

The fact that the pressure gradient from the pulmonary artery to the left atrium was reduced in some experiments as the inflation pressure was increased, suggests that one effect of inflation was to reduce right ventricular output. It appears that despite the fact that the thoracic cage was widely open in these experiments, positive pressure inflation of the lungs could still impede venous return and right ventricular output to a measurable extent.

These experiments show incidentally that a rise in vascular resistance may be present, despite a fall in vascular pressure, in circumstances where flow is greatly reduced. They emphasise again the fact that measurement of both flow and pressure are necessary before a figure for resistance can be derived with certainty.

In group (b), blood flow was held constant and so pressure could be related directly to resistance. The effects of varying the inflation pressure under these circumstances are shown in fig. 73 and the results from all these experiments are detailed in Table 39. They show that under conditions of constant flow, the perfusion pressure in a segment of the pulmonary vascular bed rises in an almost linear fashion as the inflation pressure is increased (fig. 74).

In three of these experiments, only the lobe which contained the wedge segment was subject to changes in inflation pressure -- thus elevation of left atrial pressure by over-inflation of the left lung was avoided. This modification of the preparation was made because it was noted that in some preparations, in which a right thoracotomy was used and the animal was laid in the full lateral position, inflation of the left lung could raise the heart in relation to the point of zero reference and exaggerated changes in left atrial pressure appeared (fig. 75). (This record also shows the increased amplitude of the left atrial pressure pulses which accompanies inflation. This is interpreted as being due in part to increased atrial filling as blood is squeezed out of the pulmonary veins. The diminution in the pulmonary arterial pressure pulse which occurs with inflation reflects a reduction in right ventricular output).

In the open-chest preparations in which pulmonary blood flow was not held constant but was measured, the records confirm that inflation diminishes flow while elevating the pressure. This is illustrated in fig. 76, which shows the mean pressures recorded in the right main bronchus and pulmonary artery, along with the pulmonary blood flow to the right lower lobe. At the point arrowed, the peak inflation pressure was doubled for one cycle, and the records show the consequent increase in pressure and reduction in flow.

Table 40.

Dog No.	Flow ml/min.	CONTROL			BRONCHUS OCCLUDED						BRONCHUS RELEASED		
					1 Minute			1 Hour			3 Minutes		
		N.W.P	L.A.P	R	N.W.P	L.A.P	R	N.W.P	L.A.P	R	N.W.P	L.A.P	R
114	7.6	20.0	2.0	2.37	17.0	2.0	1.97	20.0	2.0	3.68	23.0	2.0	2.76
115	3.8	12.0	3.0	2.37	10.0	3.0	1.84	17.5	3.0	3.82	13.0	3.0	2.63
116	3.8	11.0	2.0	2.37	9.0	2.0	1.84	16.0	2.0	3.68	12.0	2.0	2.63
117	2.0	11.5	2.0	4.75	9.0	2.0	3.50	16.5	2.0	7.25	13.0	2.5	5.25

The effect of absorption atelectasis on the vascular resistance in the wedge segment. $\left(R = \frac{N.W.P - L.A.P}{Flow}\right)$

Thus, where intermittent positive pressure ventilation was used, comparison of the results obtained in open-chest and closed-chest preparations showed few differences. The ability of the lungs to expand through the thoracotomy incision did not appear to affect the relationship between the airway pressures and the intra-vascular pressure, in a qualitative manner.

Group (c). The effect of atelectasis.

This was studied by using the perfused wedged catheter technique in the open-chest preparation. A wedge segment in the right lower lobe was perfused at a constant rate throughout the experiment. After control records had been obtained, the bronchus to this lobe was occluded by means of an intra-bronchial balloon, since an external clamp might interfere with peribronchial nerves. The lungs had been previously ventilated with 100 per cent oxygen and so absorption collapse of the right lower lobe was largely complete in 60 minutes. Records of the perfused wedge pressure were taken every few minutes during the hour, as atelectasis progressed. After one hour, the lobe was reinflated and further records of the perfused wedge pressure were taken. The results of these experiments are shown in Table 40. Immediately after bronchial occlusion the perfused wedge pressure fell by 2 or 3 mm. After 8 to 10 minutes it reached the control level again, then rose progressively until the bronchial occlusion was released. After

occlusion had been maintained for one hour, the perfused wedge pressure was about 50 per cent higher than the control level. Release of bronchial occlusion and reinflation of the lobe was accompanied by an immediate fall in perfused wedge pressure, followed by a slower decline to a level slightly above the control. Since the pattern was very similar in each of 4 experiments, further experiments were not done. The static wedge pressure and left atrial pressure remained unchanged throughout.

These results show that absorption atelectasis is accompanied by an increase in vascular resistance, which returns to normal when the lung segment is reinflated.

Review and Discussion:

The results of the foregoing experiments have been considered together, to reach conclusions concerning the influence of change in airway pressure on pulmonary blood flow, with due attention to the changes in the transmural pressure across the vessel wall which accompany ventilation (17).

In the intact animal, breathing spontaneously, inflation of the lungs was accompanied by an increased rate of inflow of blood into the lungs and an increased rate of outflow of blood from the lungs. The resistance to flow in the small pulmonary vessels, calculated under conditions of constant flow, was not significantly altered by inflation or deflation of the lungs

during spontaneous breathing. Under conditions in which flow could vary, there was inferential evidence that resistance falls during inspiration. The transient increase in pulmonary blood flow which accompanied spontaneous inflation of the lungs was also accompanied by an increase in systemic blood flow.

Artificial ventilation by intermittent positive pressure caused quite significant changes in the pulmonary vascular resistance and flow, both in the intact animal and in those with a thoracotomy. Inflation was associated both with an increase in vascular resistance and a reduction of inflow to the pulmonary circulation. The increase in resistance occurred whether flow was held constant or not. There was evidence that the reduction in flow was due to two factors, increased resistance at the level of the small pulmonary vessels and diminished right ventricular output. On the other hand, positive pressure inflation, like spontaneous inflation, caused an increase in the outflow of blood from the lungs. Therefore, positive pressure inflation of the lungs causes a reduction in pulmonary blood volume (12)(13).

These conclusions are in general agreement with those of previous workers who have shown that positive pressure inflation of the lungs increases pulmonary vascular resistance (18 - 21), even with the chest open (11)(22). They are also in accord with the 'sluice' concept, which was introduced by Bannister and Torrance (23) and has been supported by similar work by

Howell (24) and Permutt (25). These workers noted that the airway pressure could act as a 'sluice' to modify pulmonary blood flow (or pressure, if flow was held constant). Permutt and his collaborators (26) further studied the relationship between 'alveolar' pressure, pulmonary venous pressure and pulmonary blood flow in an isolated lobe perfused at a fixed pressure. They found that when the pulmonary venous pressure was lower than the alveolar pressure, the rate of blood flow was determined by the pulmonary artery/pulmonary alveolar pressure gradient. Alterations of venous pressure within the range below the alveolar pressure had no effect on the lobar blood flow. This conclusion has been supported recently by detailed studies done on dogs by De Bono and Caro (27). These results seem at first sight to be at variance with our observations reported in Chapter 4 on the effects of changes in left atrial pressure on the pulmonary vascular resistance, and with the work of several other workers on this subject (20)(28 - 31), but the apparent inconsistencies can be explained by considering the differences in the manner in which the airway pressure was changed in the experimental preparations used, in that the 'sluice' concept was based on experiments using isolated lungs or lobes in which inflation was held suspended at various pressures while the measurements were made. Whereas in the experiments reported here, phasic inflation and deflation of the lungs was

used, using pressures within the physiological range. The mean airway pressures cited in this study were electrically integrated, and during more than half of each respiratory cycle, the airway pressure was much lower. The results of the present study are in agreement, however, insofar that they show a linear relationship between airway pressure and pulmonary resistance under conditions of fixed flow.

Following the pioneer work of Andrus in 1925 (32) several studies on the blood flow through areas of acute atelectasis have been made and most have reported a reduction of flow (33)(34).

In our experiments in which resistance to blood flow through an atelectatic segment was studied, the results showed a marked increase in resistance after one hour. It seems probable that this is due to mechanical factors, but changes in the composition of the gases in partially atelectatic areas may play a significant role in altering the vascular resistance.

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CHAPTER 12.

SUMMARY.

> .... in an important sense a rational problem solver wants what he can get and does not try to get what he wants except after identifying what he wants by examining what he can get (1).

This investigation of the responses of the small pulmonary vessels to certain stimuli was undertaken in the belief that a deeper understanding of these reactions would be of help in the management of patients with cardio-pulmonary disease.

Results of several hundred experiments in 155 dogs are presented and discussed, along with a review of the relevant literature. Nearly all the studies were done on animals in order that the several variables which can act on the pulmonary circulation could be purposively controlled. However, the preparations were kept as physiological as possible and the principal method used is one which can be used in man with little modification. This method assumes that the pressure measured in a catheter which is wedged in a peripheral branch of the pulmonary artery and perfused at a constant flow rate, will relate to the vascular resistance in the perfused area.

Most of the results reported have been derived from two

complementary types of experimental preparation. In the one, studies of the pressure gradients were made in that portion of the pulmonary vascular bed which could be perfused by a "wedged" catheter, using autogenous venous blood as the perfusate. In the other, both flow and pressures were measured continuously in a larger segment of the intact pulmonary circulation. Where appropriate, the results obtained by the two methods are compared and contrasted and used to distinguish between local, direct actions and the indirect, consequential reactions of the pulmonary vessels.

The experiments described in the first two chapters establish the stability of the perfused wedged catheter preparation and delineate the relationship between pressure and flow in the segment of vascular bed under study, under spontaneous breathing and positive pressure ventilation. This takes the form of a flat curve which is concave towards the flow axis. In addition, the vessels show some hysteresis. These preliminary studies brought to light an important source of artefact and results are detailed to show that changes in the capacity of the right ventricle can affect the pressure in both static and perfused wedged catheters by acting on the intra-cardiac loop of catheter.

In Chapter 4, the pressures measured in a wedged catheter are compared with the pressures measured directly from the left atrium and from the pulmonary veins some 2 cm. from the atrium,

under conditions of changing pulmonary blood flow and left atrial pressure. These observations were a necessary background to the subsequent experiments in which the effects of drugs, respiratory gases and other stimuli on the vessels of the segment were studied. The measurements showed that there is normally a small pressure gradient from the catheter tip to the pulmonary veins and from the pulmonary veins to the left atrium in the segment 'subtended' by a wedged catheter. Evidence is presented to attribute this gradient to blood flow in the venous part of the segment; the flow arising from confluence of veins from adjacent segments. The gradient increased under circumstances of increased pulmonary blood flow and decreased when pulmonary flow was reduced. Attention is drawn to the haemodynamic differences between perfused and unperfused wedge segments. Acute elevation of the left atrial pressure was shown to cause a corresponding elevation of the upstream pressures in the unperfused segment, and a fall in resistance values in the perfused segment.

The effect of some drugs on the pulmonary vessels is described in Chapter 5. The perfused wedge technique lends itself particularly to studies of the direct local actions of agents on the small pulmonary vessels, and to the differentiation of these effects from the secondary consequences of distant actions of the drug. It allows the investigator to deliver drugs directly into the small pulmonary vessels in doses which have a negligible effect

in the circulation in general. These experiments showed that adrenaline, nor-adrenaline, 5-hydroxytryptamine, metaraminol and acetylcholine had a constrictor effect on the pulmonary vessels. Tolazoline had no effect on normal vessels, but could reverse or prevent the constrictor influence of adrenaline and nor-adrenaline. Iso-propyl-nor-adrenaline had a local dilator effect on the pulmonary vessels, under conditions of constant flow. When the drug was administered intravenously, however, its powerful inotropic effect on the myocardium increased pulmonary flow markedly and this overshadowed its local action. Aminophylline also had a local dilator action on normal pulmonary vessels and could reduce the constrictor effect of serotonin. When aminophylline was administered systemically, however, its dominant effect was to increase cardiac output, and no consistent pattern of change in total pulmonary vascular resistance was seen in either the animal experiments or the clinical measurements made in this study.

The important influences of the respiratory gases on the pulmonary vessels are considered in Chapters 6, 7 and 8. An increased alveolar P_{CO_2} was followed consistently by vasoconstriction of the small pulmonary vessels. This effect was locally mediated and due to a direct effect of raised CO_2 tension on the vessels. The effect was not modified by tolazoline. The experiments to study the effects of alveolar hypoxia yielded interesting results.

The acute induction of hypoxia by ventilation with five to eight per cent oxygen in nitrogen was always followed by an increase in pulmonary flow and pressure, and usually accompanied by an increase in total pulmonary vascular resistance. In the perfused wedge segment, however, hypoxia always caused a fall in resistance under conditions of fixed flow. This reduction in resistance appeared to be locally mediated and occurred only when the alveoli related to the perfused segment were exposed to hypoxia. There was not sufficient evidence in this study to explain why hypoxia increased total pulmonary resistance, while at the same time decreasing resistance in the pre-venous part of the wedge segment. Measurements made during hypoxic stimuli also showed an increase in the pressure gradient from pulmonary vein to left atrium. It is noted that this rise in pressure could be a passive consequence of the greatly increased pulmonary flow, and there was no evidence of venoconstriction nor of a veno-atrial "throttle".

The effects of perfusing the pulmonary vascular bed with arterial blood and with blood containing supra-normal oxygen tensions are presented in Chapter 6. These experiments showed that such perfusion was followed by local vasoconstriction, which was reversible by perfusion with venous blood.

The experiments concerning pulmonary embolism were designed to explore the occurrence of reflex vasoconstriction in association with the impaction of emboli. The results showed no constriction

in the wedge segment during embolisation of the rest of the pulmonary vasculature with glass beads (500 u.). An incidental finding was that airway resistance increased as a consequence of miliary embolisation of the pulmonary vascular bed.

The results presented in Chapter 10 show that a reduction in the temperature of the perfusate causes vasoconstriction in the small pulmonary vessels.

In the last chapter the important interplay between the intra-vascular pressures and the airway pressures is described. The experiments showed that changes in both intra-thoracic and airway pressures are reflected in the intra-vascular compartments. Spontaneous ventilation was associated with little change in vascular resistance during the phases of breathing. Intermittent positive pressure ventilation on the other hand increased vascular resistance, and when the mean airway pressure was raised above the pulmonary venous pressure, resistance to blood flow was related in a linear fashion to the airway pressure. These experiments also showed that inflation of the lungs, whether spontaneous or by positive pressure, was followed by a rise in the systemic blood pressure. This was interpreted as being due to increased filling of the left atrium during inspiration. Experiments in this section showed that absorption atelectasis is associated with a rise in local vascular resistance which is reversible when the lung is re-inflated.

In conclusion, this study shows that the small pulmonary vessels are capable of active vasomotion in response to certain drugs, to changes in the composition of the gases in the alveoli and in the perfusing blood, and to physical stimuli. A method for assessing these vascular changes has been thoroughly evaluated in the animal experiments presented, and since the completion of this work it has been applied in clinical practice in a few cases. It is a safe extension of routine right heart catheterisation procedures and promises to add useful information concerning the small pulmonary vessels in disease states.

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PULMONARY VASOMOTOR ACTIVITY

VOLUME III

Figures.

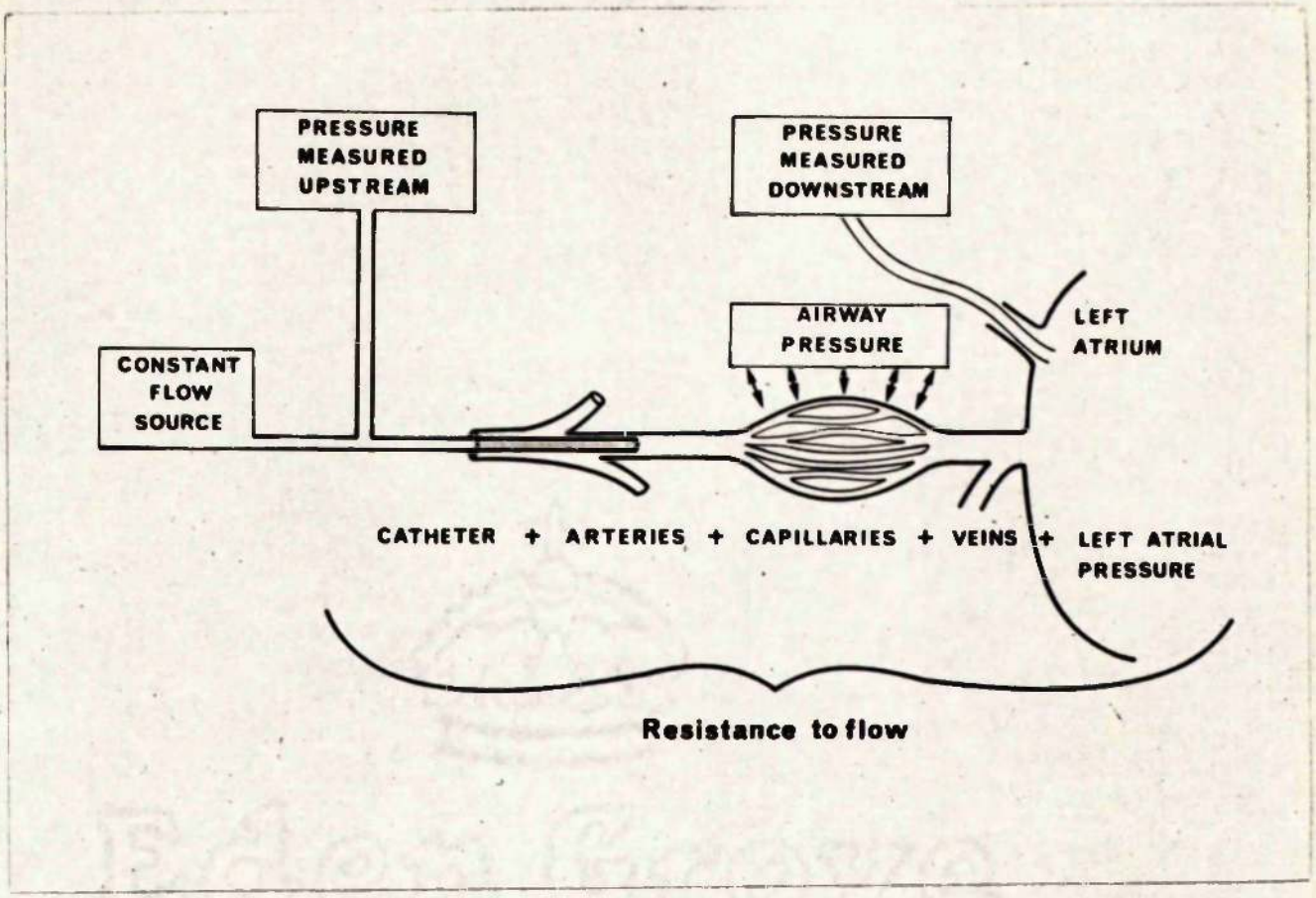


Fig. 1.

A diagram of the system used to perfuse a wedged pulmonary artery catheter.

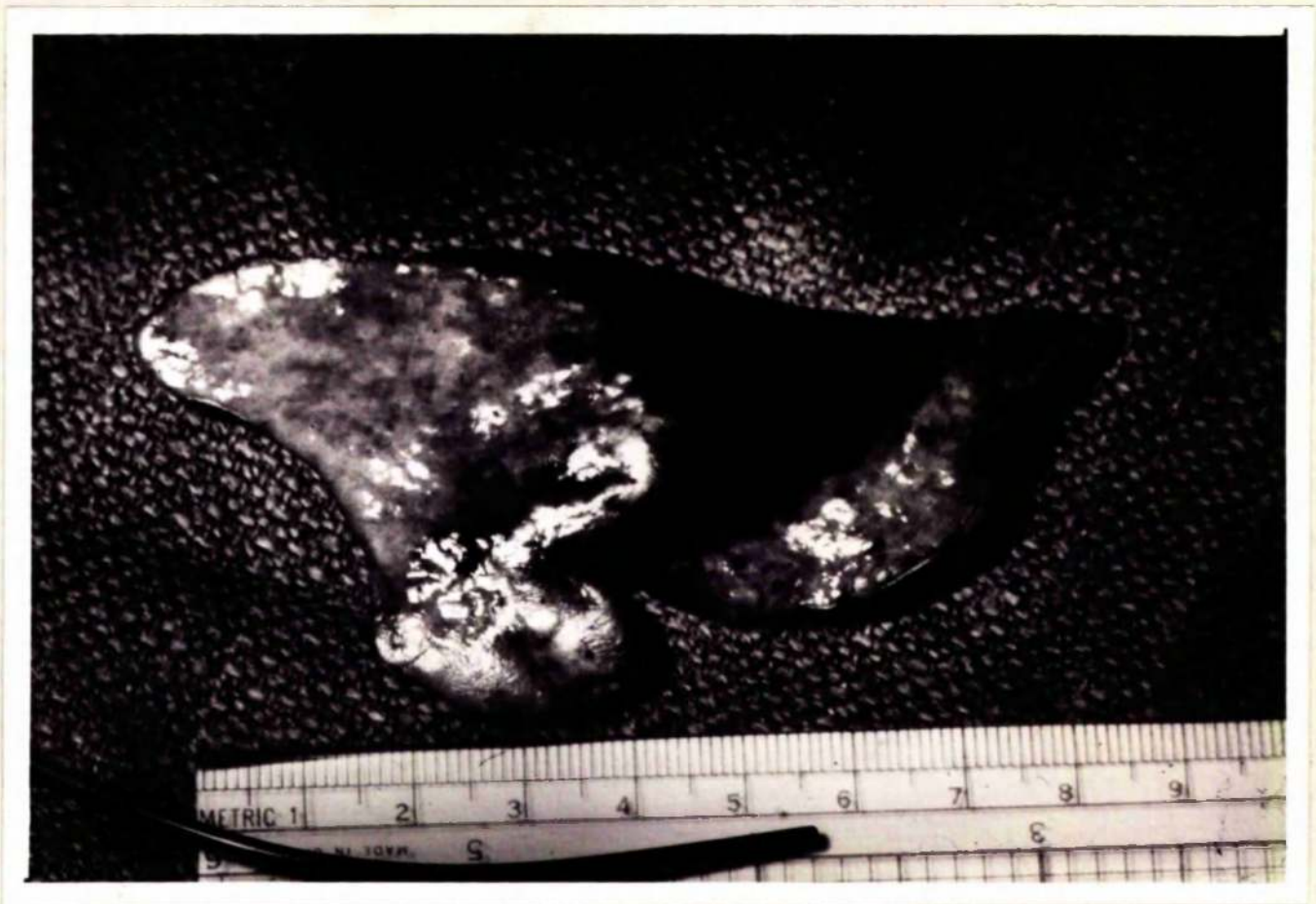
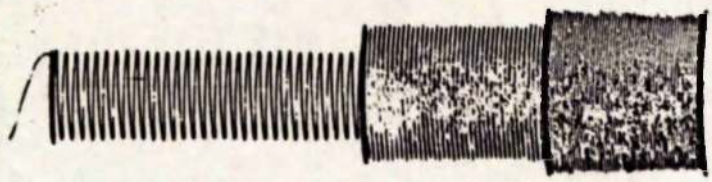


Fig. 2.

A photograph of the right lower lobe of the lung in the dog, with a wedge segment filled with blue dye. The segment was perfused through a No. 7 (F.G.) catheter.



30 c.m.s. Catheter: Bore 1·5mm.

30 c.m.s. Catheter: Bore 0·4mm

20 30 40
cycles per second.

(3)

Fig. 3.

The frequency response pattern through two catheter–manometer systems. A sine wave of constant amplitude was applied at 20, 30 and 40 cycles/second. The only difference in the two systems was the bore of the catheter; the transducers were matched. The tracings are reproduced to demonstrate how a catheter can modify pressure waves.

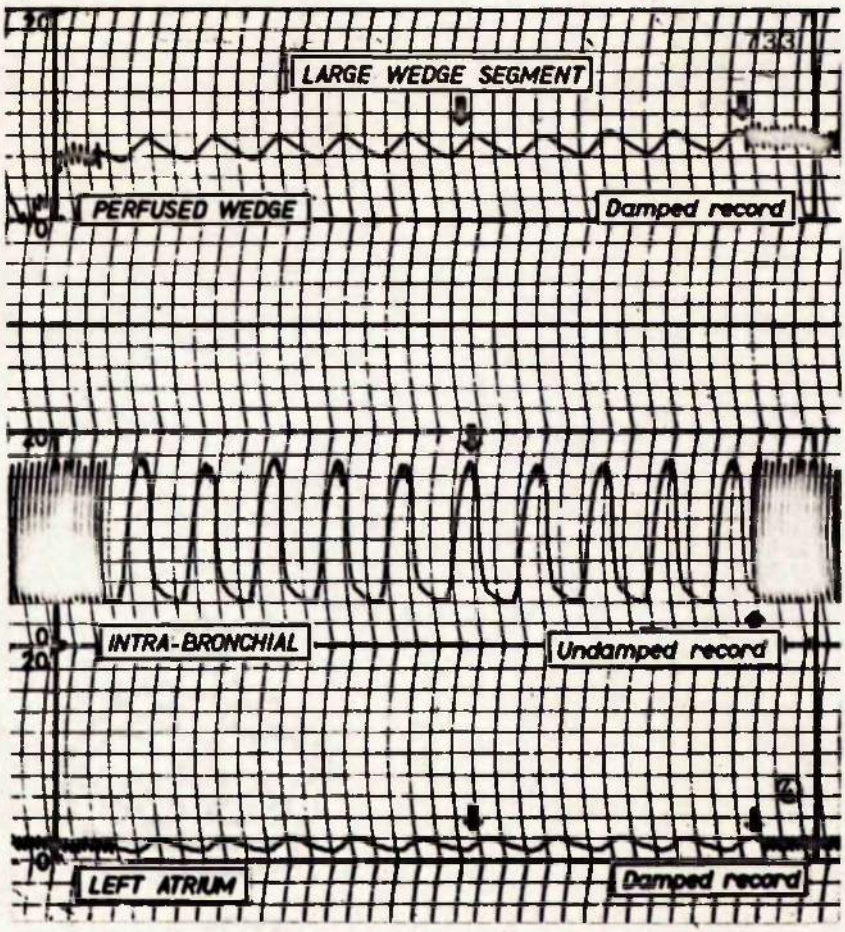


Fig. 4.

The record shows three pressure tracings taken with unequal degrees of damping. The arrows denote simultaneous points in time. The peak pressures in each tracing should be virtually simultaneous; the delay in the perfused wedge and left atrial tracings is exaggerated and due to the damping used.

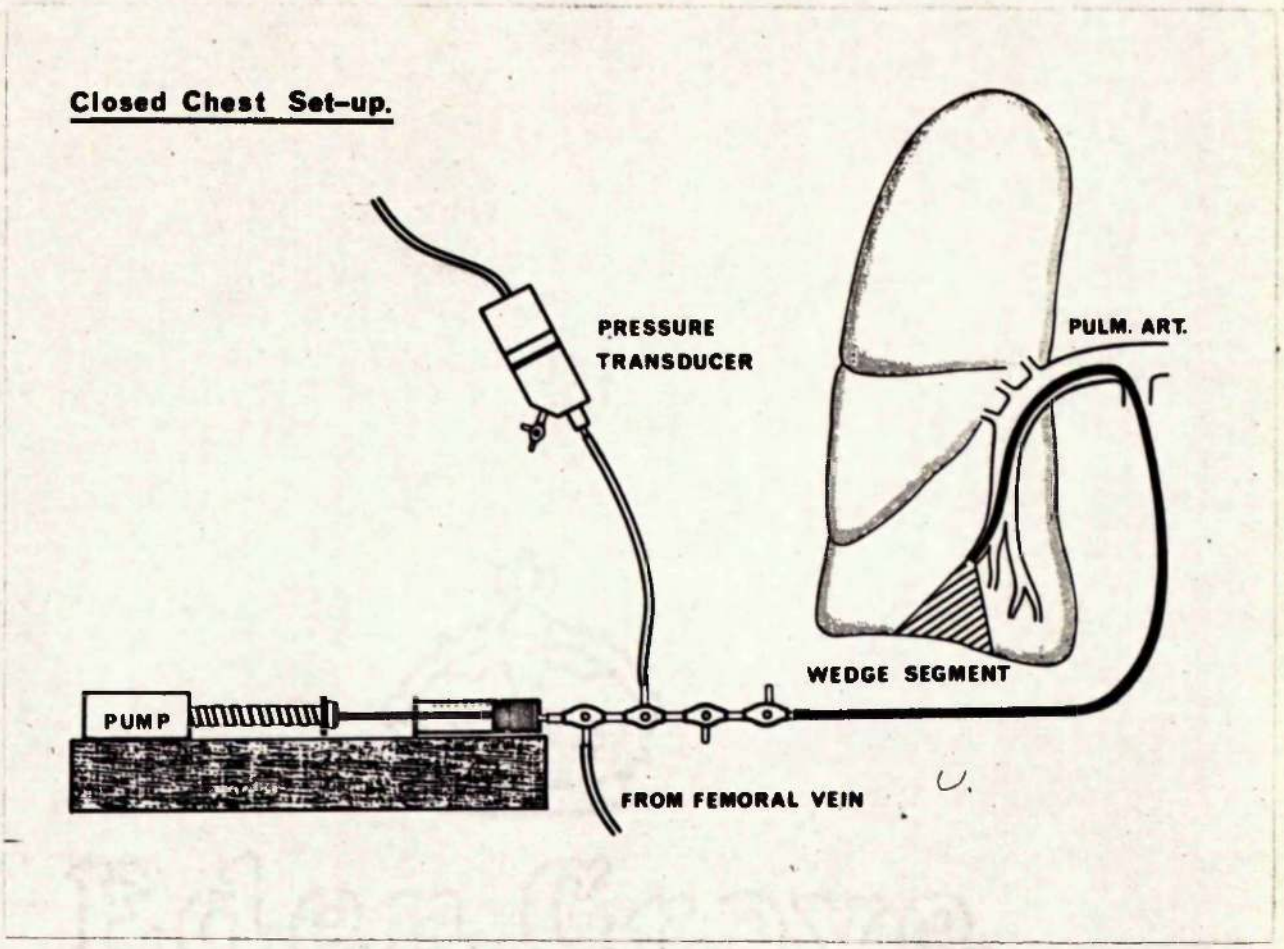


Fig. 5.

A diagram of the system used to perfuse the wedged catheter.

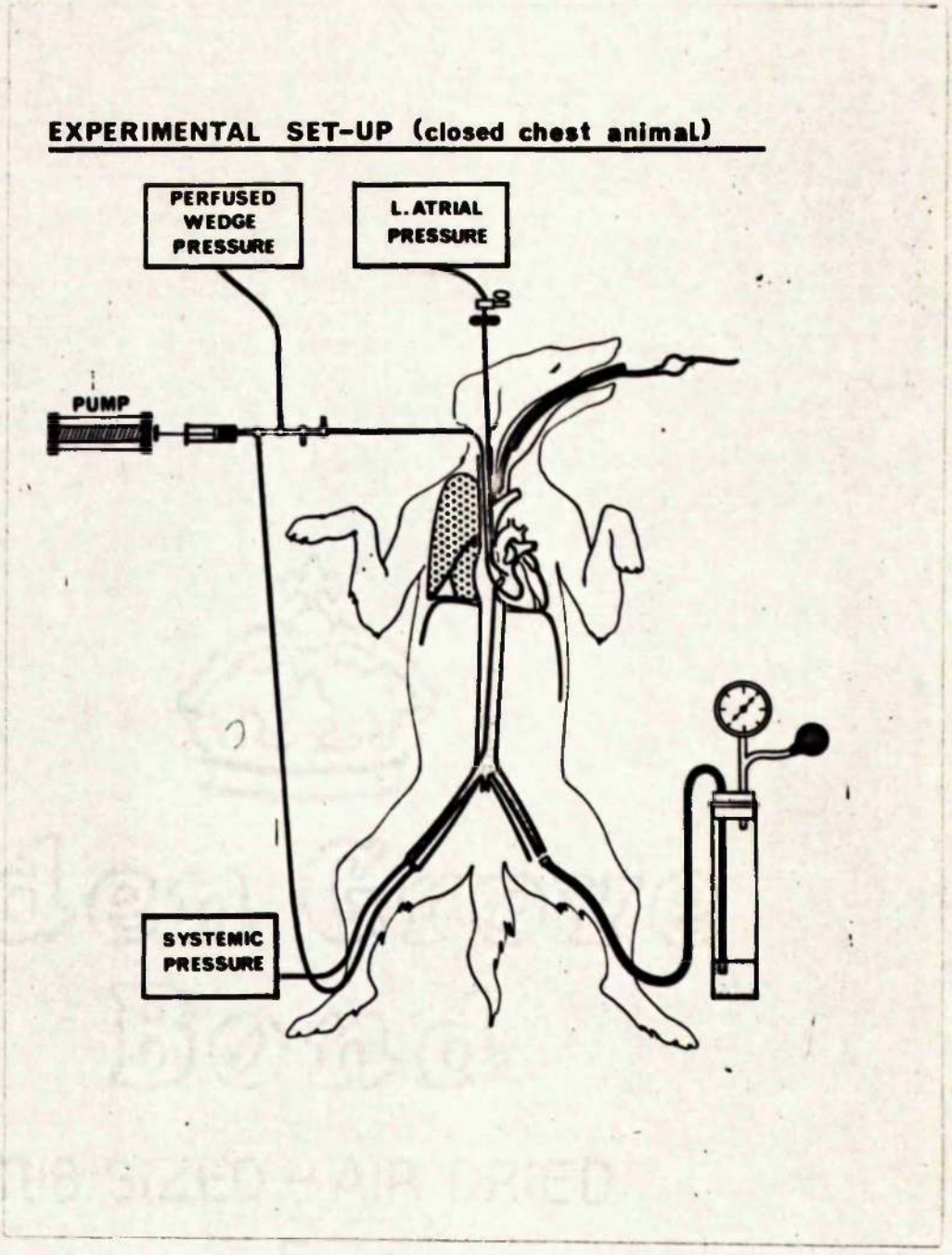


Fig. 6.

A diagram of the experimental preparation used in the closed-chest group of experiments.

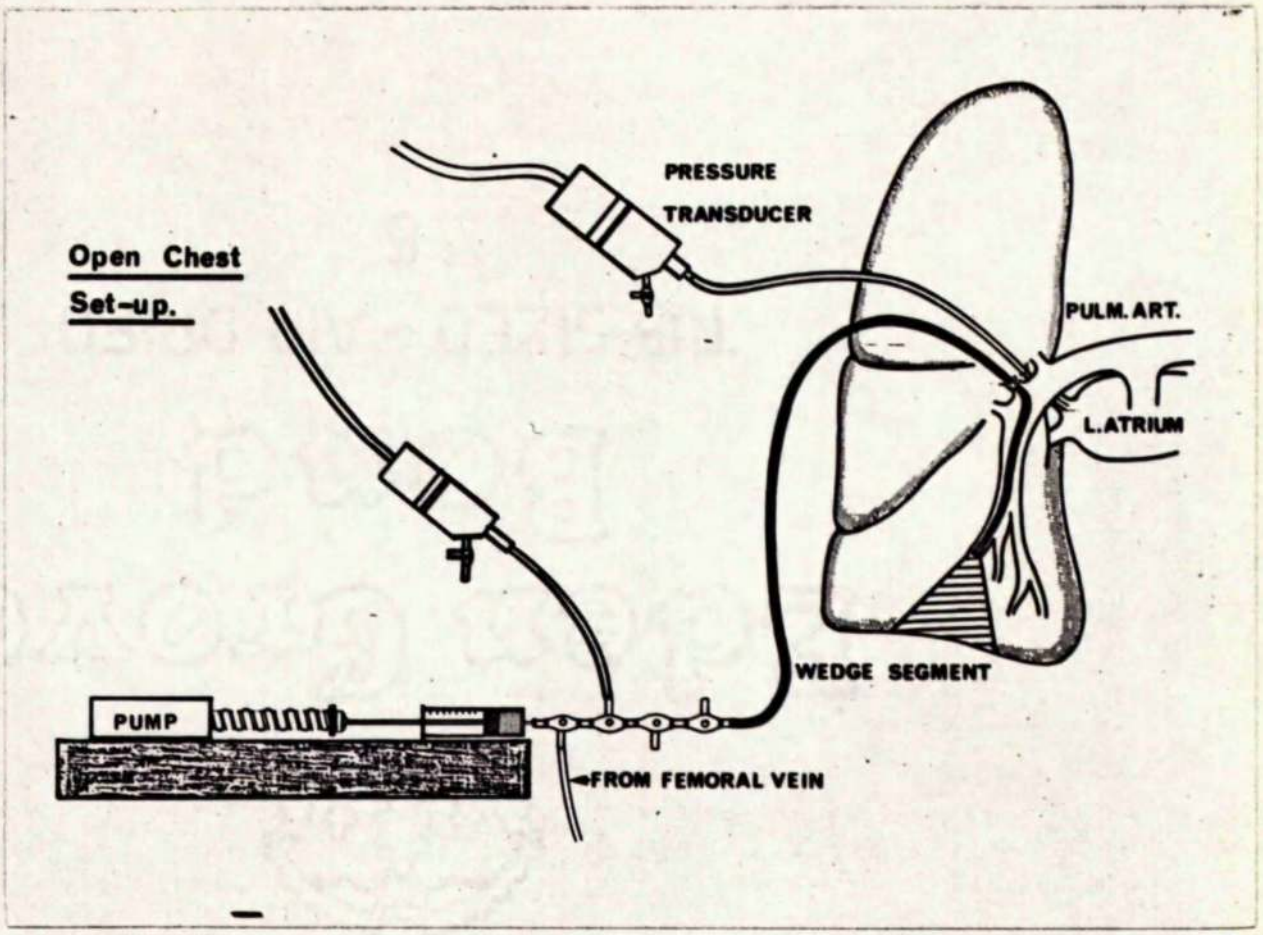


Fig. 7.

A diagram of the experimental preparation used in the open-chest group of animals.

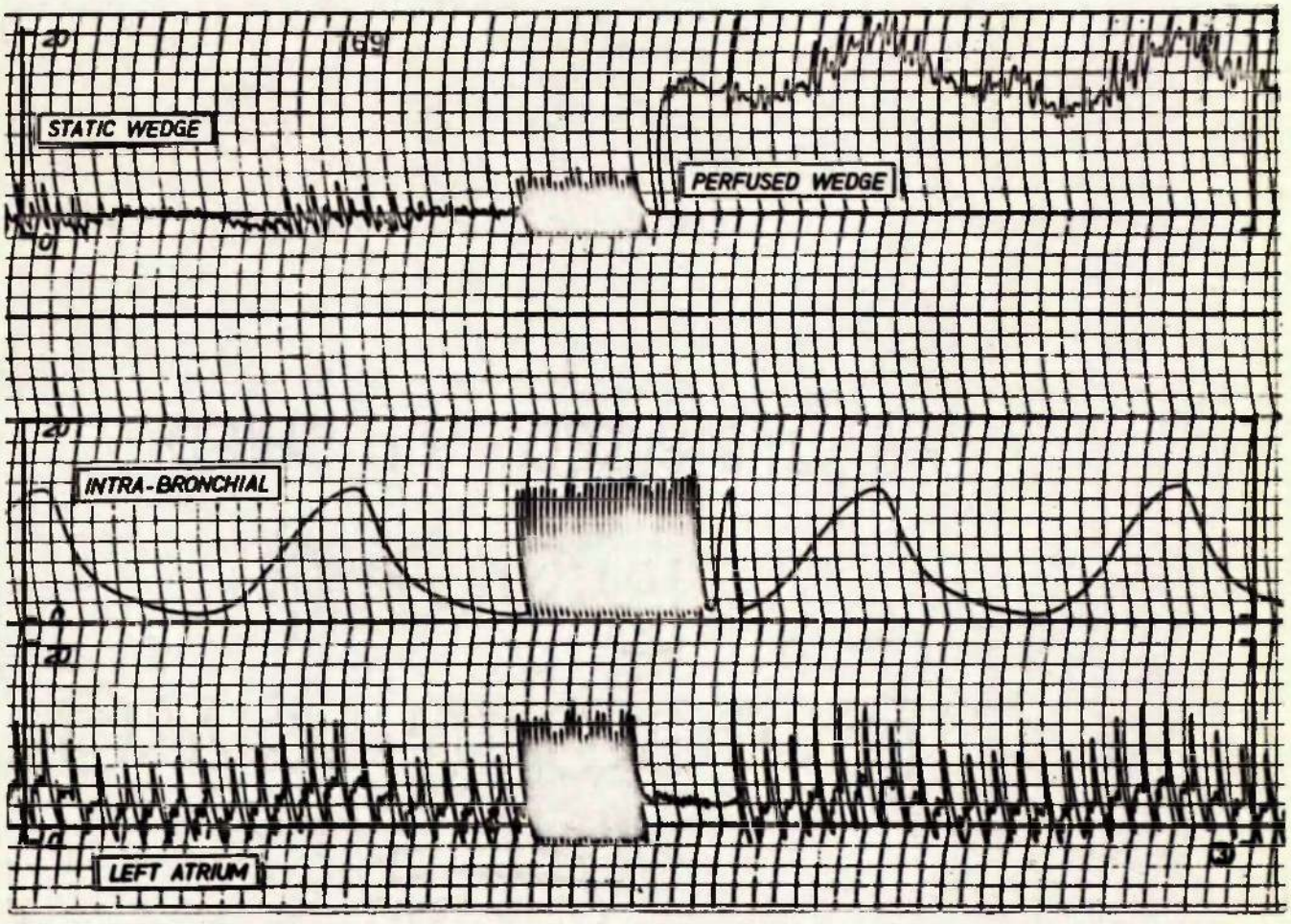


Fig. 8.

Records taken through a wedged catheter, before (static wedge) and during perfusion (perfused wedge). The tracings show that there is damping out of left atrial wave forms in the unperfused catheter during expiration, and that there is an extra positive pressure wave in the perfused wedge tracing during the same phase of ventilation. This signifies kinking of the vessel at the catheter tip. (Ventilation was by intermittent positive pressure).

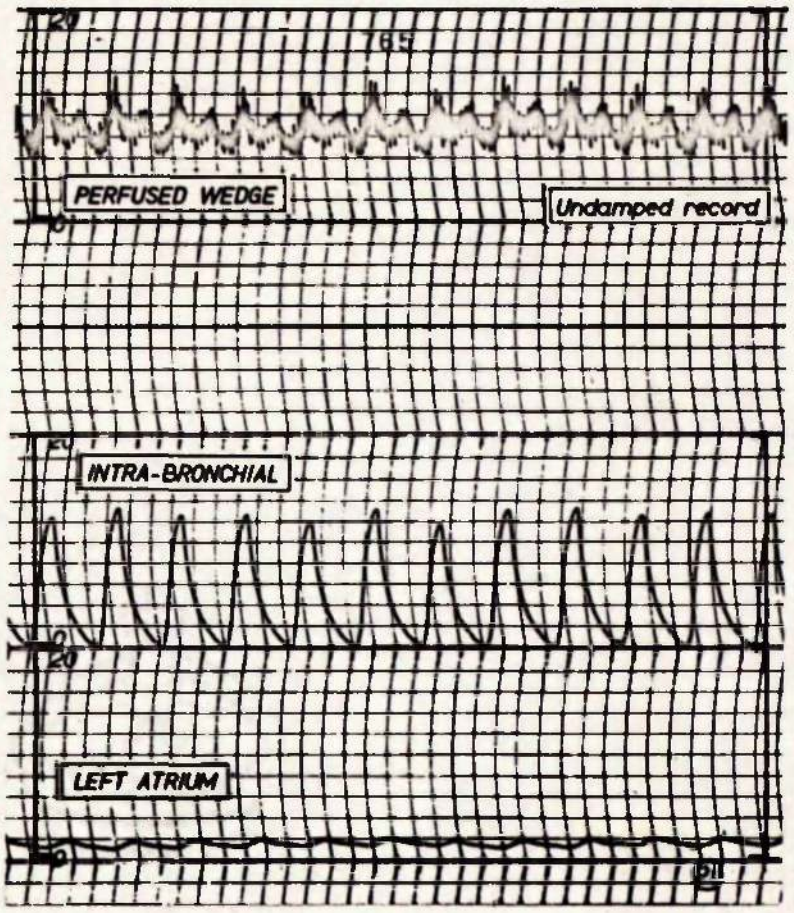


Fig. 9.

The perfused wedge pressure record shows an extra positive wave during each expiratory phase of ventilation. This is due to kinking of the perfused artery beyond the catheter tip. -

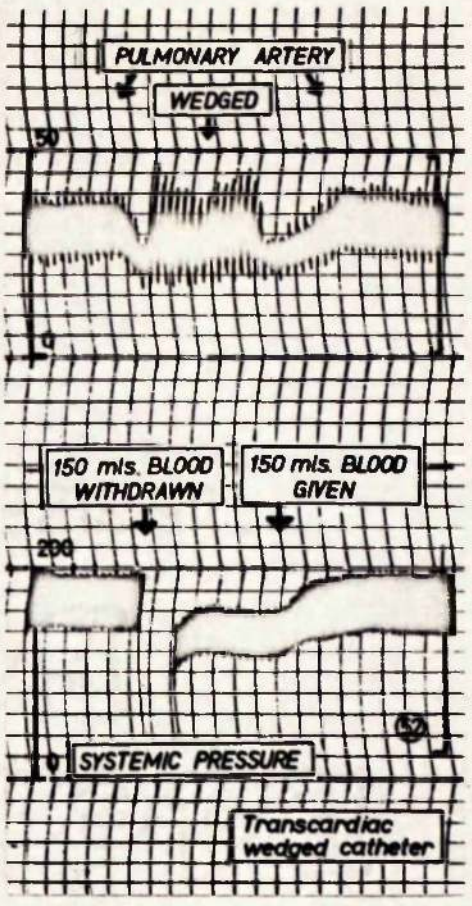
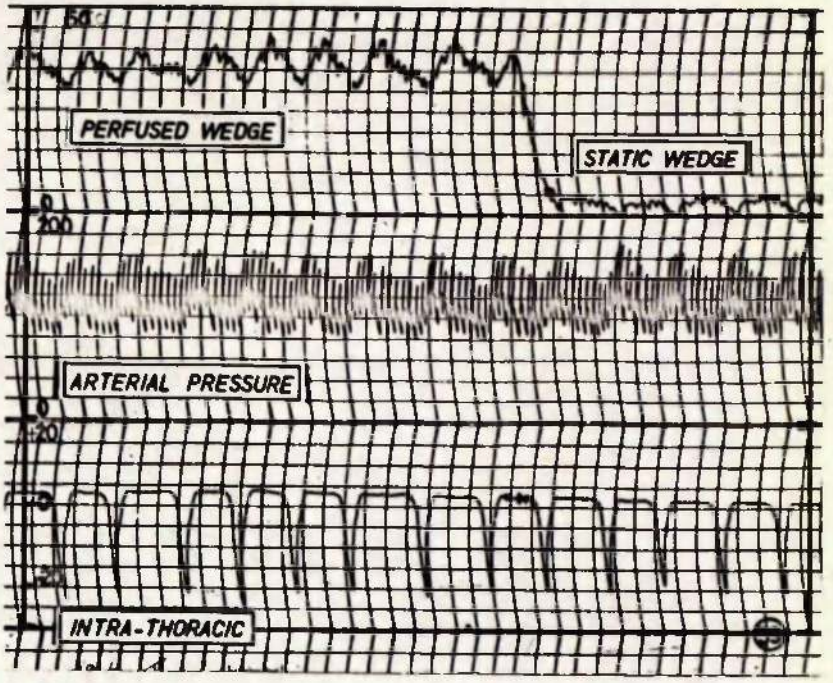


Fig. 10.

The upper record, of the pressure in a catheter in a small pulmonary artery, shows a change in the character of the tracing which was induced by the withdrawal of blood from a systemic artery. Re-infusion of the blood was accompanied by re-appearance of the original pressure tracing. The catheter tip was just proximal to a wedged position, the reduction of blood volume caused it to become wedged; restoration of volume allowed disimpaction. (The catheter was being perfused.)

(a)



(b)

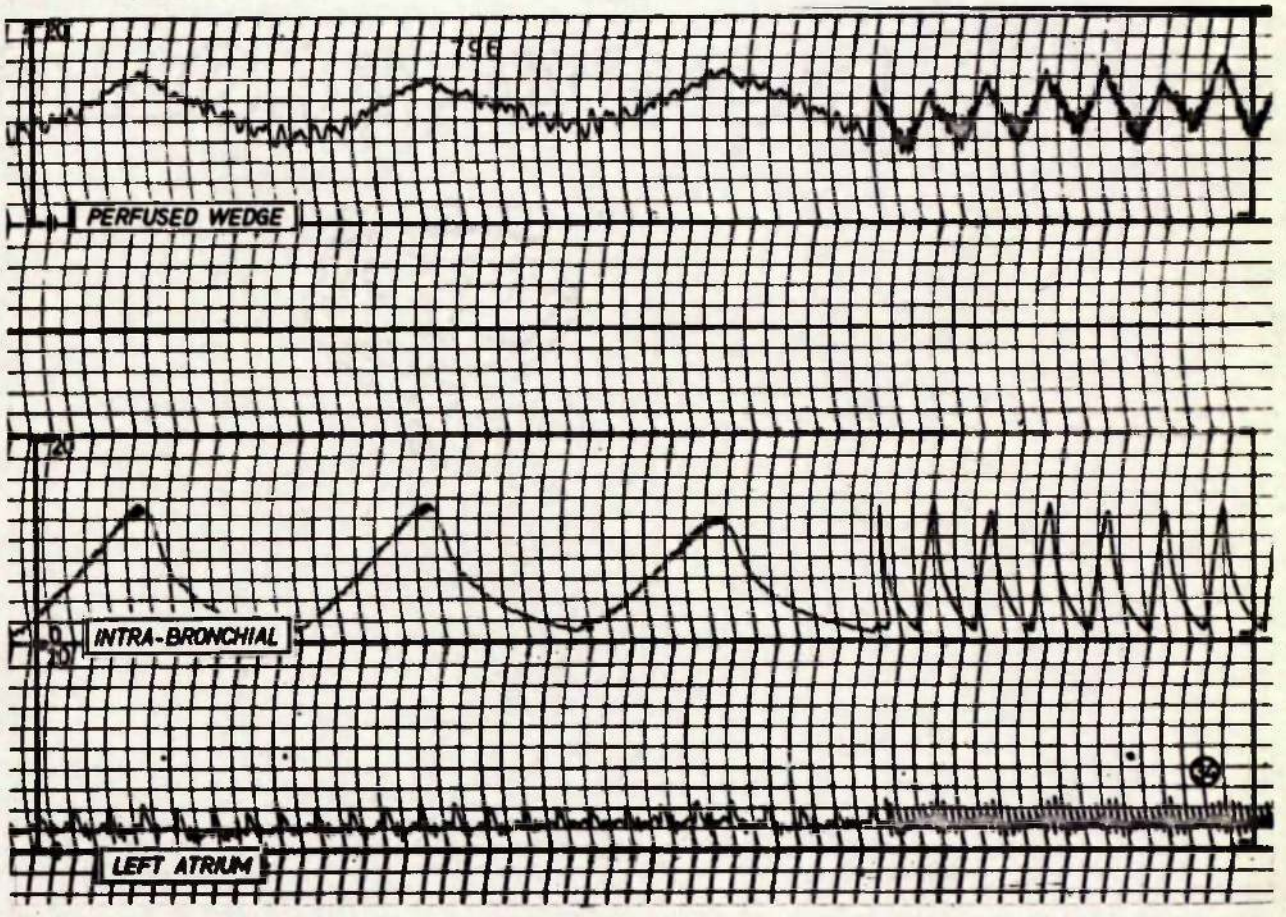


Fig. 11. Tracings to show that the dominant pressure waves in the wedge pressure tracings are respiratory in origin, both with spontaneous breathing (a) and intermittent positive pressure ventilation (b). (Undamped records)

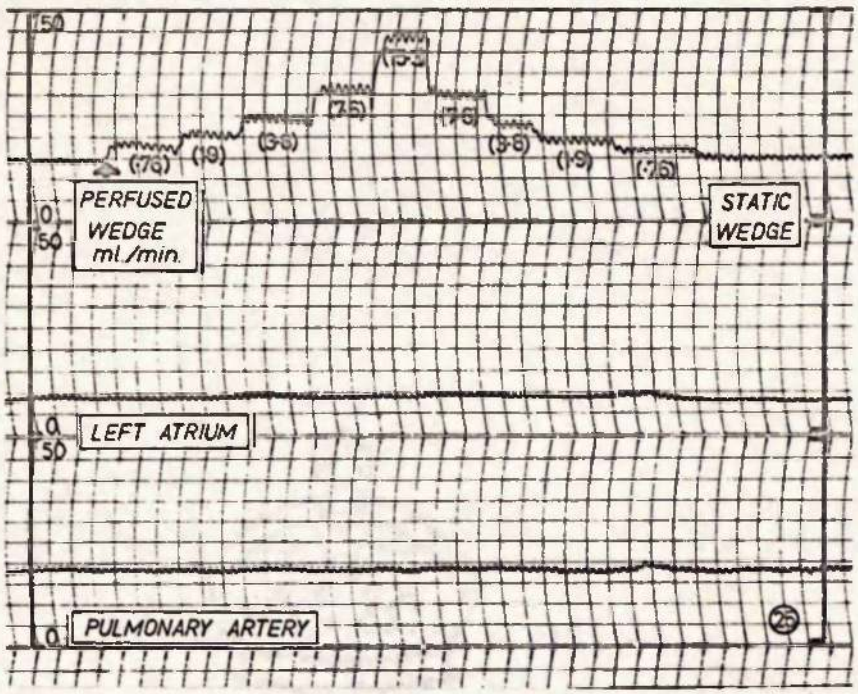


Fig. 12.

The upper tracing is of the pressure recorded in the perfused wedged catheter during alteration of the rate of perfusion. The figures in parentheses are the flow rates used (0.76 to 15.3 mls/minute).

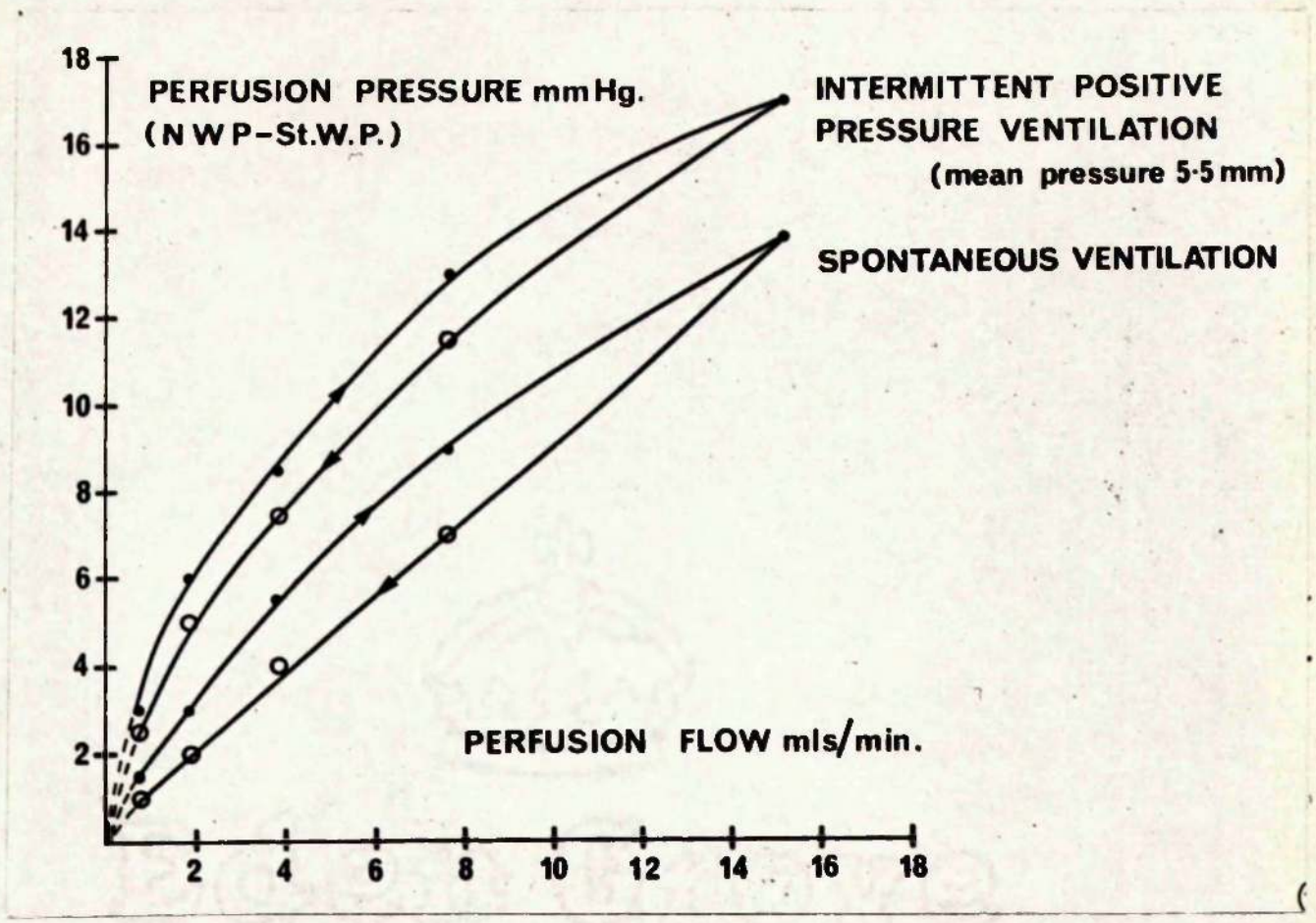


Fig. 13.

The pressure/flow relationship in the segment perfused by a wedged catheter, during spontaneous and controlled ventilation.

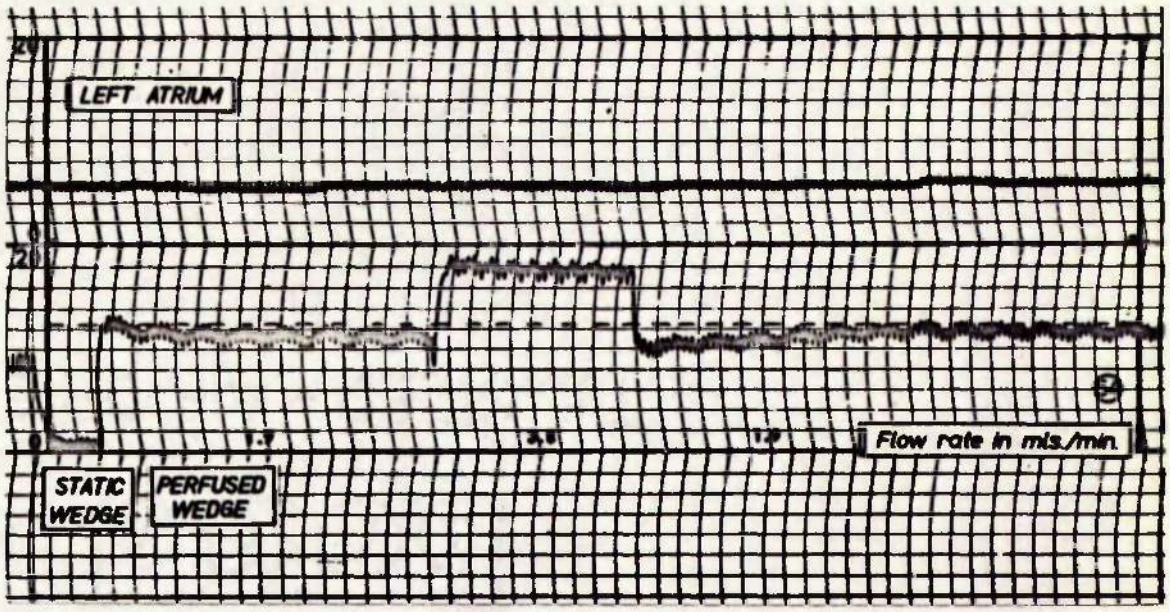


Fig. 14.

A record of the pressure in a perfused wedged catheter. The perfusion rate has been doubled for one and a half minutes. With each change of flow rate there was a lag period before the pressure stabilised.

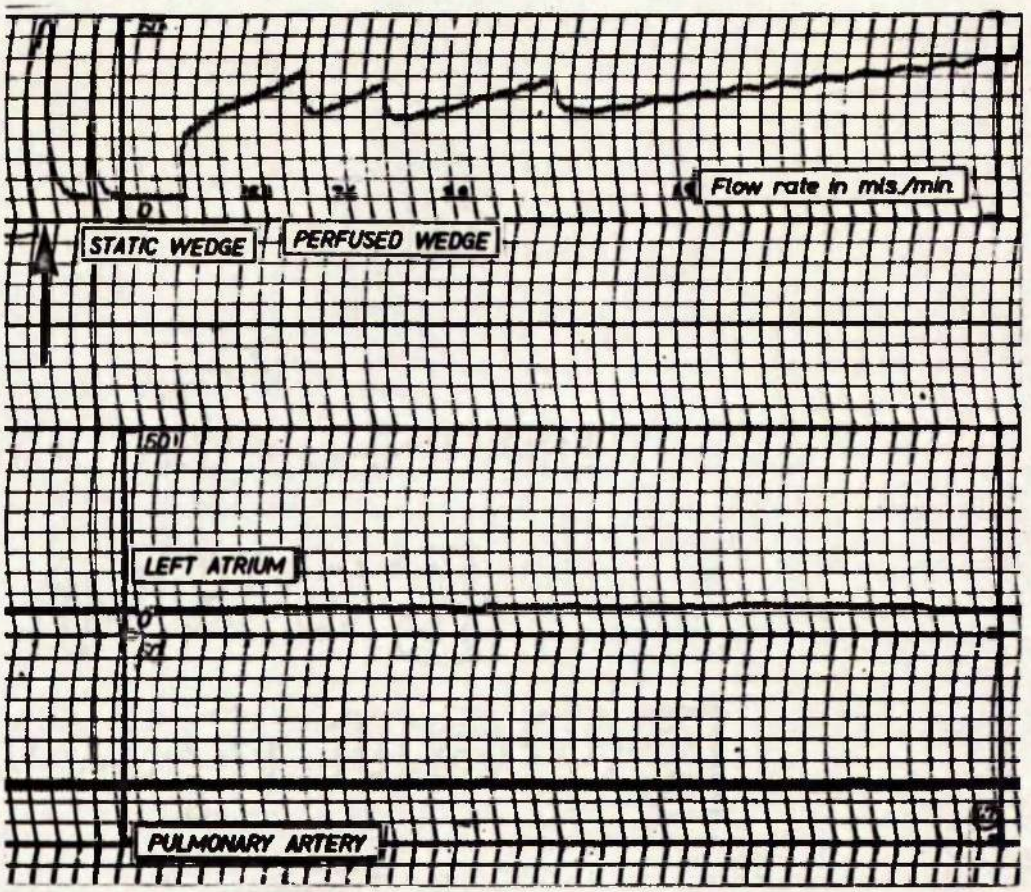


Fig. 15.

The upper tracing, of the perfused wedge pressure, shows a progressive increase in pressure despite reduction of the flow rate. The vessels of the wedge segment were damaged by a surge of pressure (marked by the arrow at the beginning of this section of record).

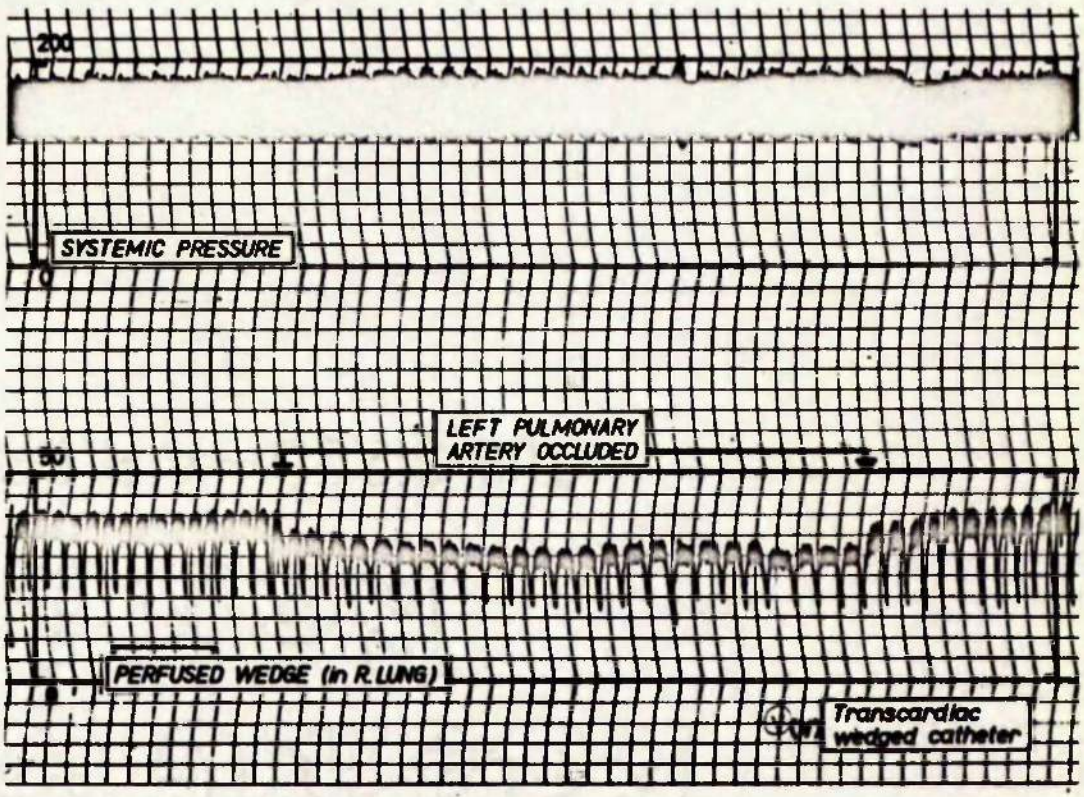


Fig. 16.

The effect of abrupt occlusion of one pulmonary artery on the perfused wedge pressure in the other lung. Breathing was spontaneous.

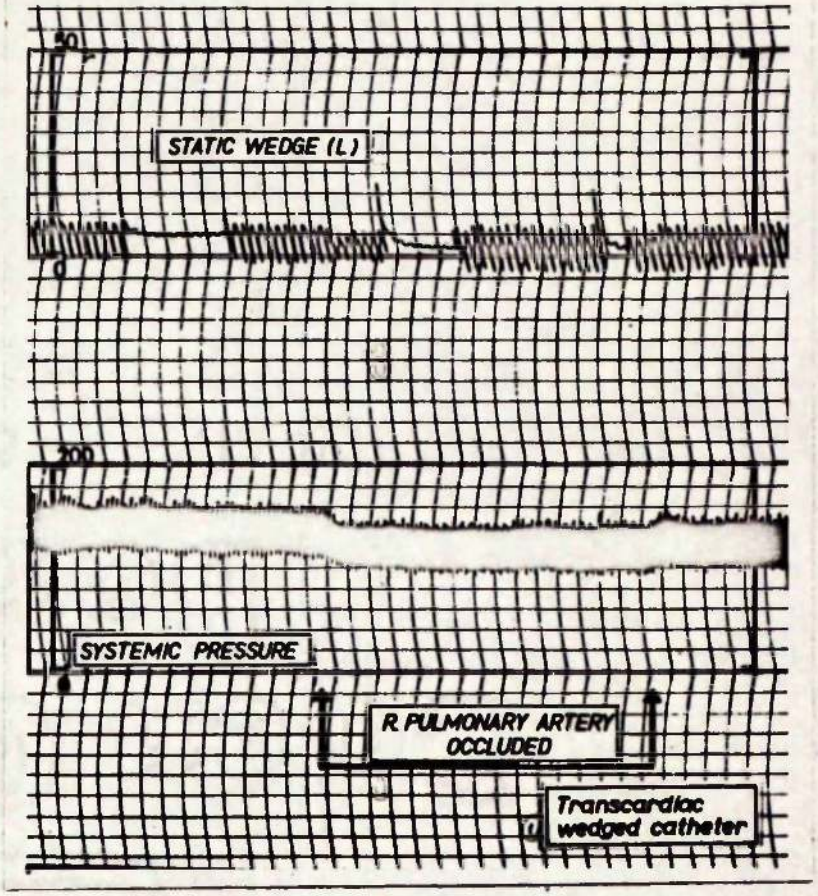


Fig. 17.

Shows a fall in the mean pulmonary artery wedge pressure following occlusion of one main pulmonary artery.

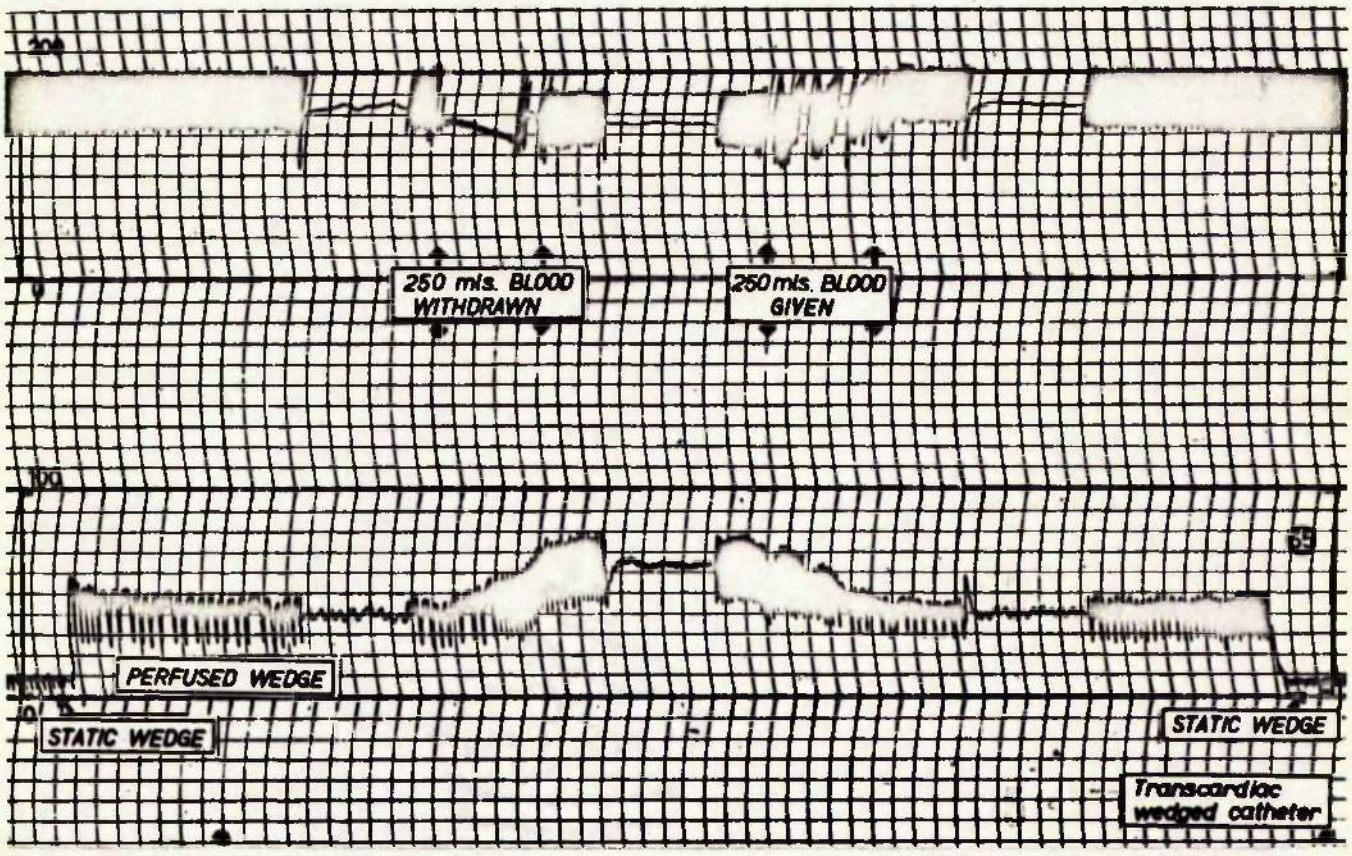


Fig. 18.

Shows elevation of the perfused wedge pressure (phasic and mean) associated with the rapid withdrawal of blood from the systemic circulation, with a return to control levels when the blood was re-infused. The upper record is of the systemic arterial pressure.

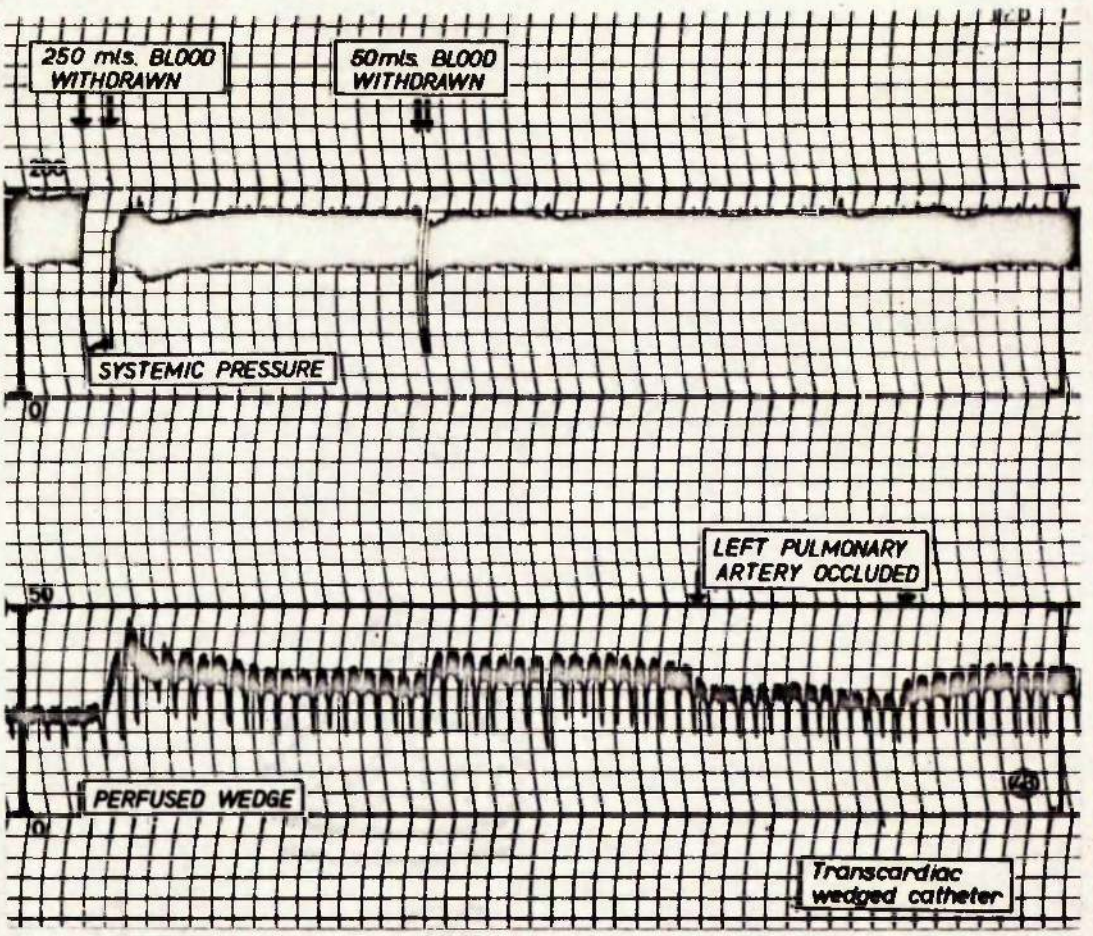


Fig. 19.

Shows elevation of the perfused wedge pressure in response to a systemic loss of blood, and a fall in perfused wedge pressure during occlusion of the contra-lateral pulmonary artery.

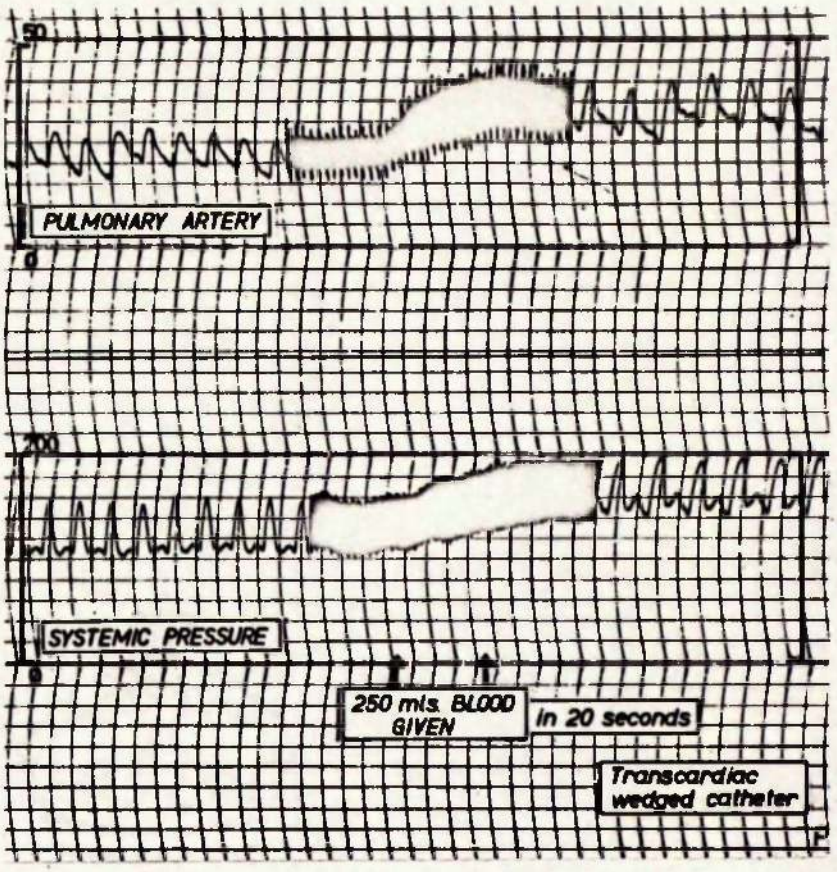


Fig. 20.

The effect of a rapid infusion of blood on the pulmonary and systemic arterial pressures. The infusion was intra-venous.

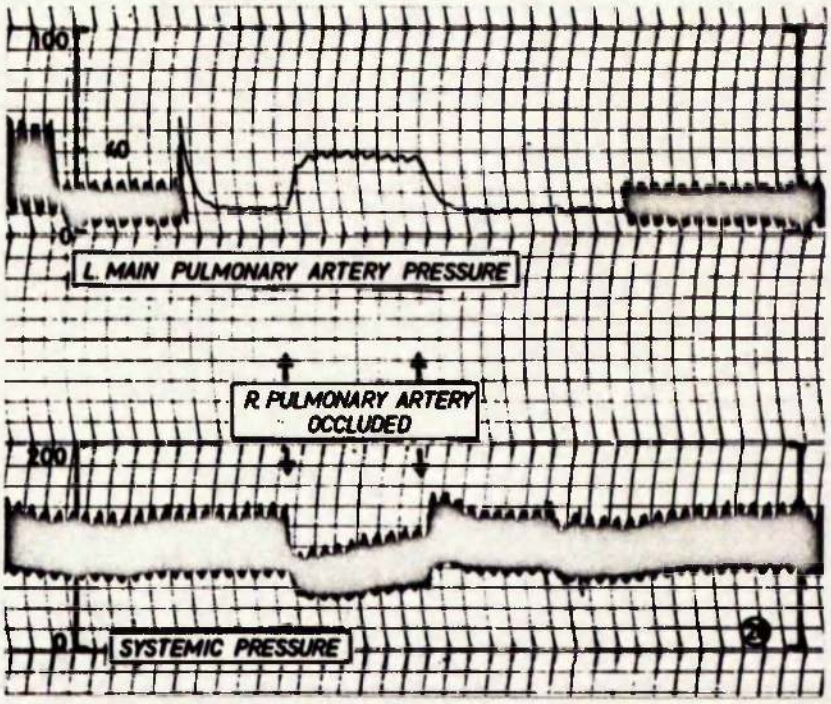


Fig. 21.

The effect of occlusion of one pulmonary artery on the pressure in the other.

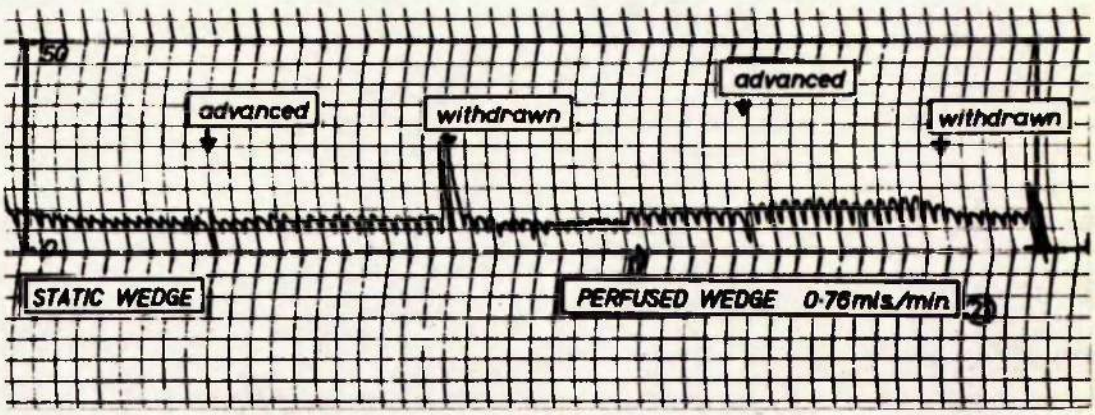


Fig. 22.

Shows the effect on the wedge pressures of a change in the size of the intra-cardiac catheter loop, (produced by advancing and withdrawing the proximal part of the catheter).

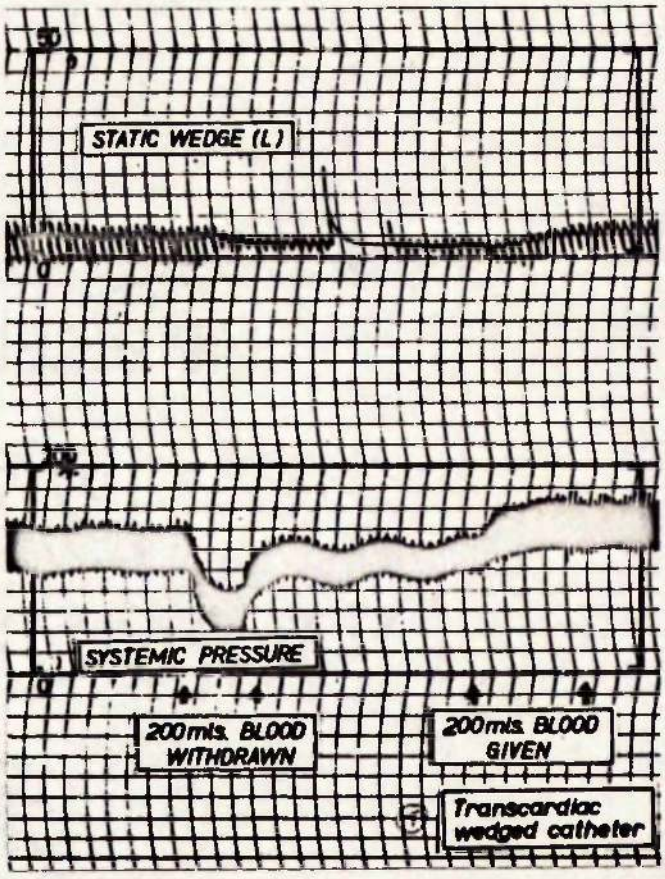
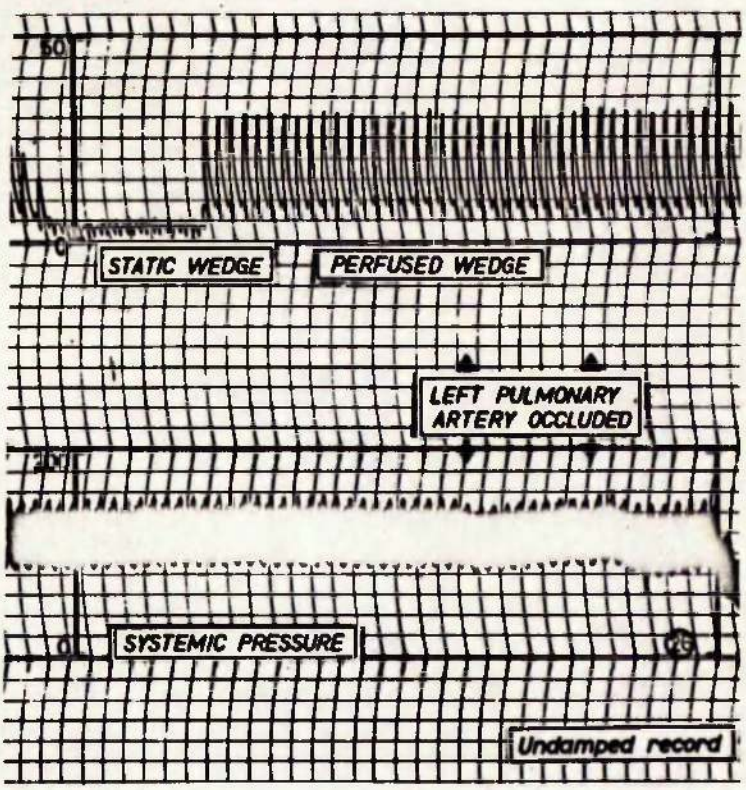


Fig. 23.

The upper tracing shows a reduction in both the amplitude and absolute level of the pulmonary artery wedge pressure record (static wedge) following the withdrawal of blood.

(a)



(b)

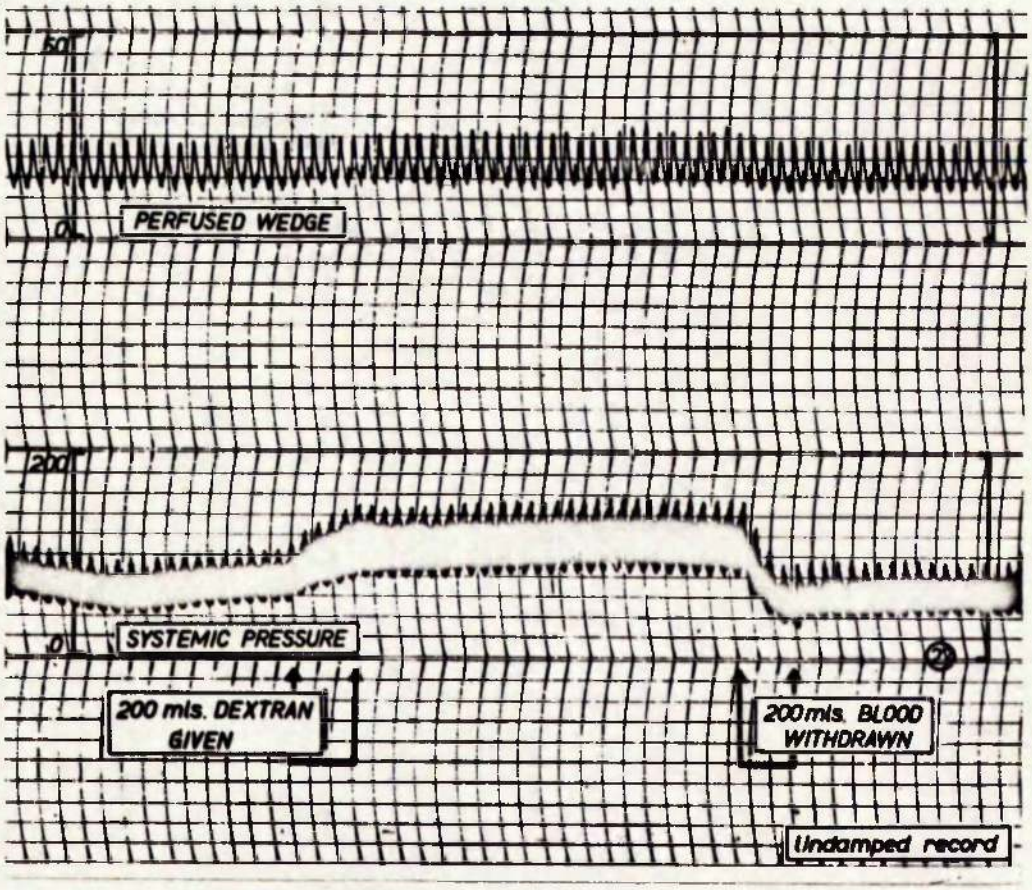


Fig. 24. Records of perfused wedged catheter pressure, (using open-chest preparations, with direct introduction of the catheter into the pulmonary artery), during unilateral pulmonary artery occlusion (a), and the infusion and withdrawal of blood (b).

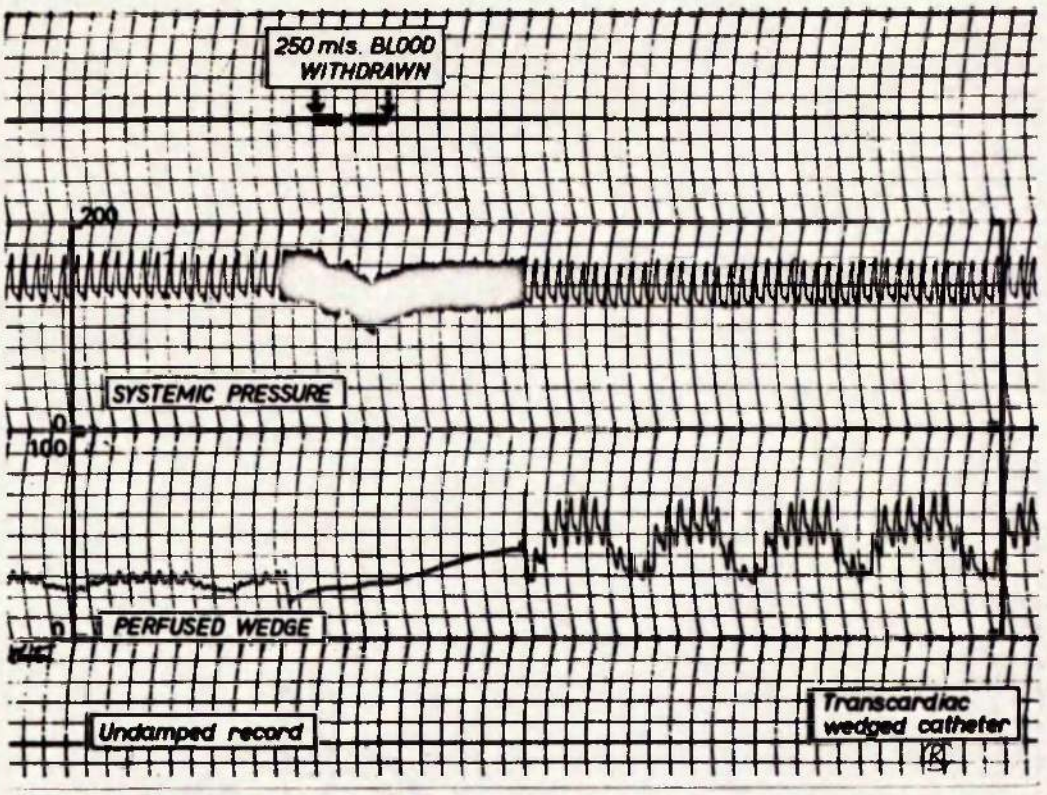
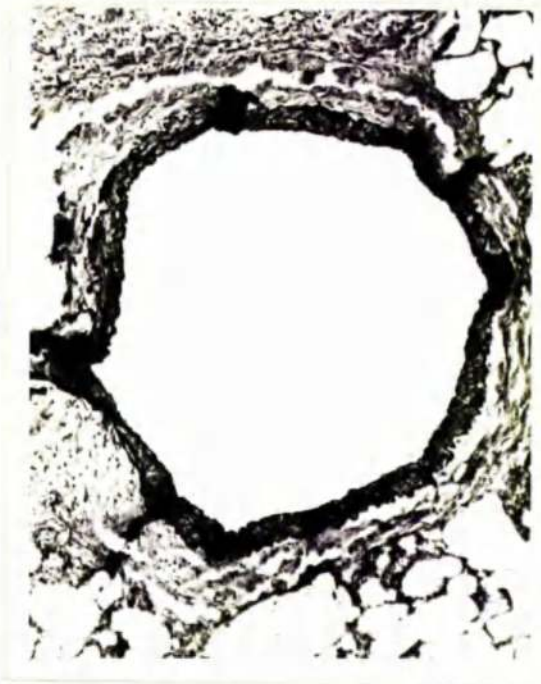
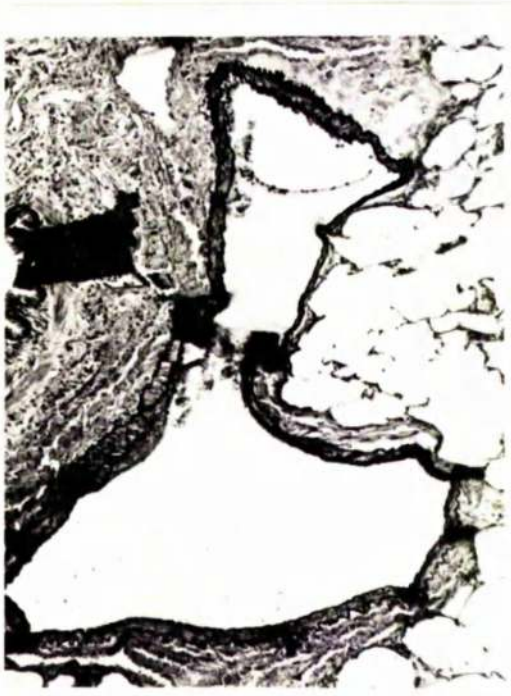


Fig. 25.

Tracings of the perfused wedge pressure, with a large intra-cardiac loop of catheter, suggesting that the high-frequency waves are derived from ventricular action.



A
(2 cms.)



B
(4 cms.)

C (7 cms.)

Fig. 26. Photomicrographs of sections of a wedge segment cut in a plane at right angles to the wedged catheter, at sites 2 cms., 4 cms., and 7 cms. from the catheter tip. They show an elastic artery (A), a muscular artery (B) and transition to arteriole (C).

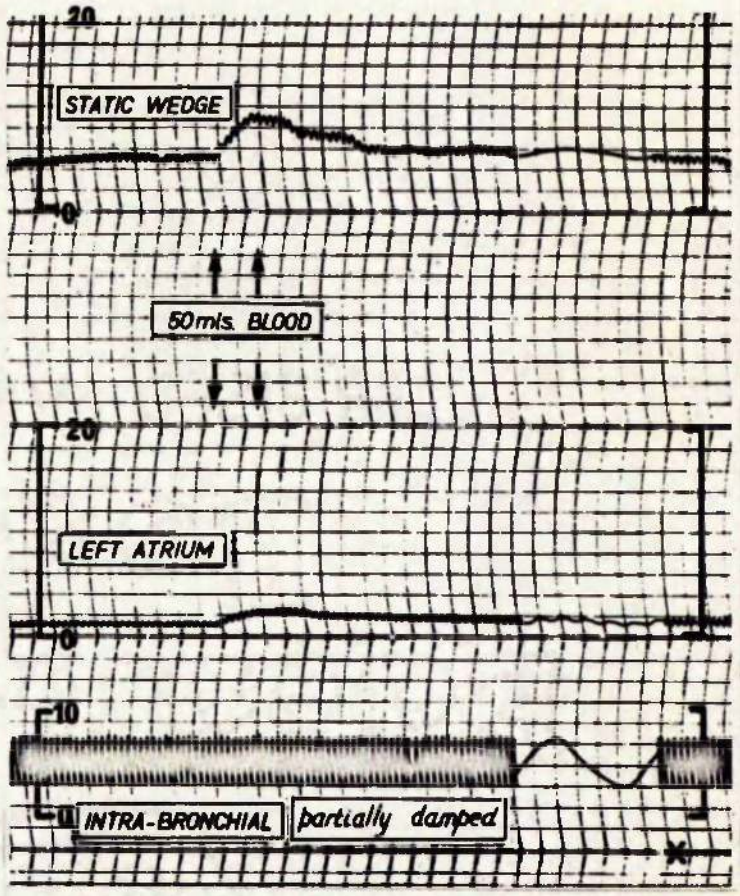


Fig. 27.

Shows the effect of a rapid intra-venous infusion on the pulmonary artery wedge pressure and the left atrial pressure.

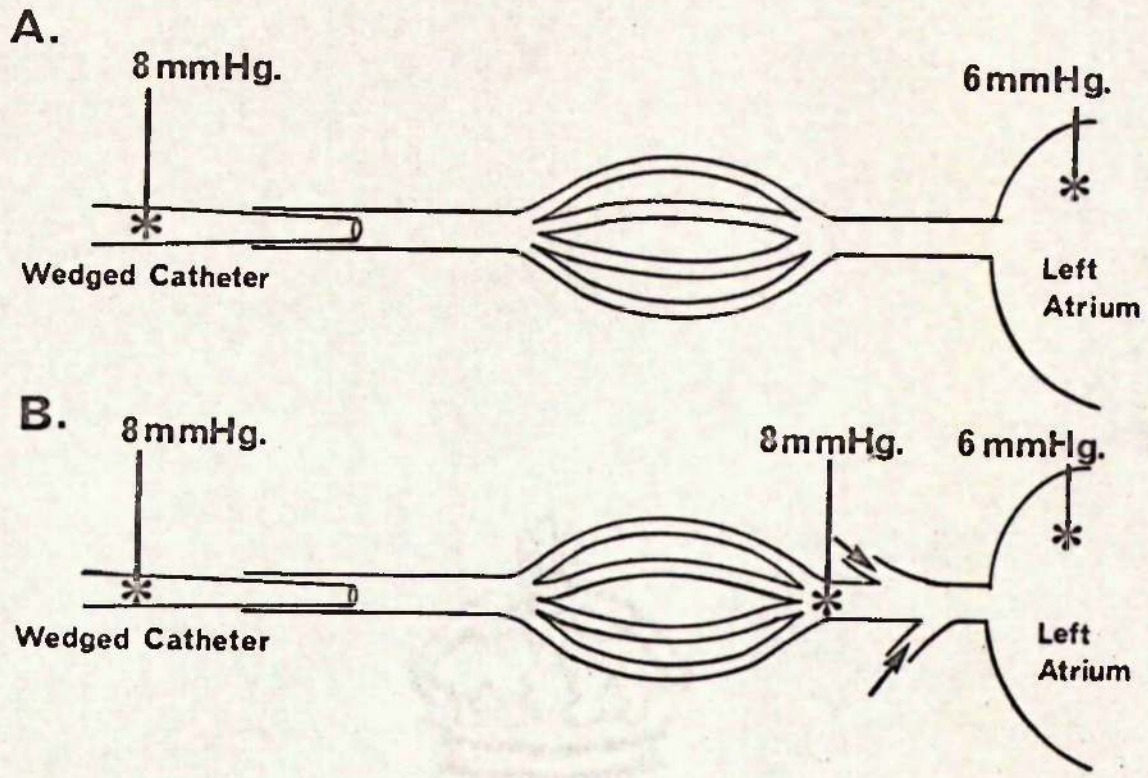


Fig. 28.

Diagrammatic representations of the pulmonary vascular bed between the tip of the wedged catheter and the left atrium to demonstrate the possible influence of confluent veins from adjacent segments on the pulmonary artery wedge pressure.

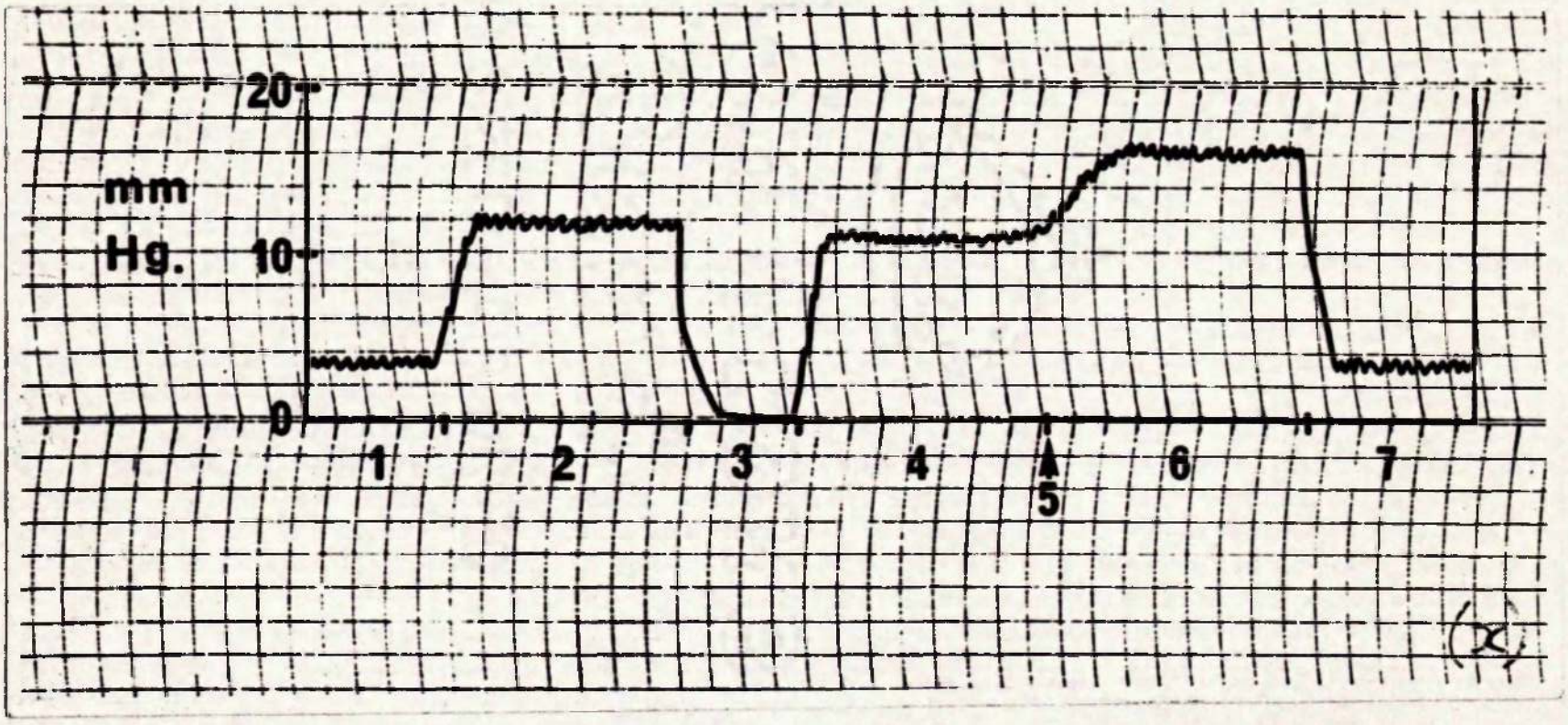


Fig. 29.

A stylised drawing of perfused wedge pressure record in the group of experiments concerned with the local effects of drugs.

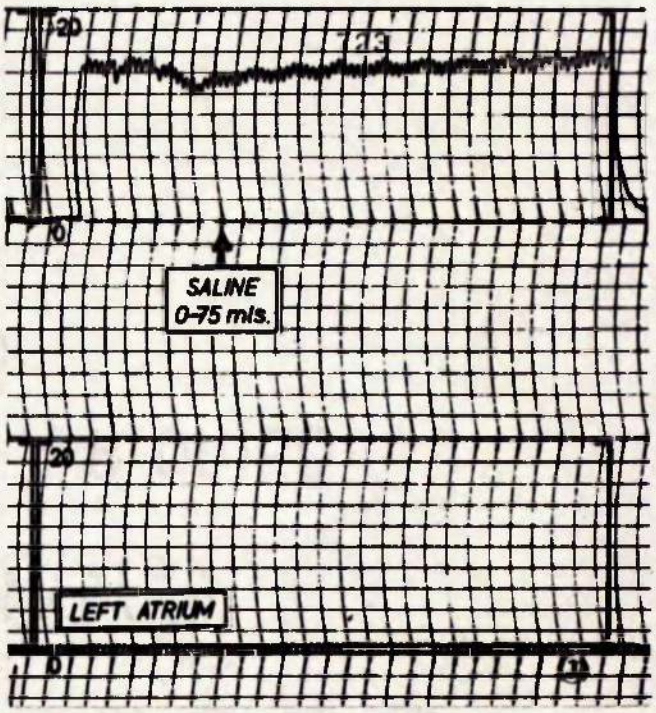


Fig. 30.

Shows the effect of the introduction of a bolus of saline into the perfused wedged catheter.

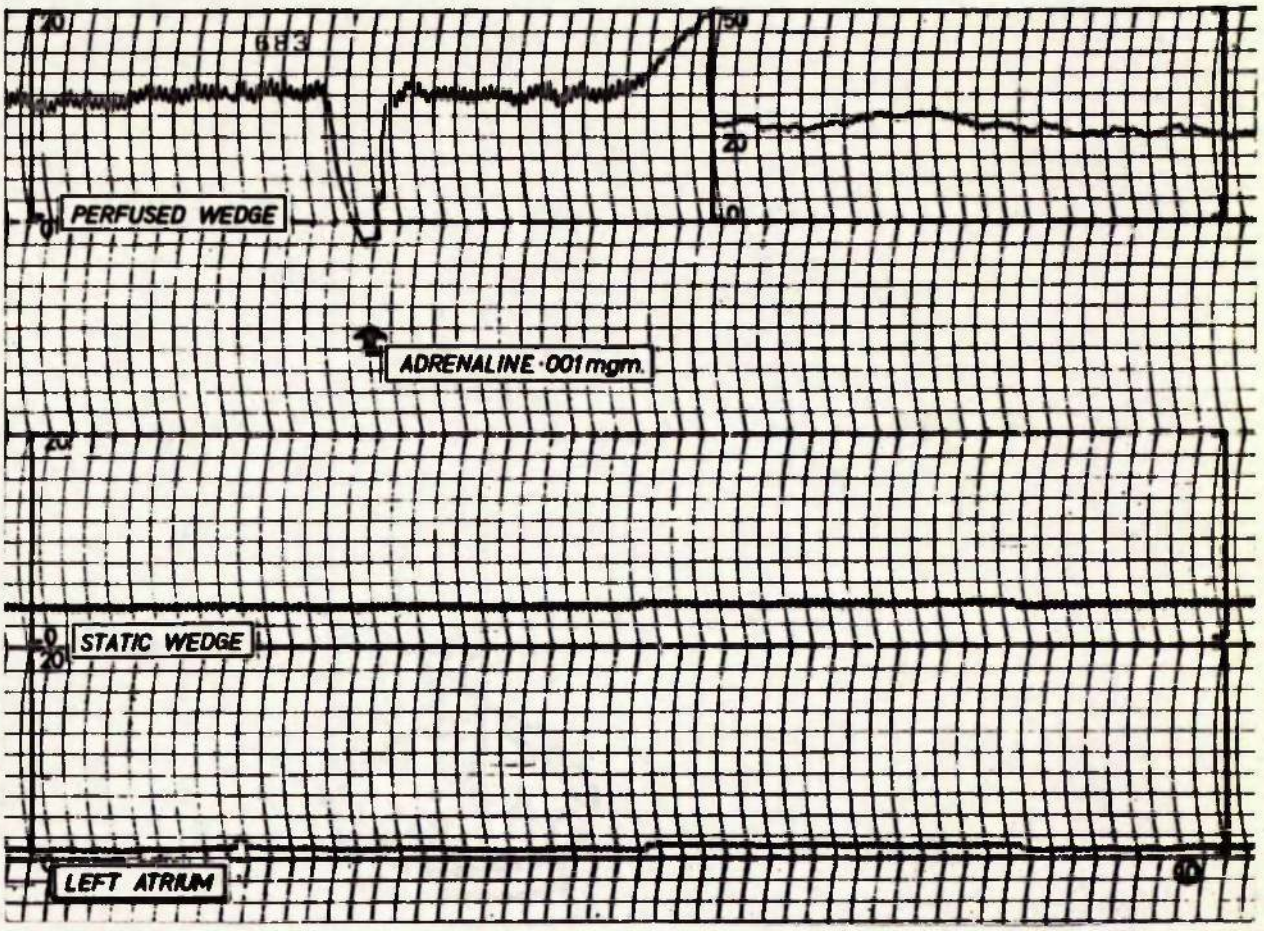


Fig. 31.

The record demonstrates the constrictor effect of adrenaline in the perfused wedge segment.

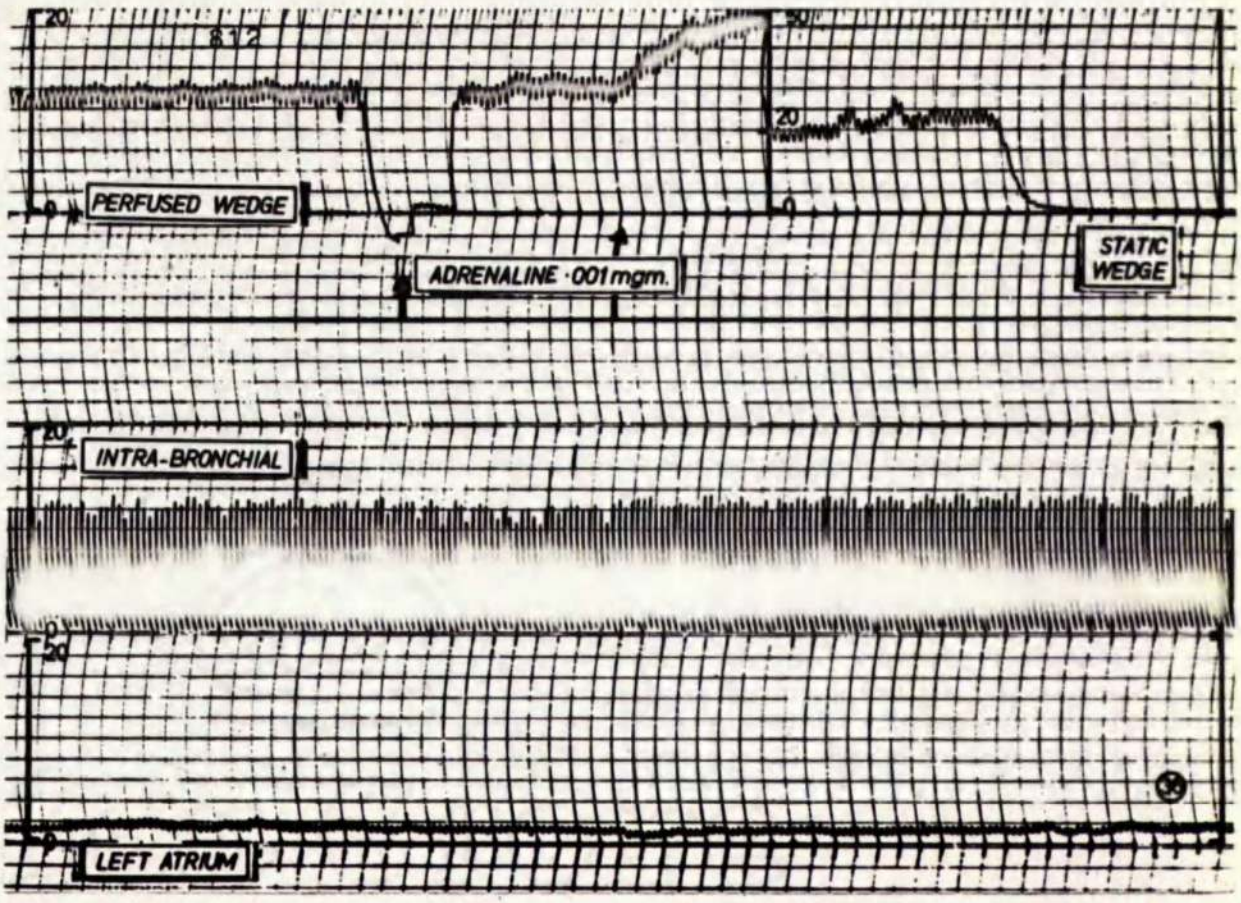


Fig. 32.

The record demonstrates the constrictor effect of adrenaline in the perfused wedge segment. The intra-bronchial pressure was unaffected.

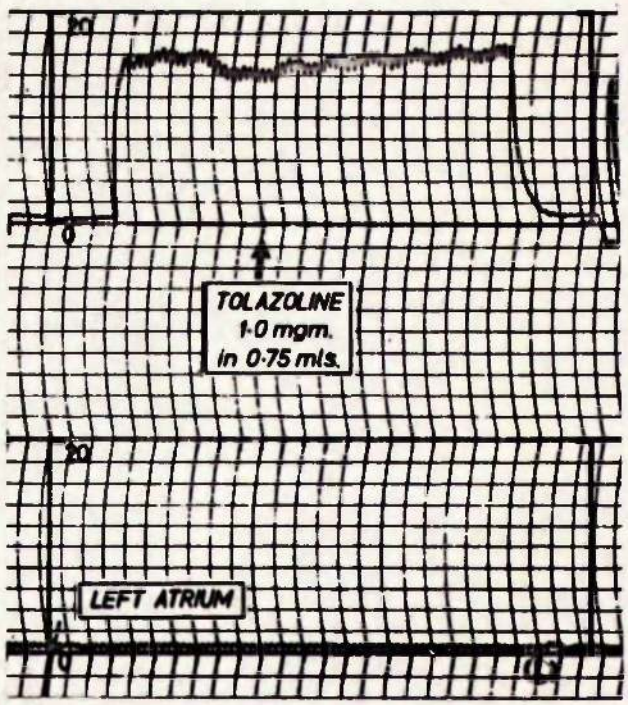


Fig. 33.

Showing the effect of a single dose of tolazoline on the perfused wedge segment. (Compare with Fig. 30, showing the effect of the same volume of saline.)

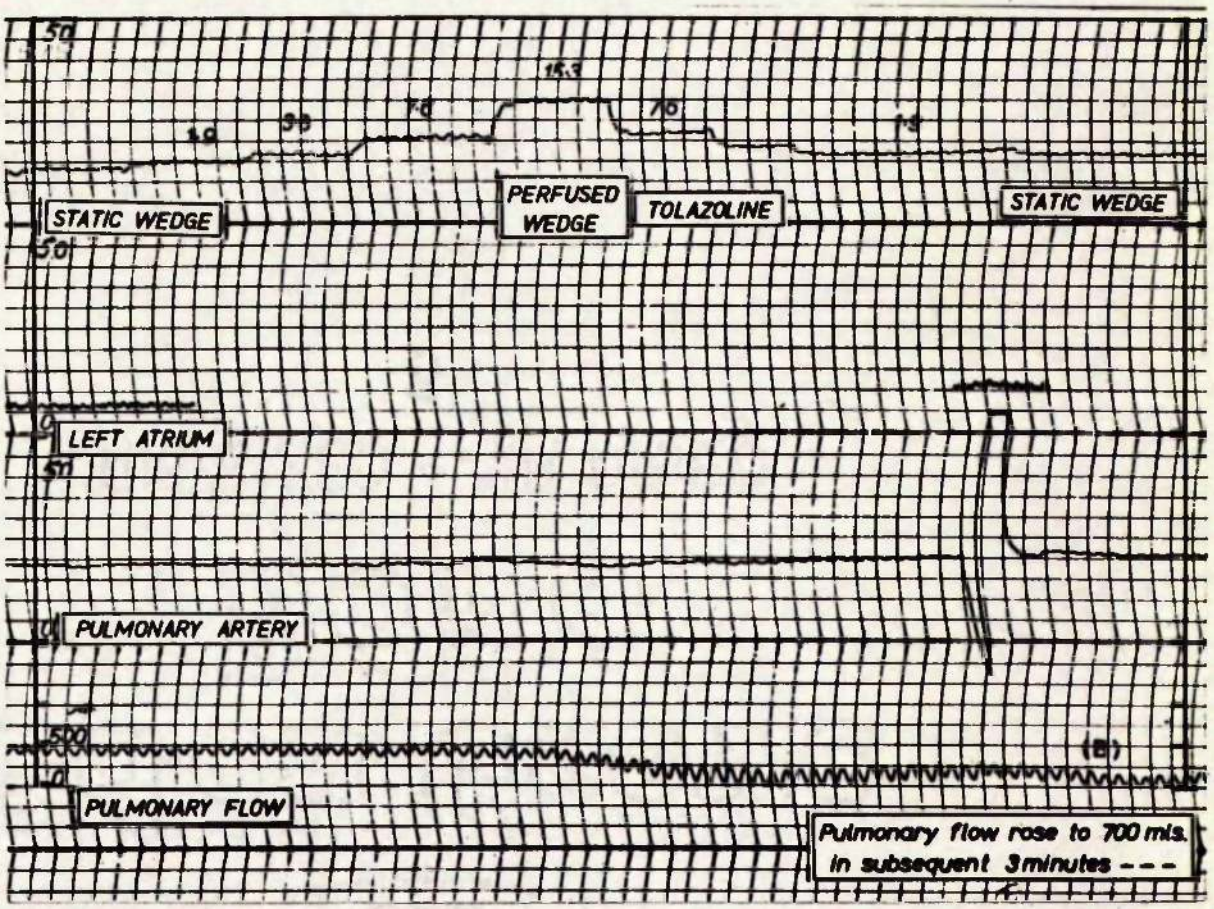


Fig. 34.

Records to show the effect of a relatively large infusion of tolazoline. There is an elevation of static wedge pressure and of left atrial pressure with a marked temporary fall in pulmonary blood flow.

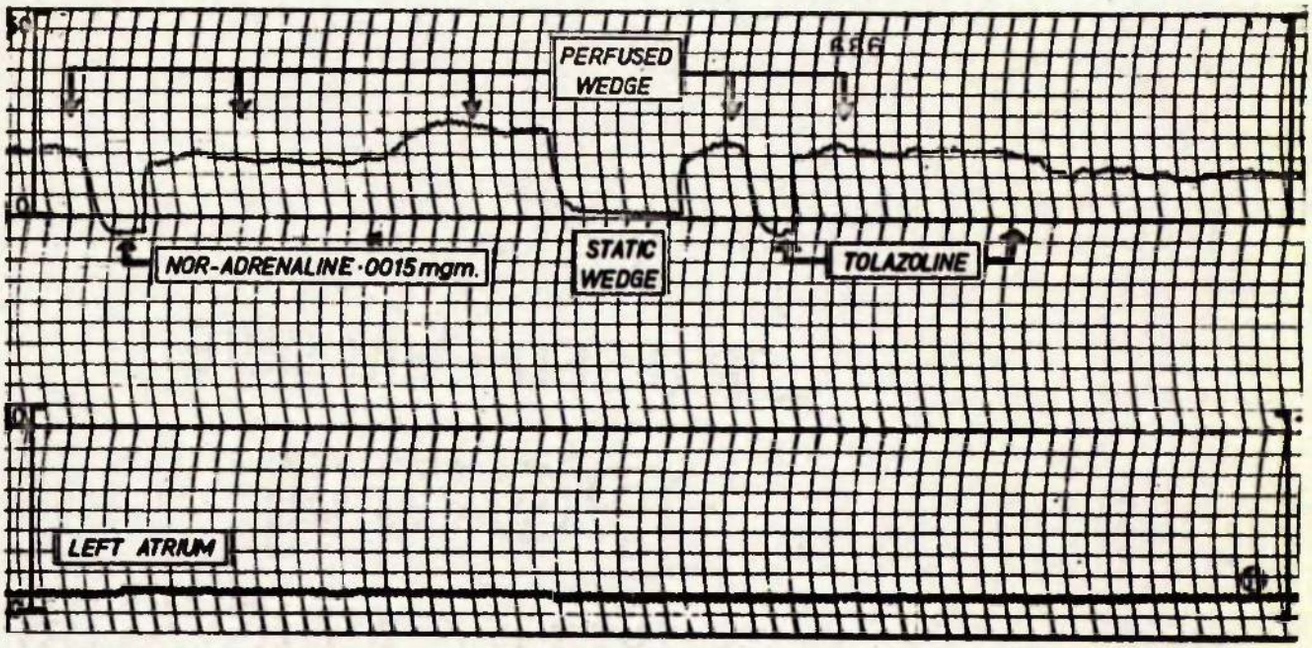


Fig. 35.

Records to show the effect of a single dose of tolazoline on the perfused wedge pressure, after a pressor response had been produced with nor-adrenaline. (The perfused wedge scale is 0 - 50 mm.Hg., the left atrial is 0 - 20 mm.Hg.)

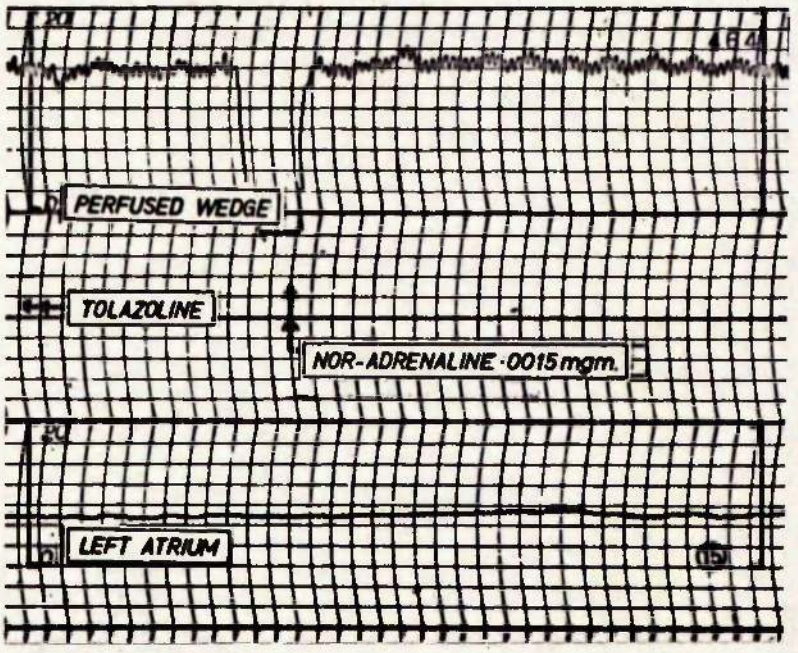


Fig. 36.

Abolition of the pressor response to nor-adrenaline, in a wedge segment which was previously treated with tolazoline.

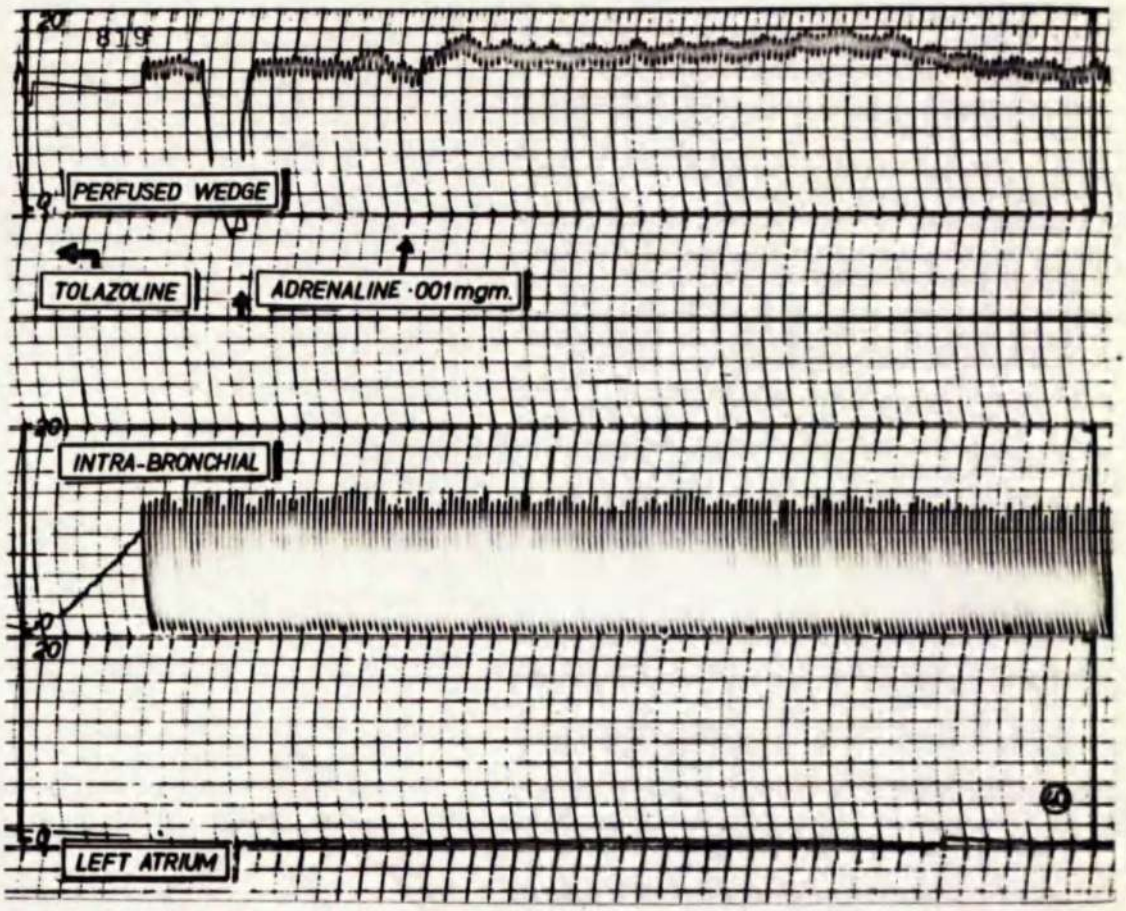


Fig. 37.

Marked diminution of the pressor response to adrenaline in a wedge segment which was previously treated with tolazoline.

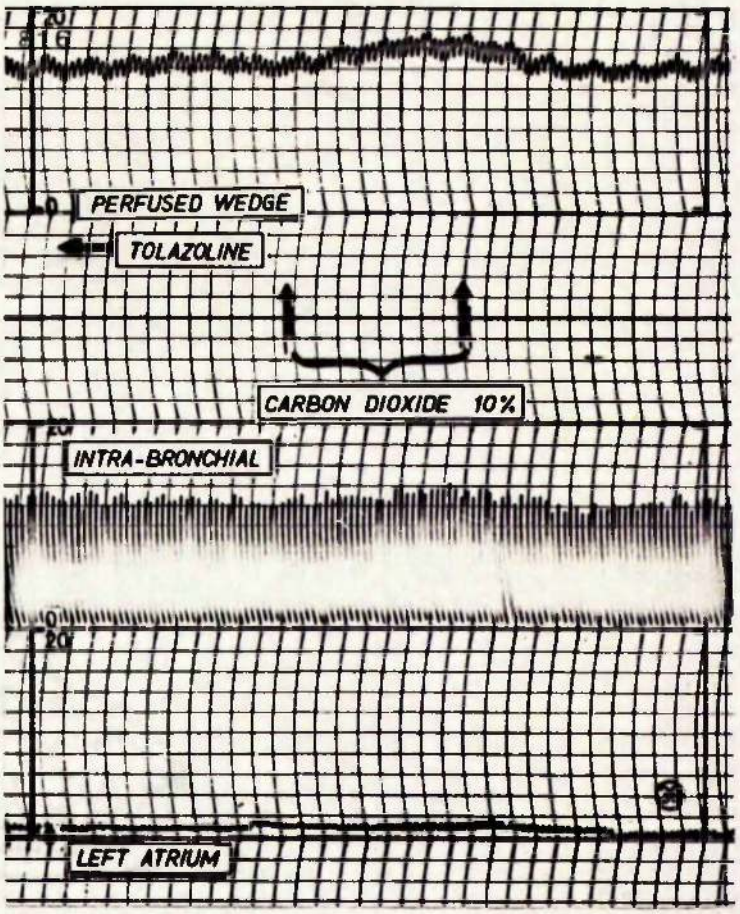


Fig. 38.

The effect on the perfused wedge segment of elevation of the alveolar P_{CO_2}, in a segment previously treated with tolazoline.

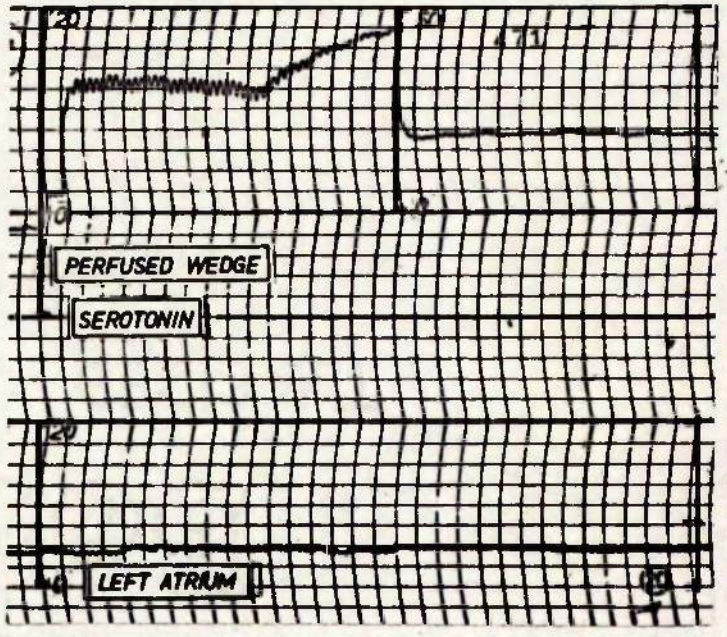


Fig. 39.

The local effect of serotonin (0.25 µgm.) on the perfused wedge segment.

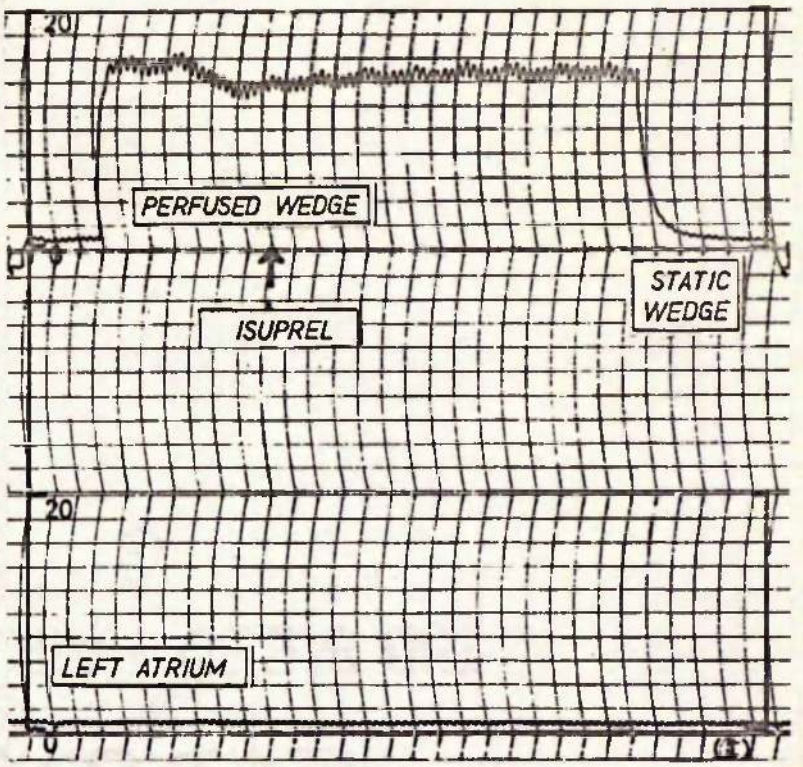


Fig. 40.

The effect of Isuprel on the vessels of the perfused wedge segment.

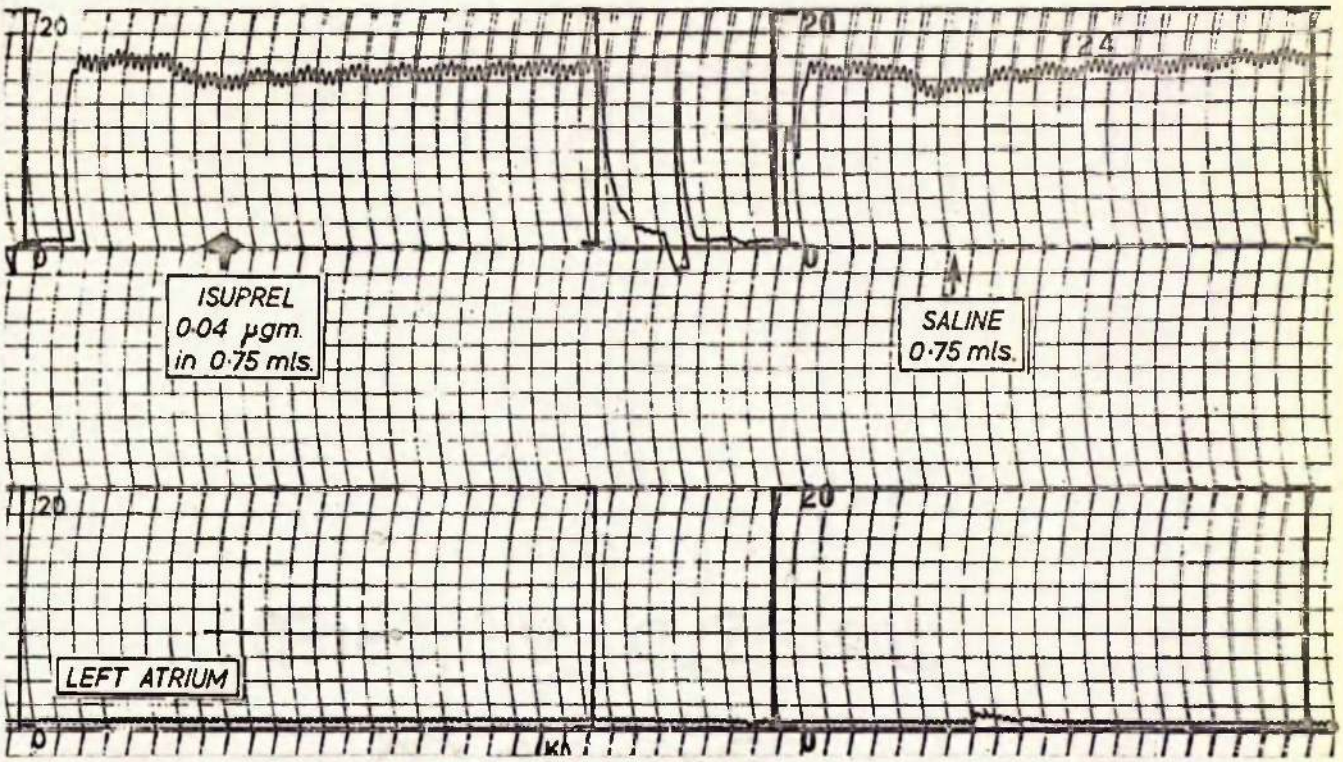


Fig. 41.

The effect of Isuprel contrasted with the effect of an equal volume of saline, given as consecutive injections in the same preparation.

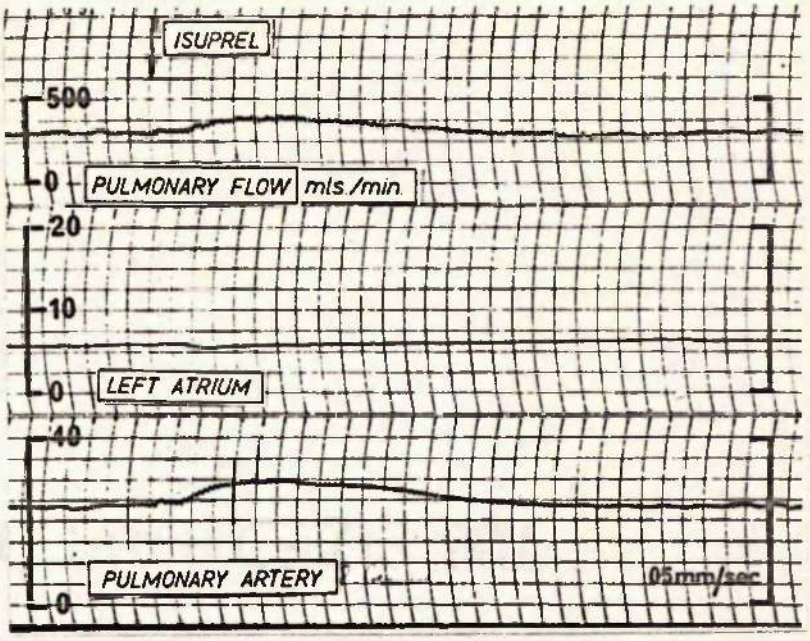


Fig. 42.

The effect of Isuprel (0.1 ug. intra-venously) on pulmonary blood flow and pressure.

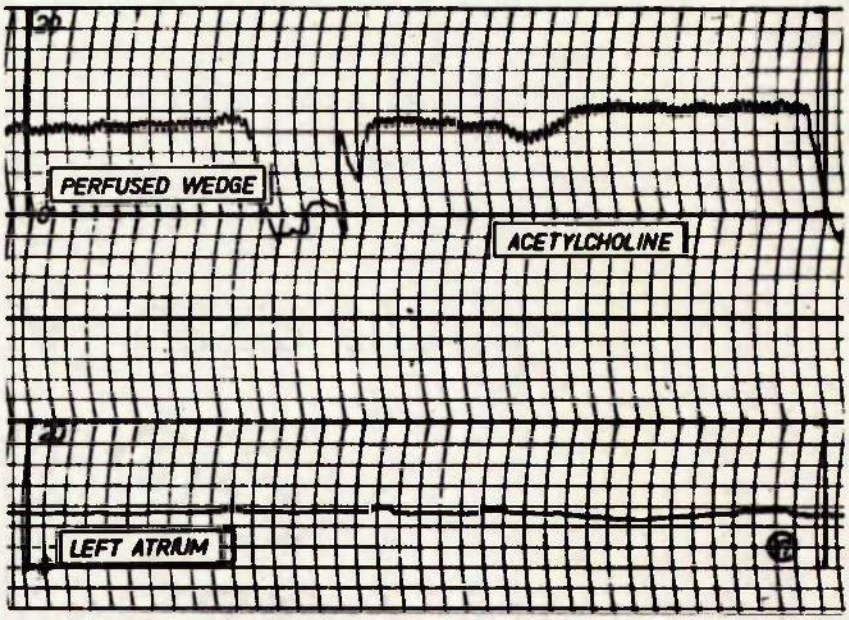


Fig. 43.

The local effect of a small dose of acetylcholine on the perfused wedge pressure and left atrial pressure.

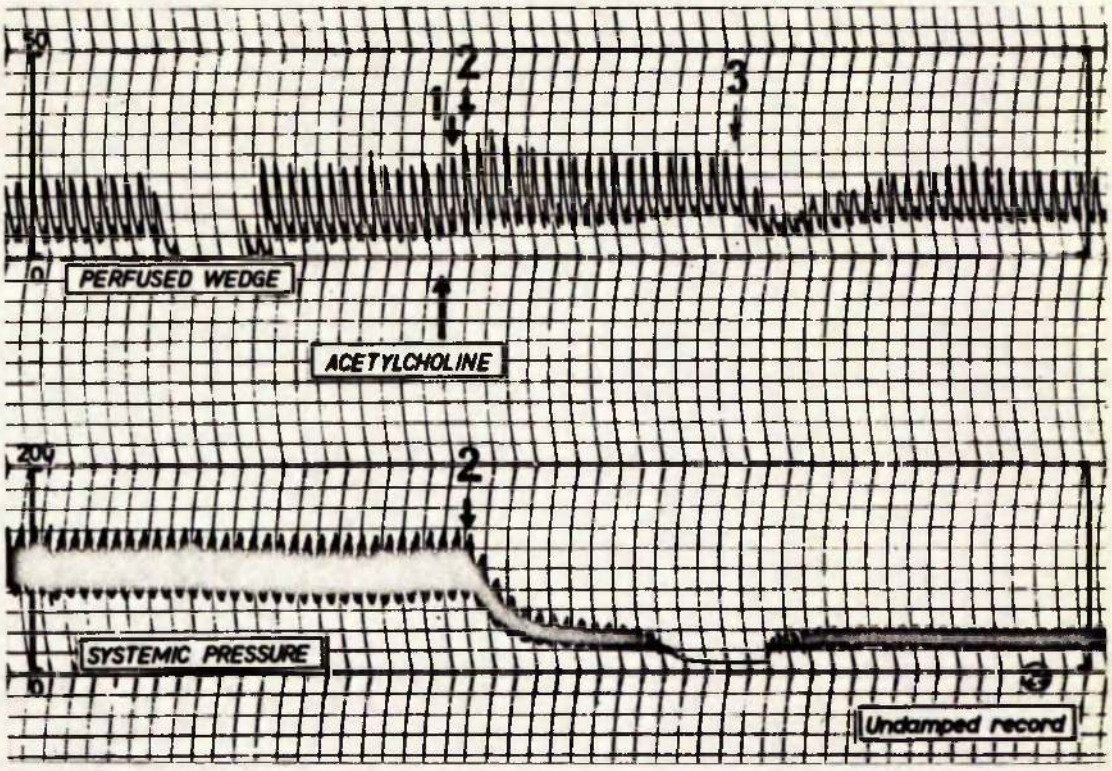


Fig. 44.

The tracings show the local and distant effects of a cardioplegic dose of acetylcholine introduced into the wedged catheter. At the point marked (1), the drug is exerting a constrictor effect in the wedge segment. At the point (2), it has reached the coronary circulation and bradycardia followed by cardioplegia ensues. With continued asystole, resistance in the perfused segment falls (3).

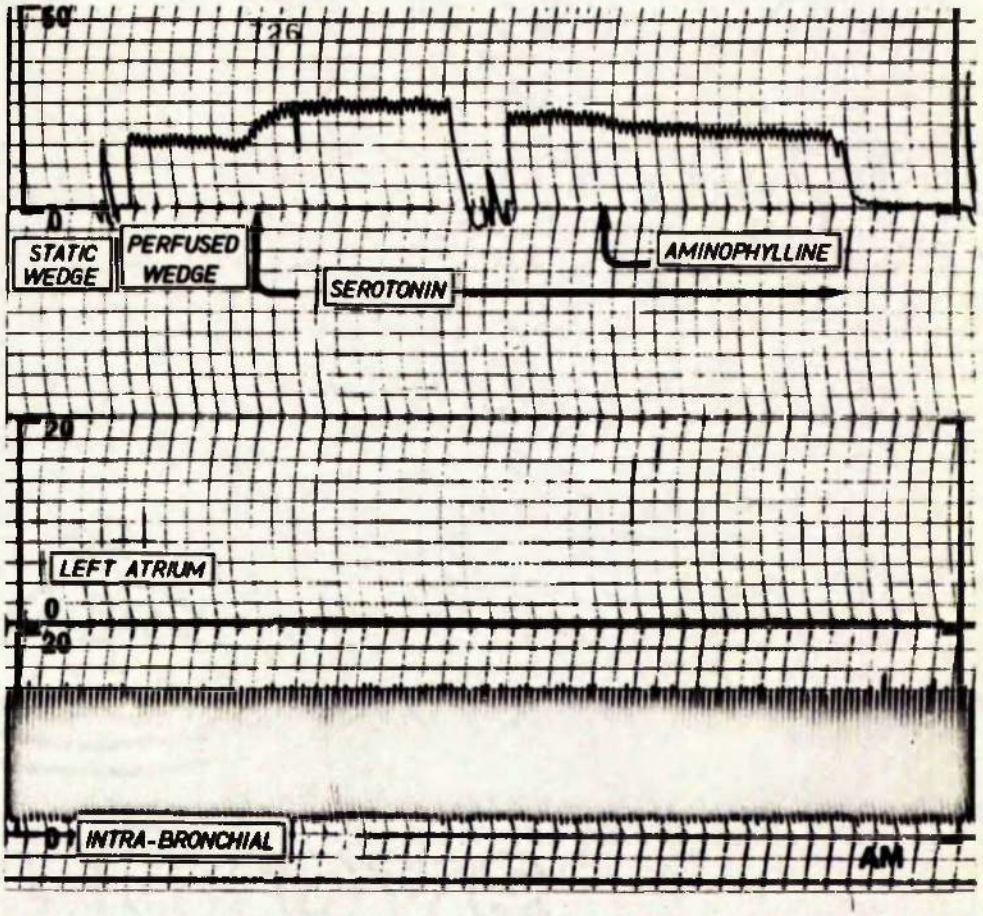


Fig. 45.

The local effect of aminophylline on a wedge segment perfused with serotonin.

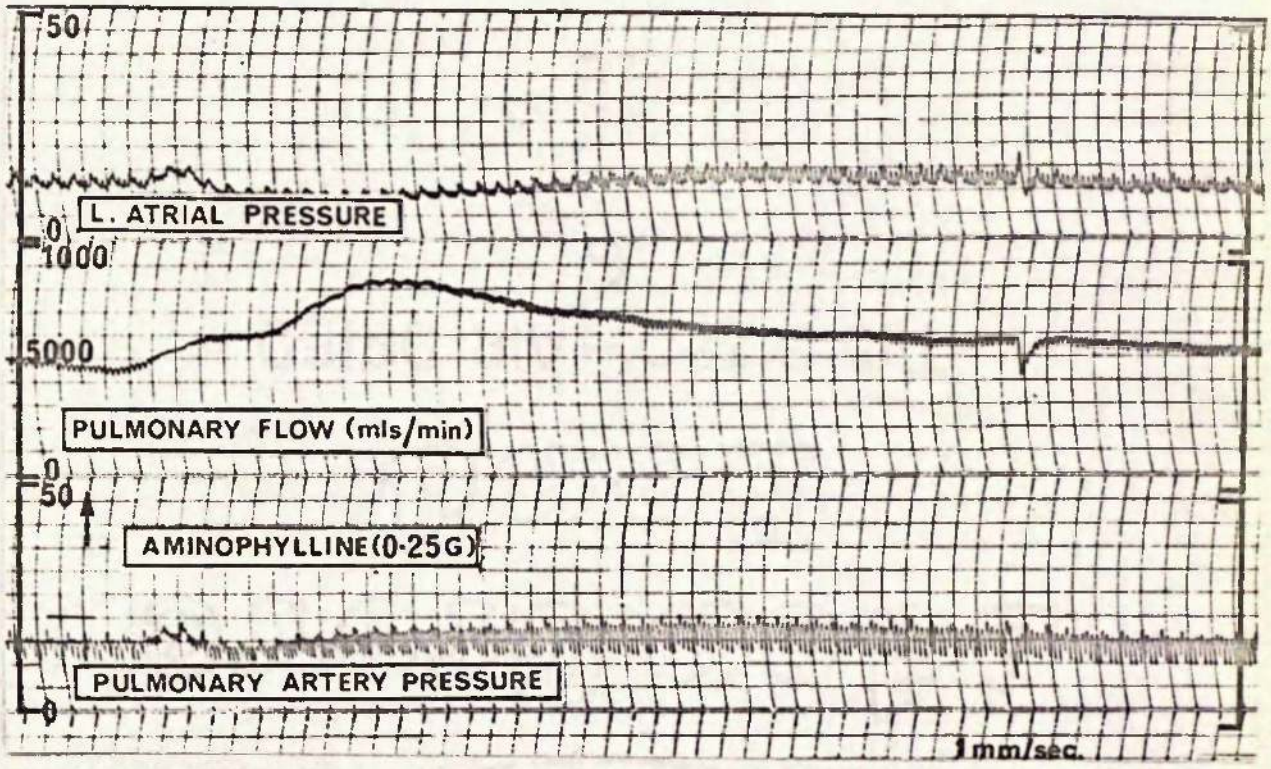


Fig. 46. The effect of aminophylline on the pulmonary arterial pressure and flow, and the left atrial pressure, in man.

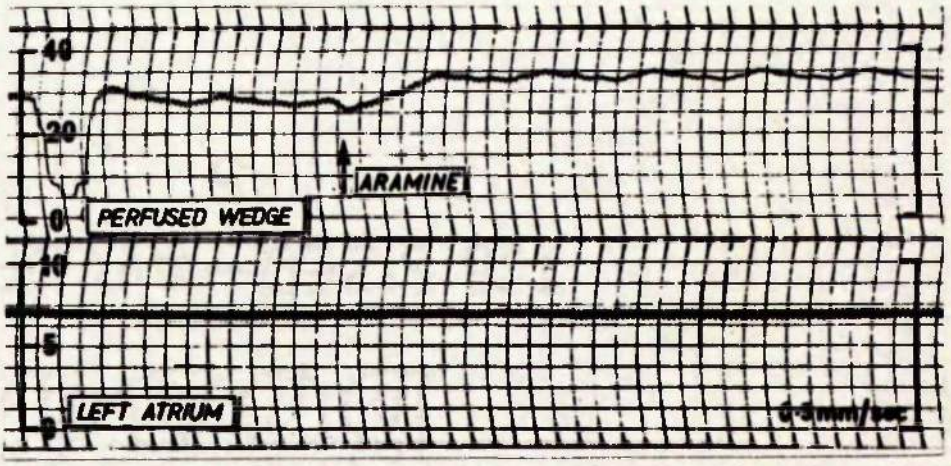


Fig. 47.

The local effect of aramine on the perfused wedge segment. (The slow waves in the perfused wedge pressure tracing were due to the perfusion pump).

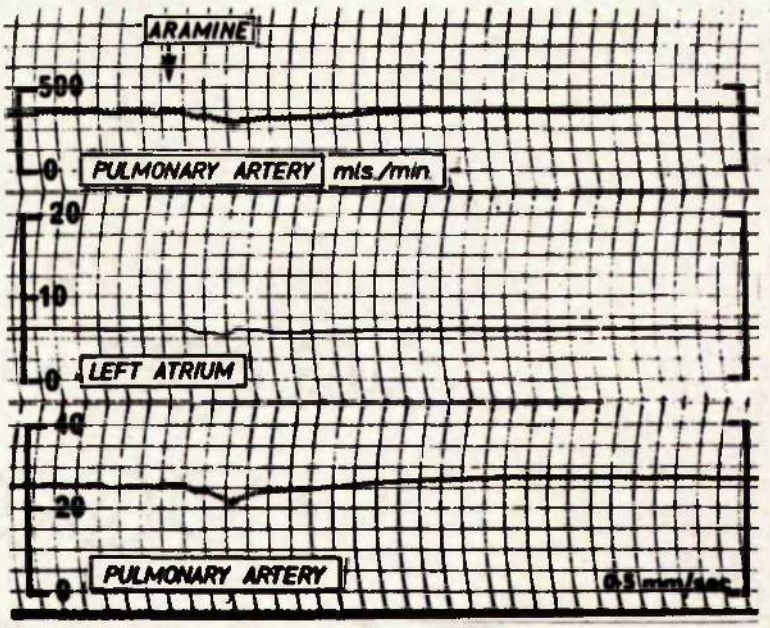


Fig. 48.

The effect of aramine administered intra-venously on pulmonary flow (upper record) and pressure (lower record).

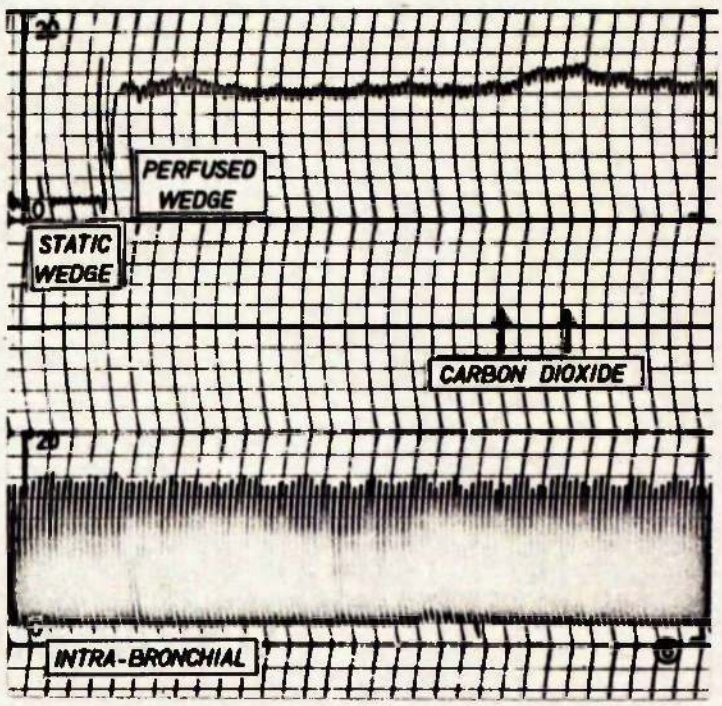


Fig. 49.

The effect of ventilation with an 8 per cent carbon dioxide mixture on the perfused wedge and intra-bronchial pressures.

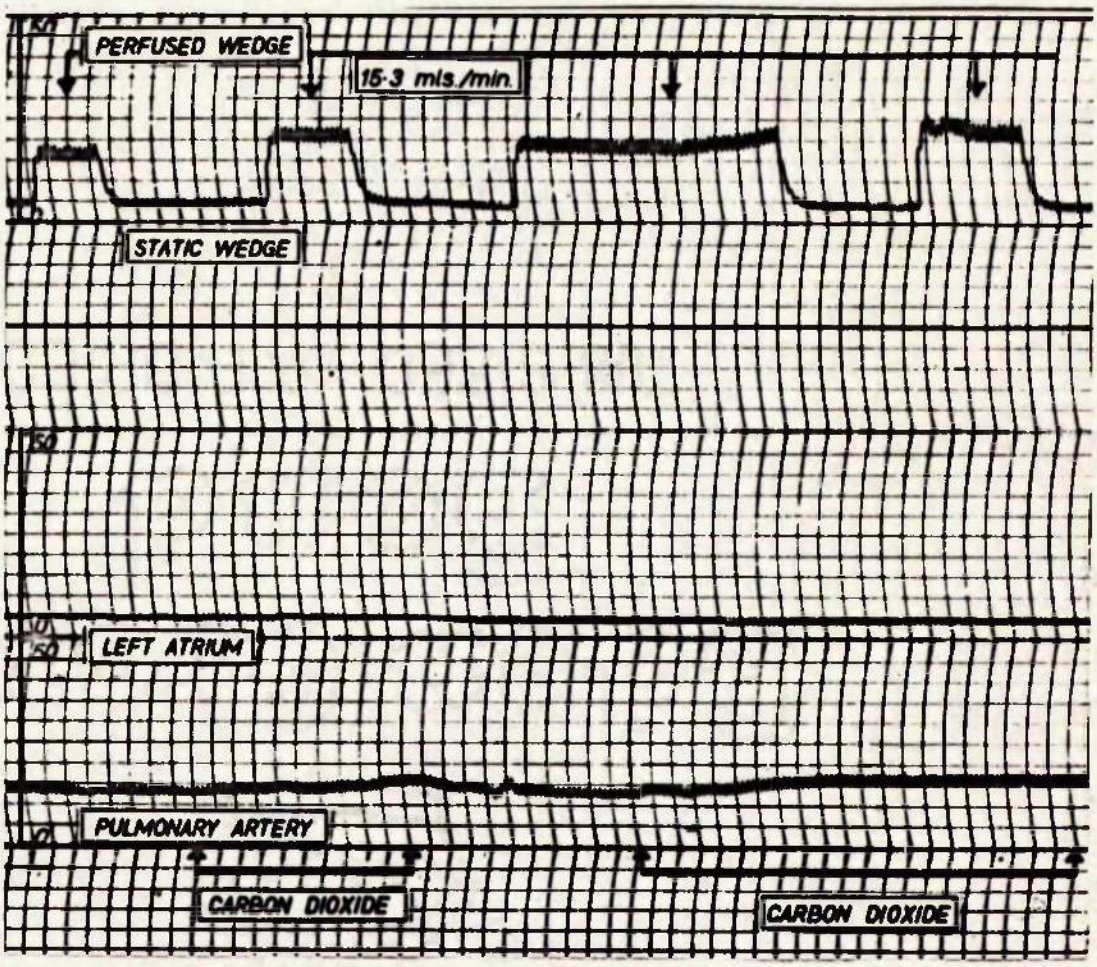


Fig. 50.

The effect of ventilation with 8% carbon dioxide on the perfused and static wedge pressures and the pulmonary arterial and left atrial pressures.

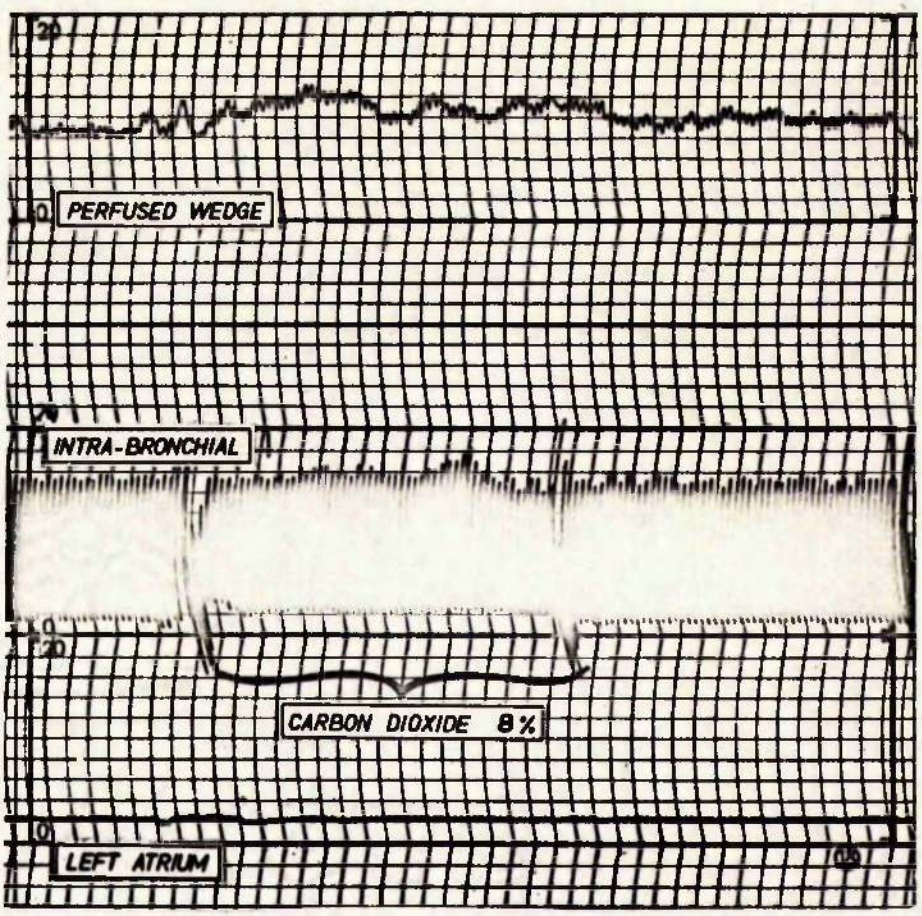


Fig. 51.

The change in the perfused wedge pressure (with the wedge segment in the right lower lobe) during selective ventilation of that lobe only with 8 per cent carbon dioxide.

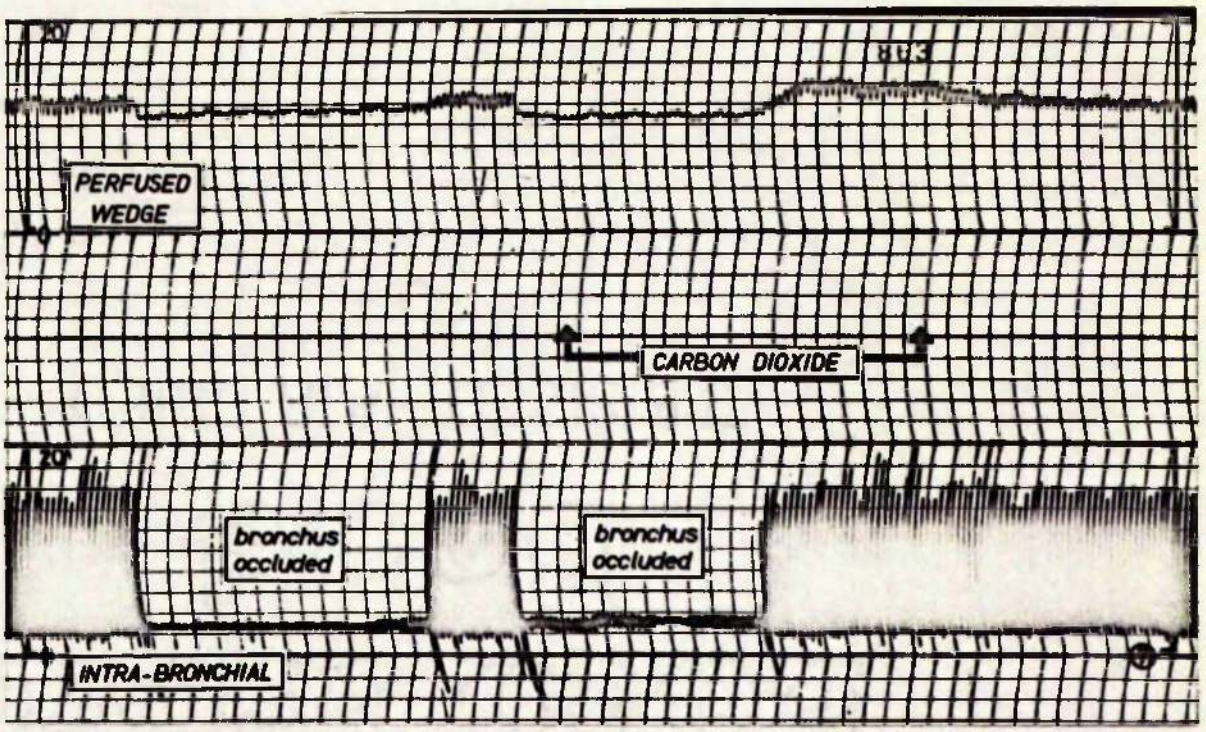


Fig. 52.

The perfused wedge pressure and intra-bronchial pressure recorded during two periods of bronchial occlusion. Ventilation with 8 per cent carbon dioxide, to both lungs was commenced during the second period of occlusion. The tracings show a rise in the perfused wedge pressure only when the second occlusion was released.

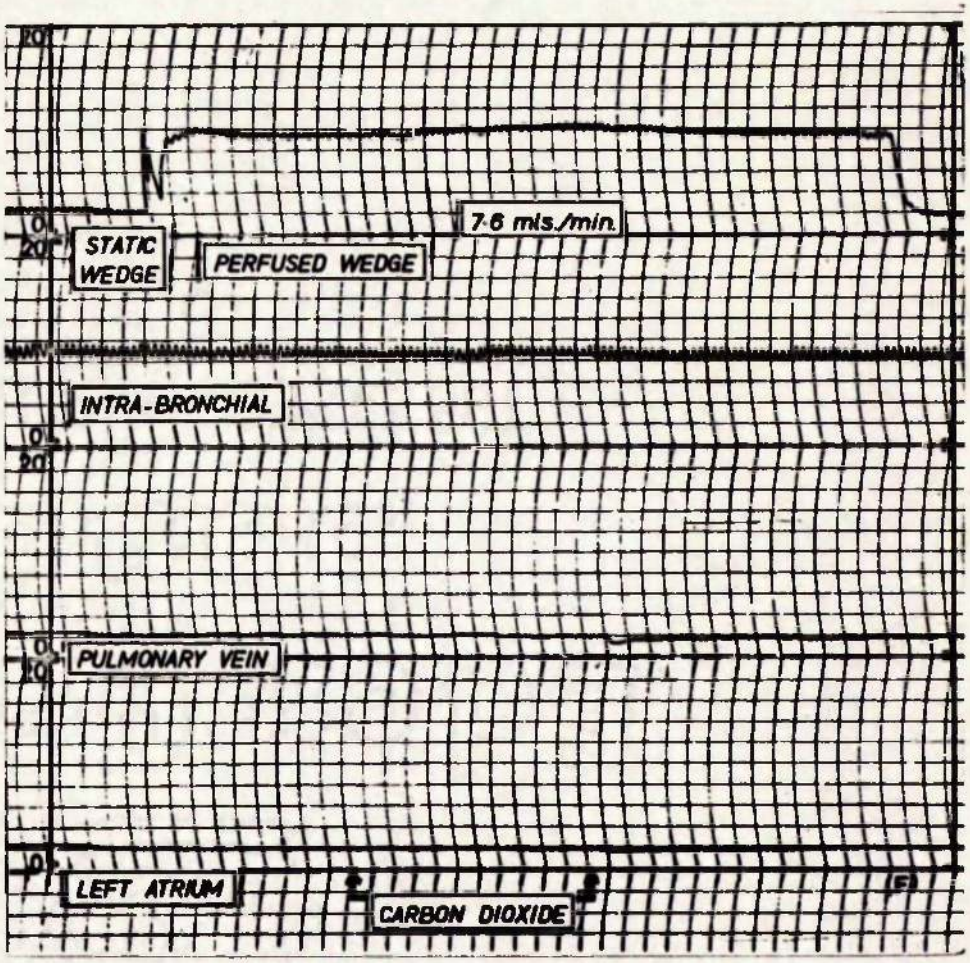


Fig. 53.

Showing the relationship between the pulmonary venous pressure and left atrial pressure during ventilation with 8 per cent carbon dioxide. (The abrupt dip in the pulmonary venous pressure just after the conclusion of ventilation with carbon dioxide is an artefact.)

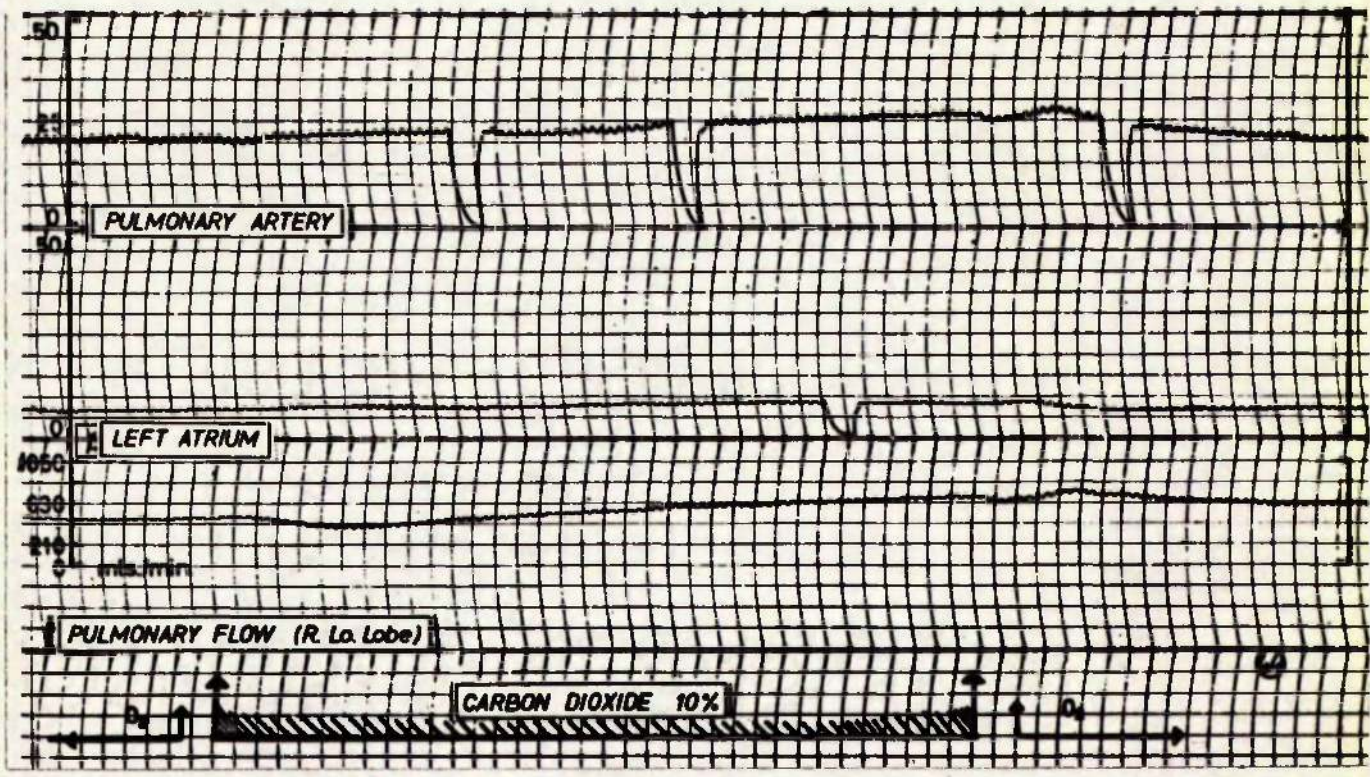


Fig. 54.

The effect of ventilation with gas mixture containing 10 per cent carbon dioxide on pulmonary blood flow, the pulmonary arterial pressure and the left atrial pressure. (The dips on the pressure tracings signify zero calibrations.)

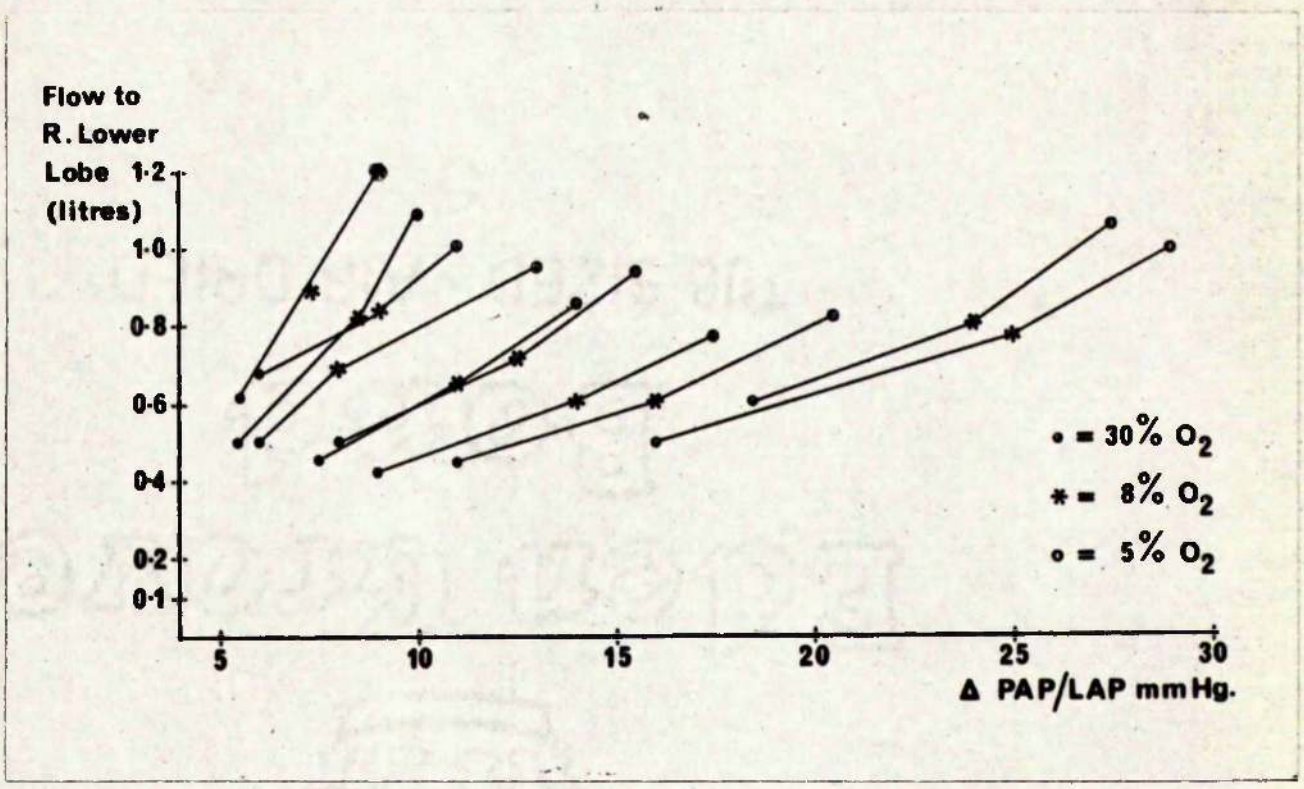


Fig. 55.

The relationship between pulmonary flow and pressure during ventilation with hypoxic gas mixtures.

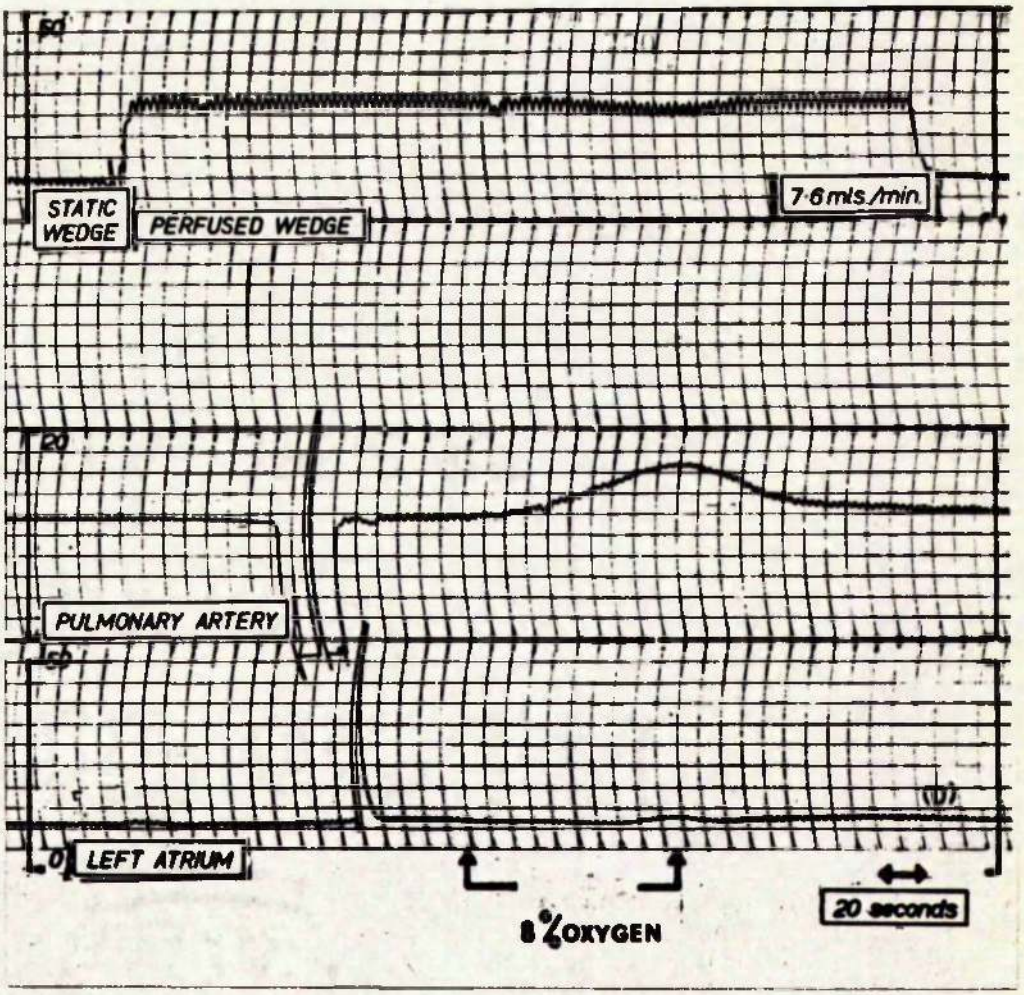


Fig. 56.

The effects of ventilation with a gas mixture containing 8 per cent oxygen on the perfused wedge pressure, pulmonary arterial pressure and left atrial pressure.

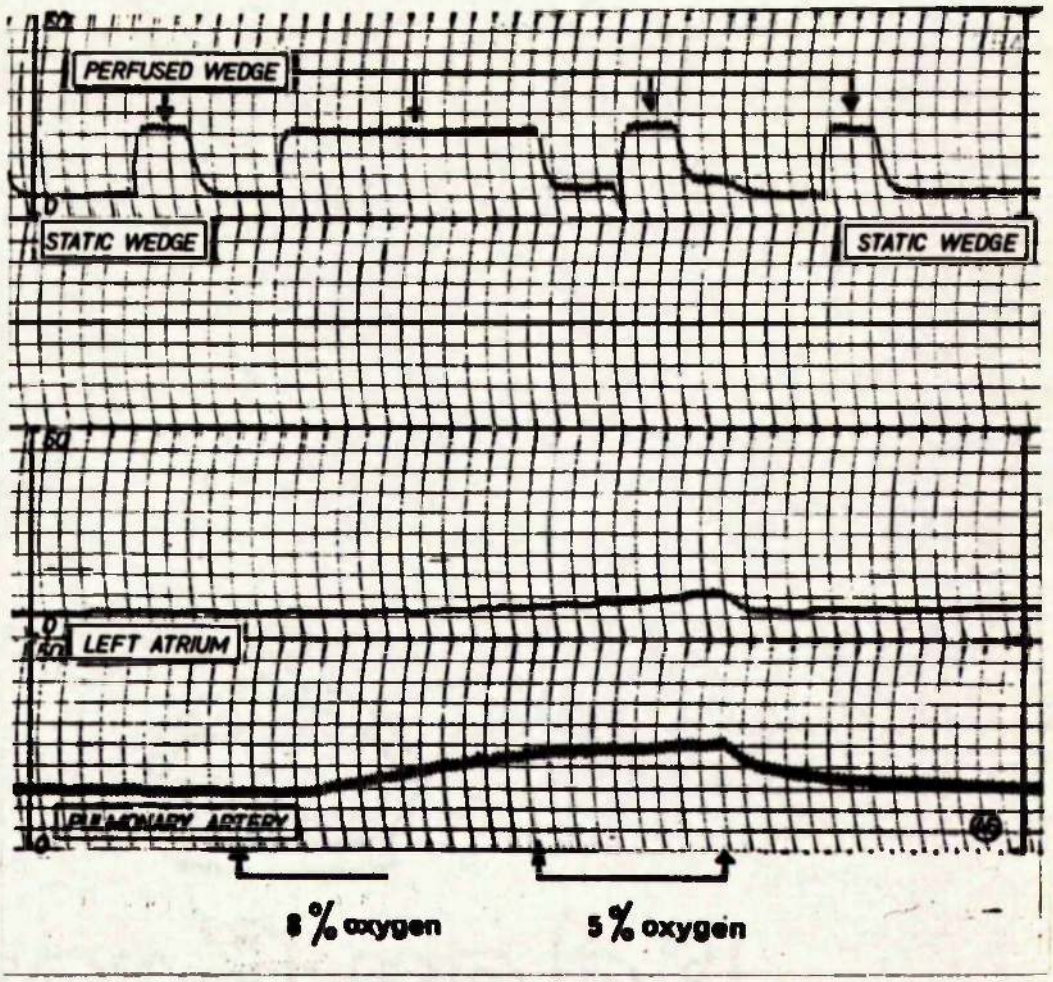


Fig.57.

Shows the relation between the perfused wedge pressure, static wedge pressure and left atrial pressure during ventilation with hypoxic gas mixtures.

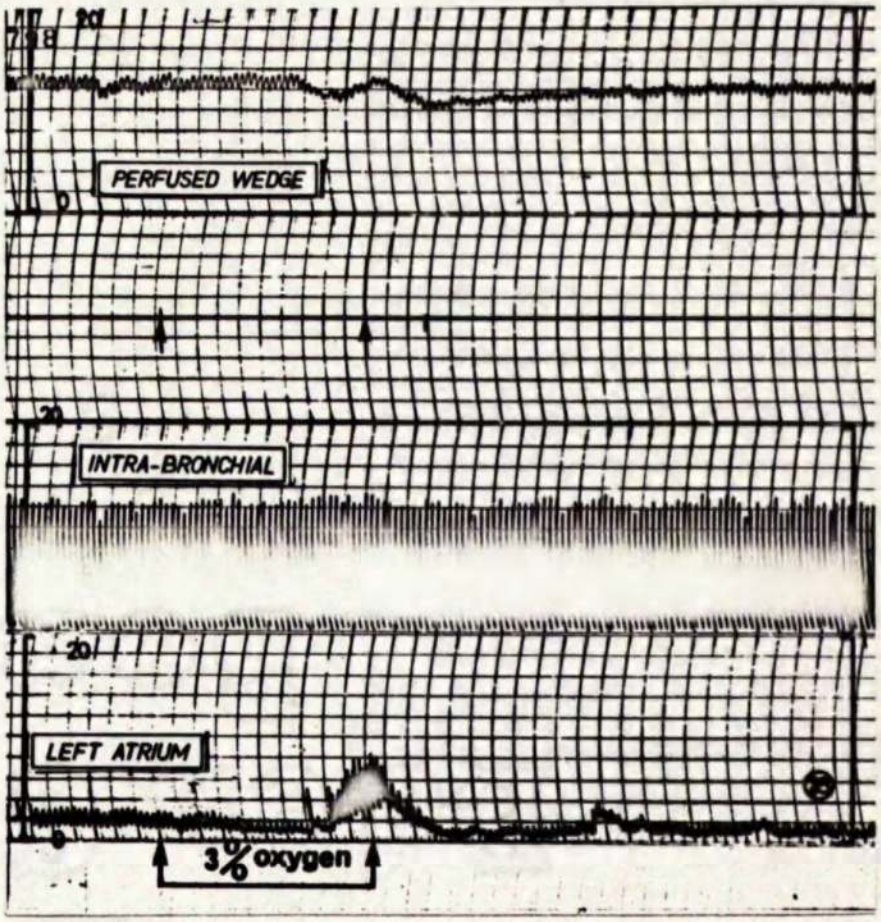


Fig. 58.

Shows the relationship between the perfused wedge pressure and the left atrial pressure when the latter is raised by severe hypoxia.

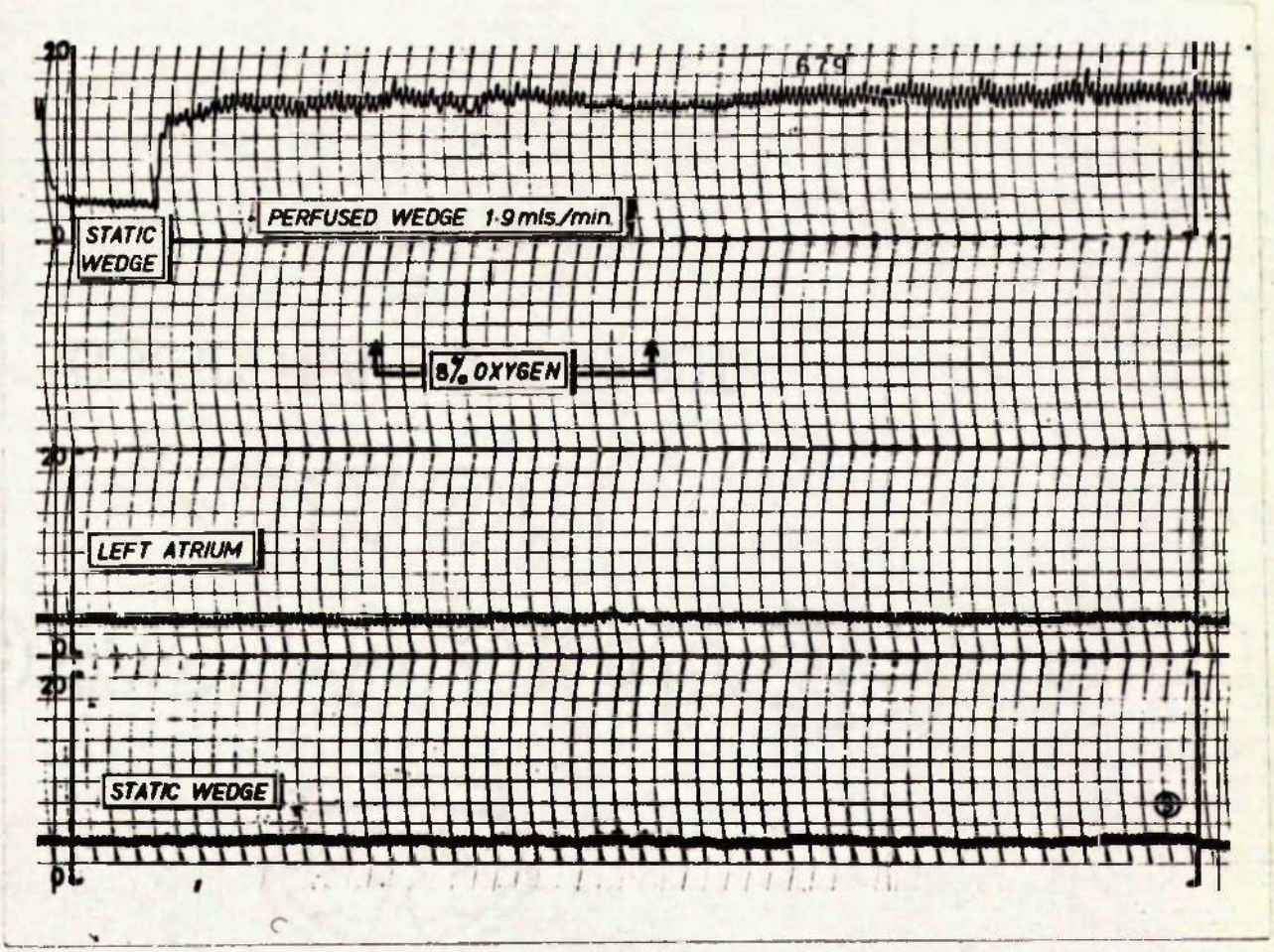


Fig. 59.

The effect of hypoxia on the perfused wedge pressure, left atrial pressure and static wedge pressure.

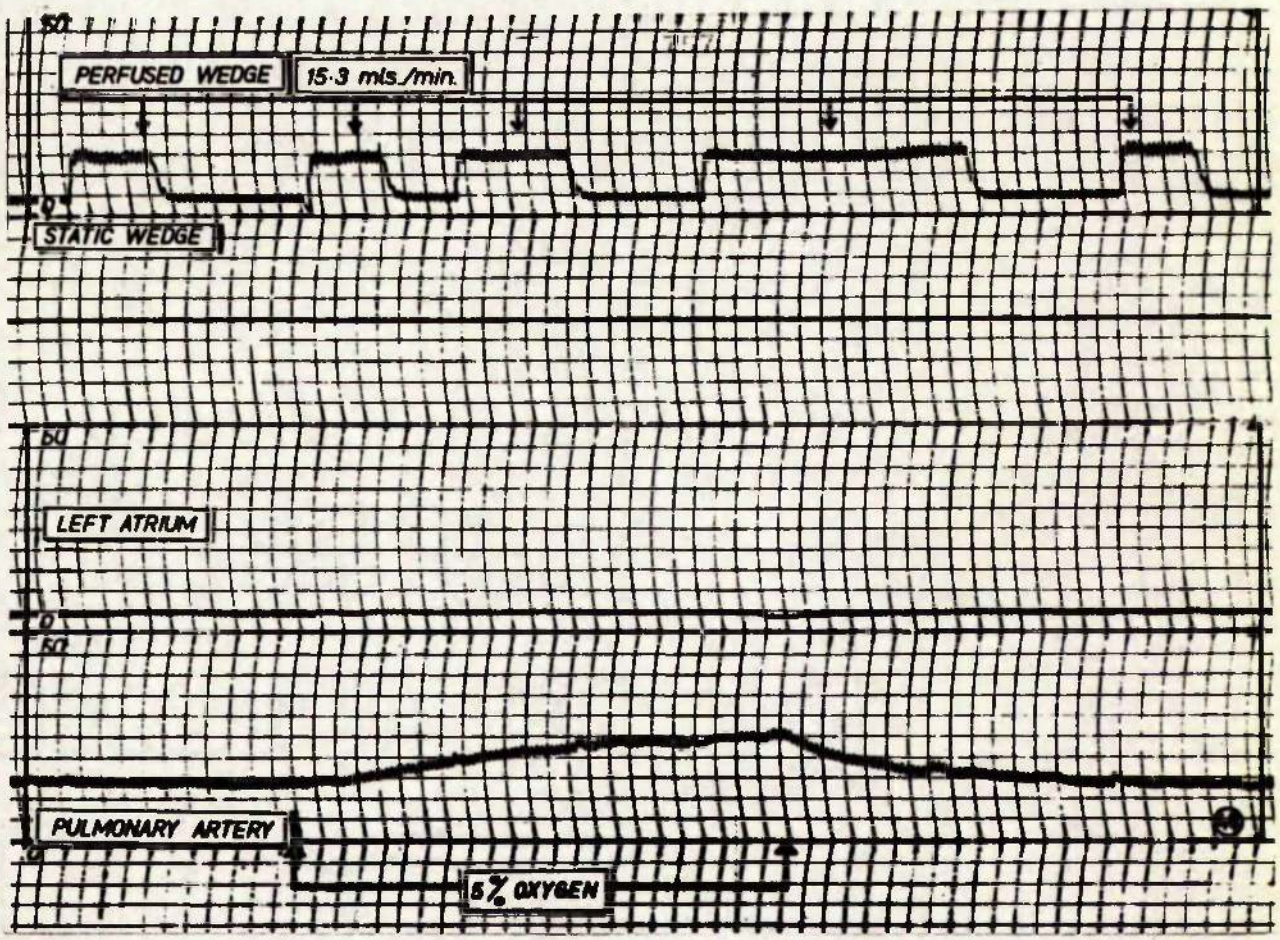


Fig. 60a.

This figure and that overleaf (60b) are reproduced to contrast the effects of hypoxia and hypercarbia on the perfused wedge pressure, static wedge pressure, left atrial pressure and pulmonary arterial pressure.

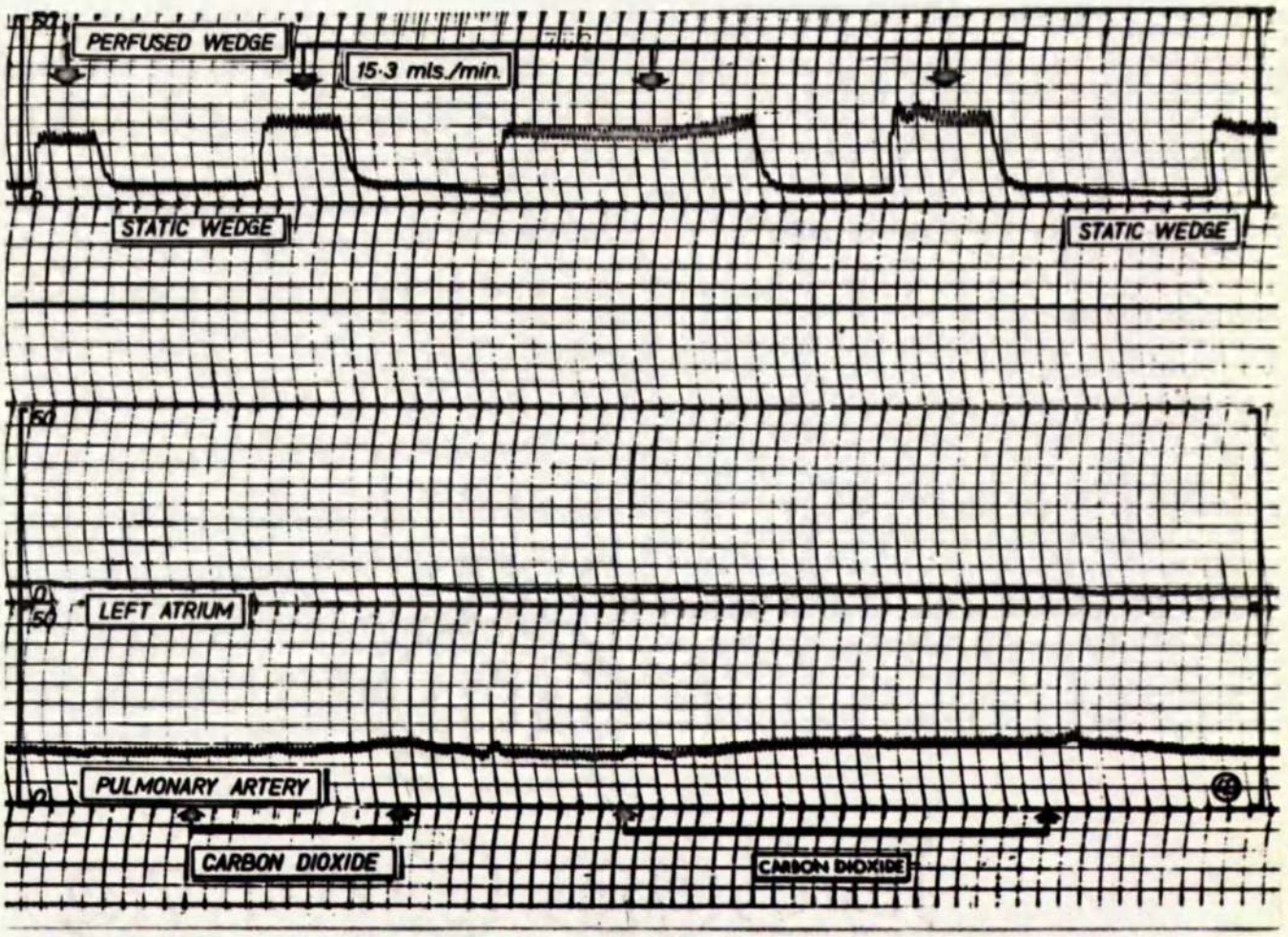


Fig. 60b.

For comparison with figure 60a.

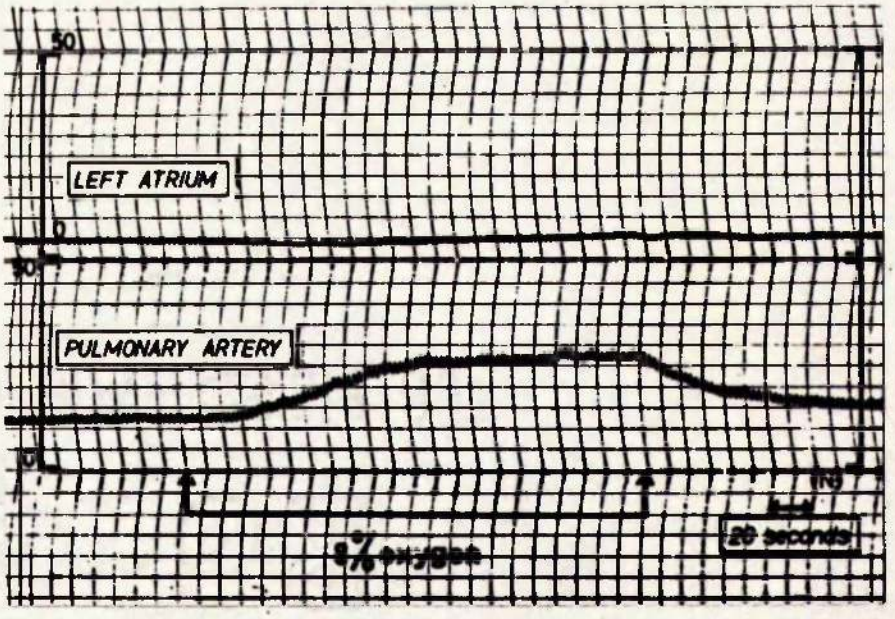


Fig. 61.

The effect of hypoxic ventilation on the pulmonary arterial pressure.

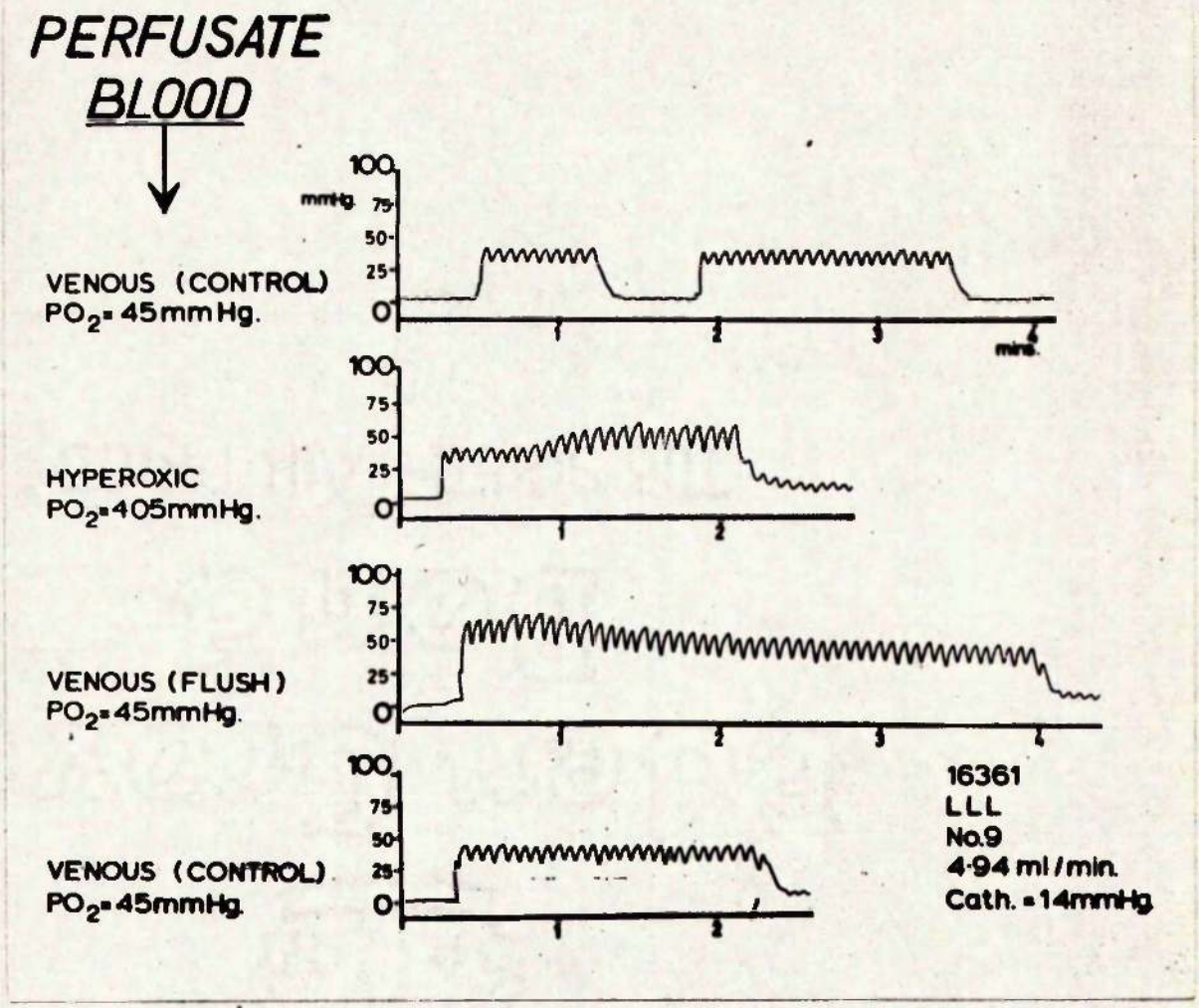


Fig. 62.

The response of the perfused wedge pressure to increases in the oxygen tension of the perfusate.

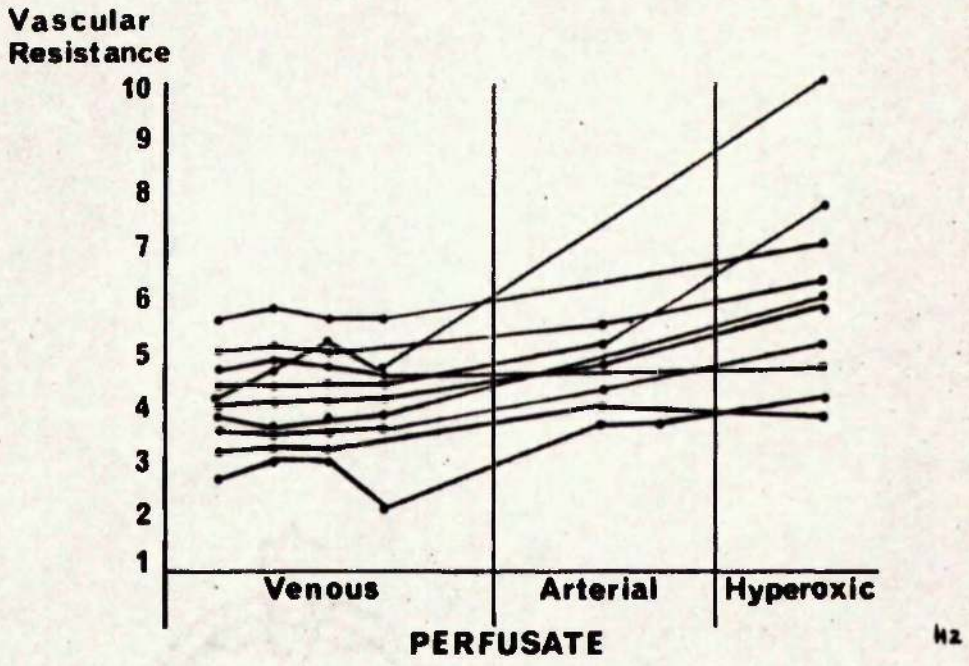


Fig. 63.

The results of experiments to show the effect of increasing the oxygen tension in the perfusate on the vascular resistance of the perfused wedge segment.

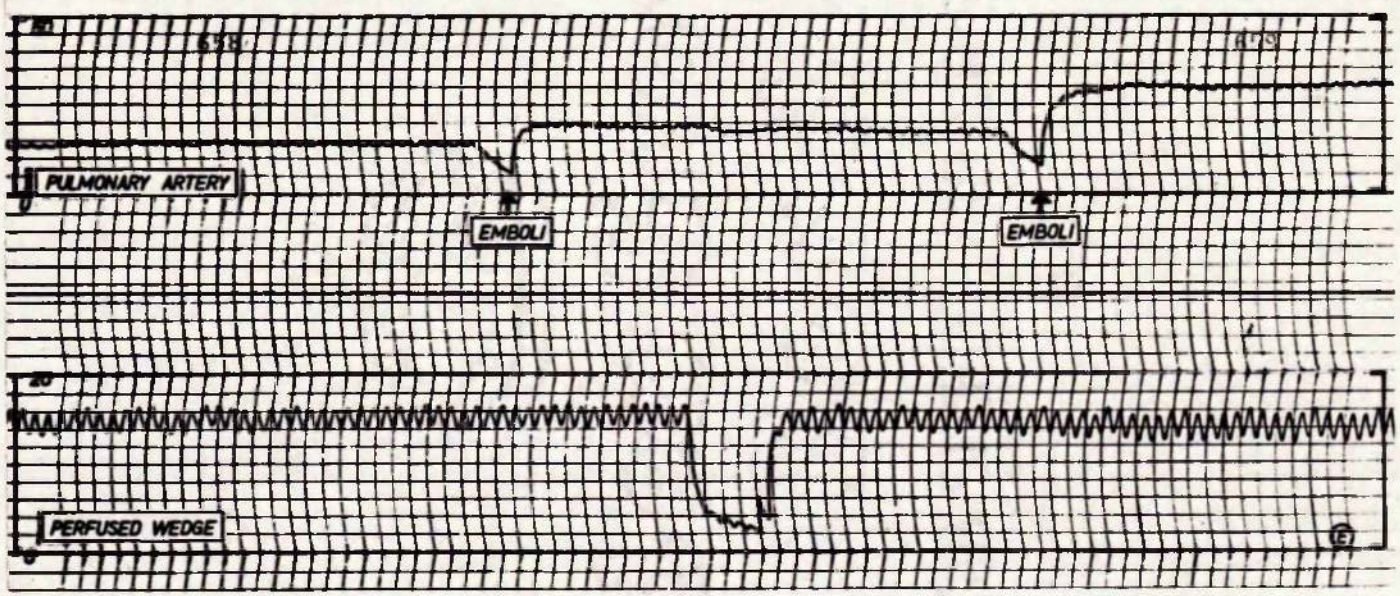


Fig. 64.

The effect of three increments of glass-bead emboli on the mean pulmonary arterial pressure and the perfused wedge pressure.

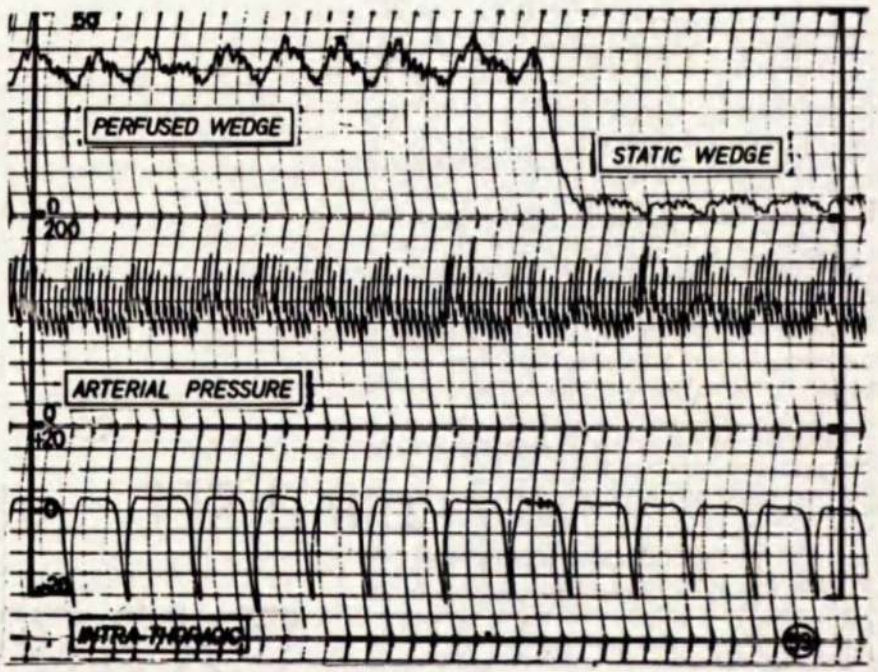


Fig. 65.

Records from an experiment to illustrate the phasic relationship between the intra-thoracic pressure, perfused wedge pressure, static wedge pressure and systemic arterial pressure. The catheter was wedged by the conventional trans-cardiac route in an animal who was breathing spontaneously. Paper speed = 2.5 mm./sec.

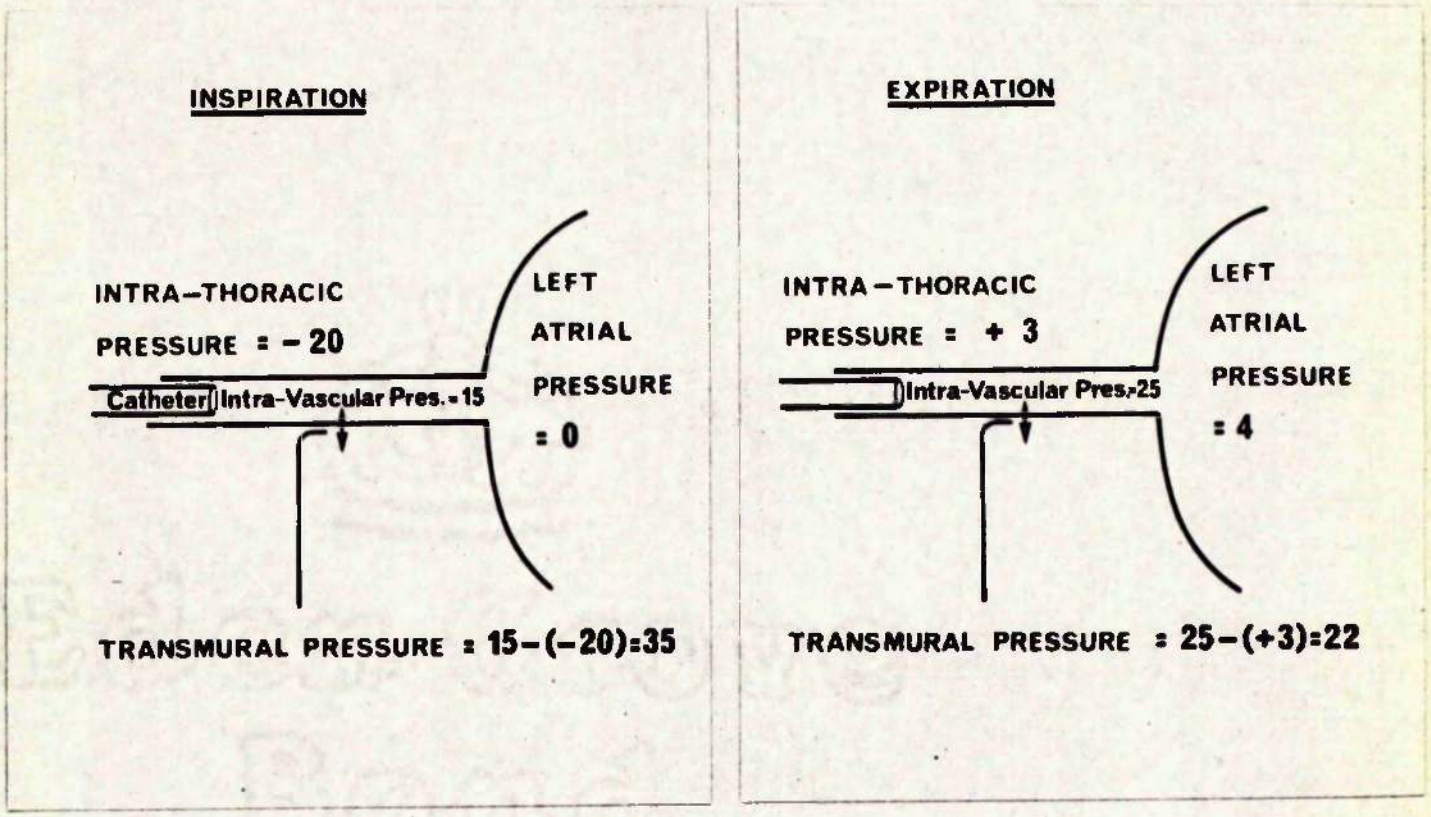


Fig. 66.

A diagram showing a derivation of figures for the true intra-vascular pressures, if it were assumed that the vessel and atrial walls were totally compliant.

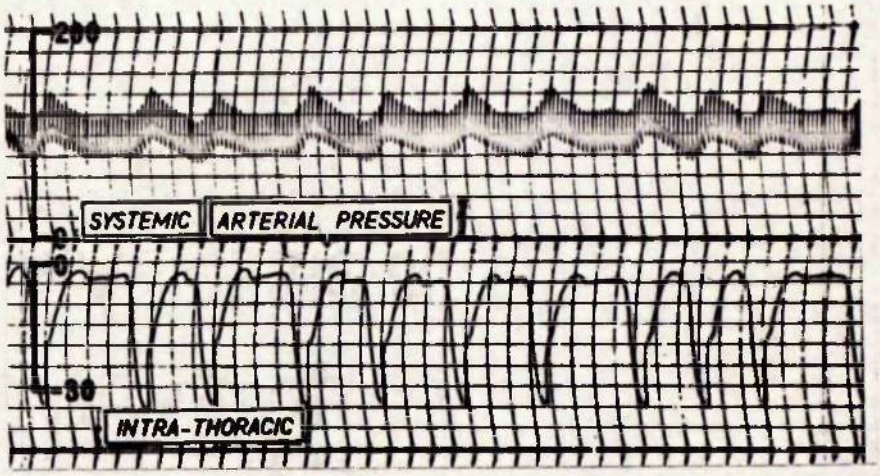


Fig. 67.

The phasic relationship between the systemic arterial pressure and the intra-thoracic pressure during deep spontaneous breathing in the dog with an intact thorax.

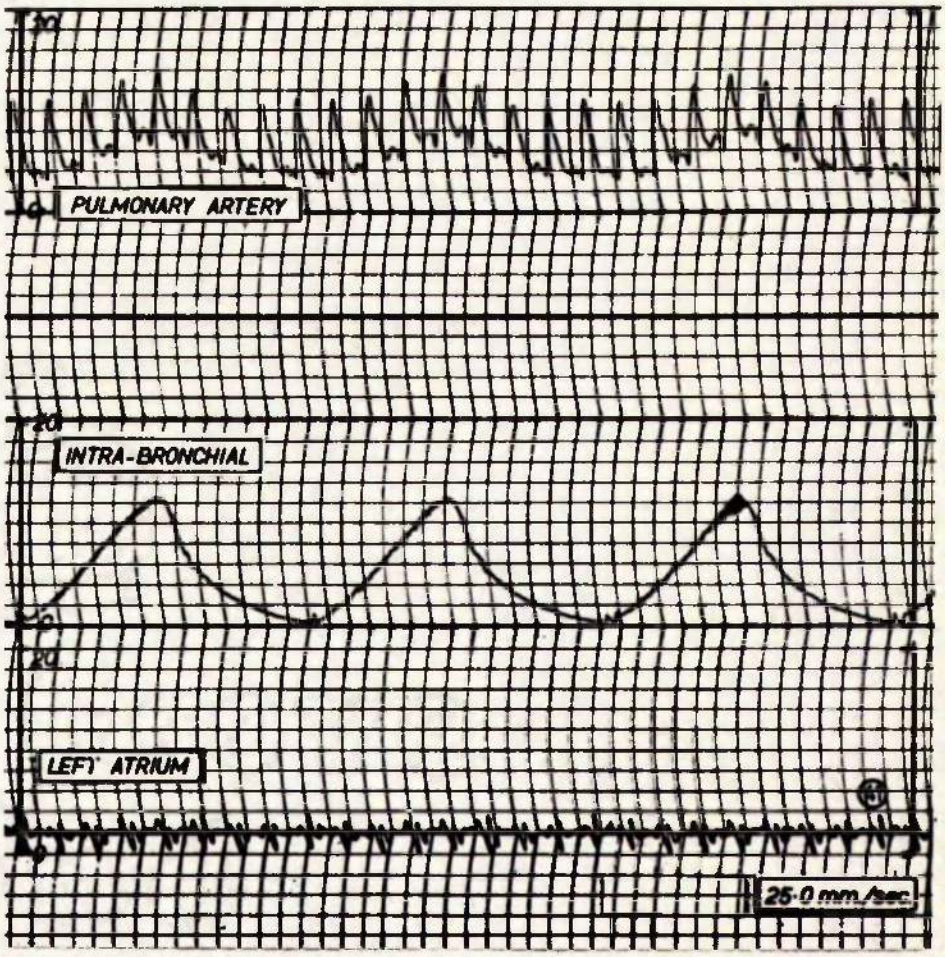


Fig. 68.

Records of the pulmonary arterial and left atrial pressures during positive pressure ventilation of the lungs.

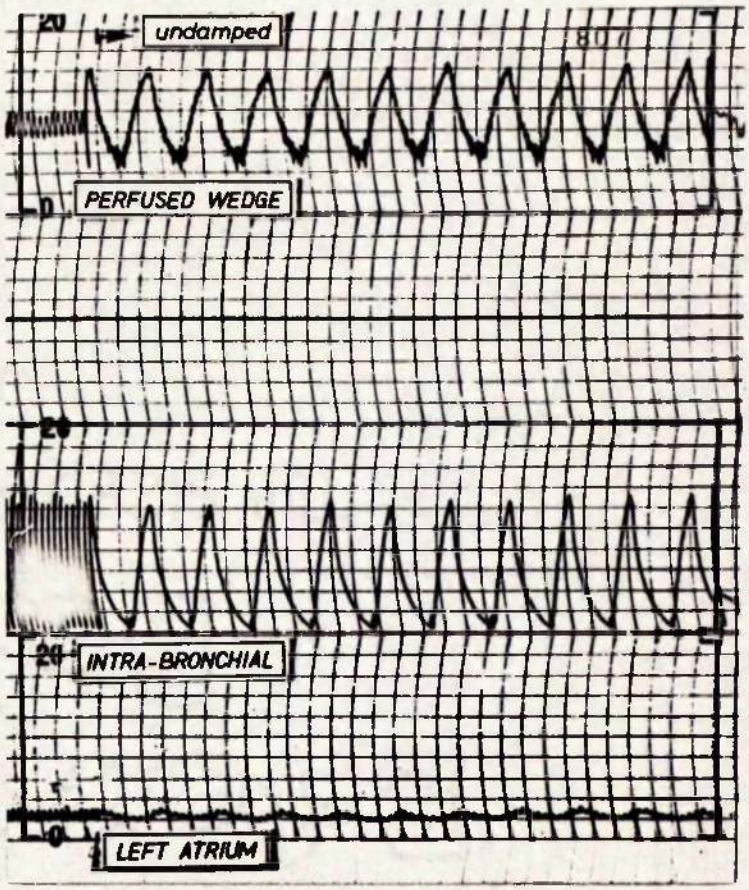


Fig. 69.

The phasic relationship between the perfused wedge pressure (undamped record) and the intra-bronchial pressure during positive pressure ventilation. (Paper speed in the expanded part of the record was 5 mm./sec.)

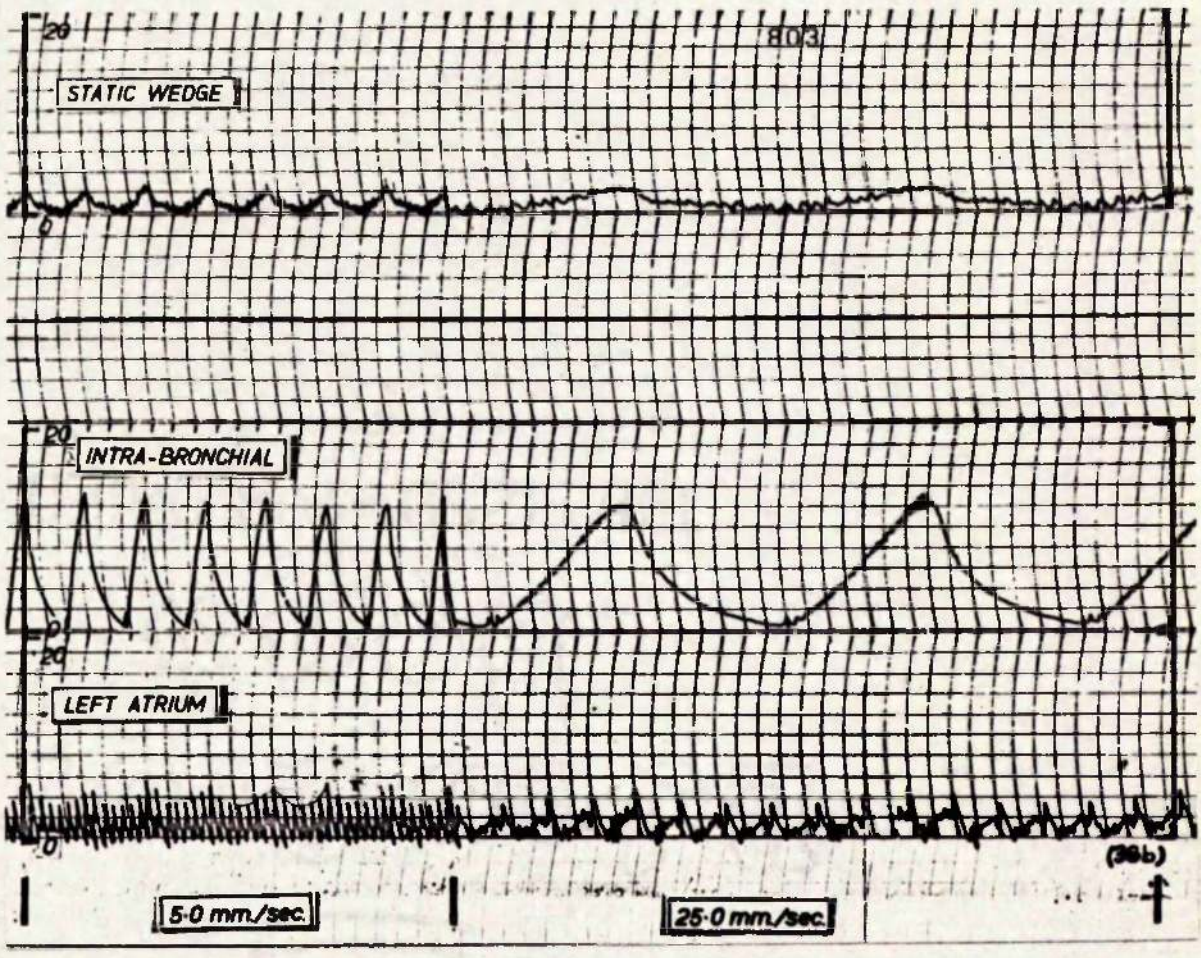


Fig. 70.

The phasic relationship between the static wedge pressure, the left atrial pressure and the intra-bronchial pressure during positive pressure ventilation (in a dog with an intact thorax).

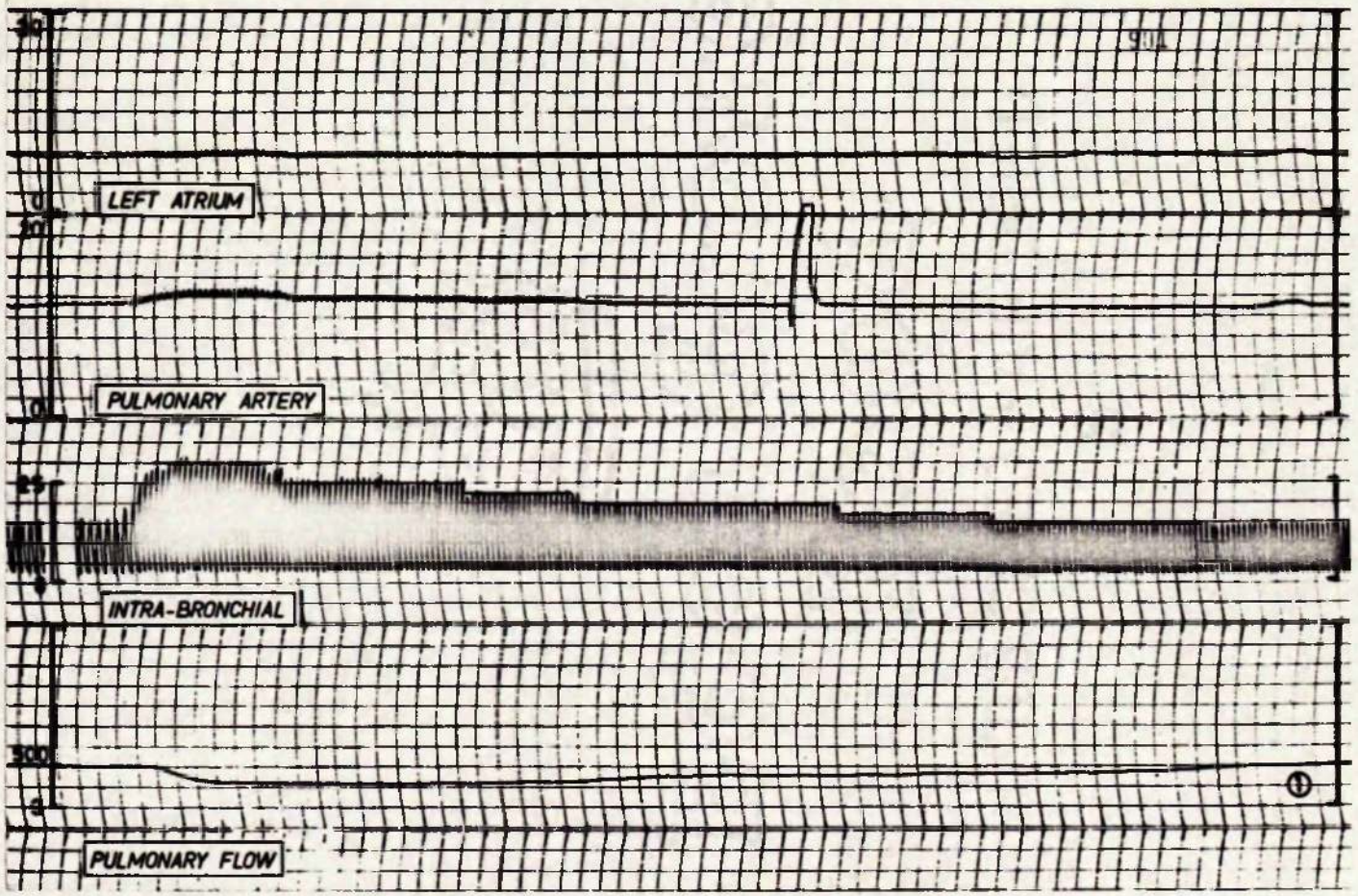


Fig. 71.

The changes in pressure measured in the main pulmonary artery and left atrium, and in pulmonary flow (to the right lower lobe) during alteration of the ventilation pressure.

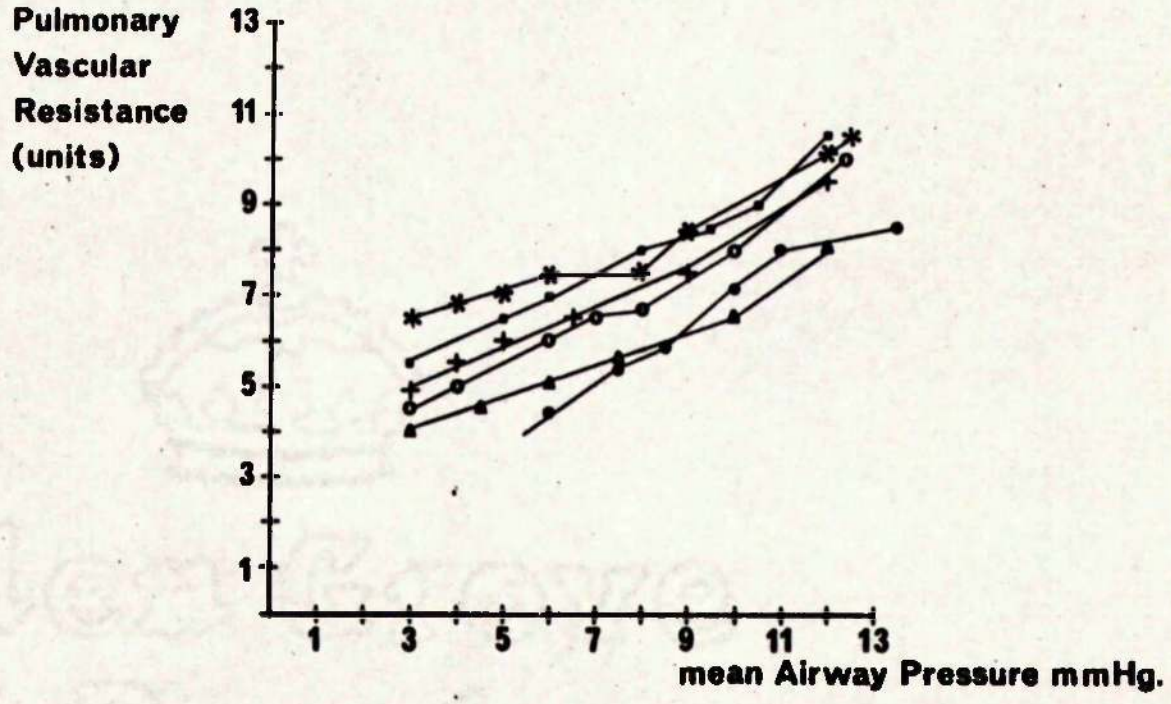


Fig. 72.

A graphic presentation of the results tabulated in table 38.

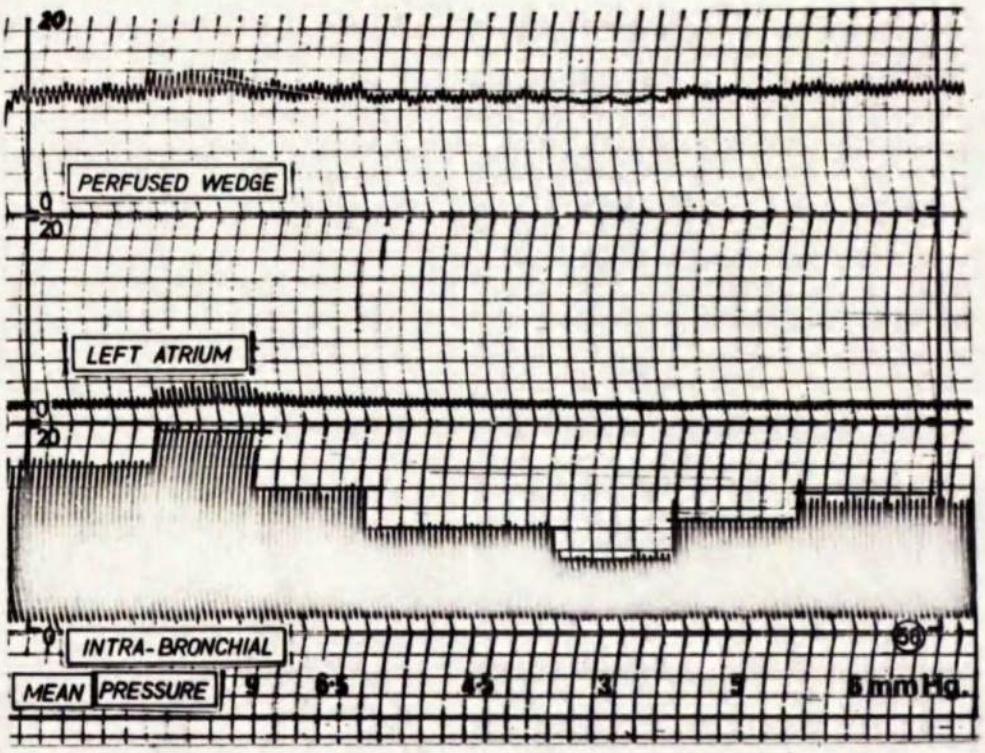


Fig. 73.

Changes in the perfused wedge pressure and left atrial pressure during alteration of the ventilation pressure.

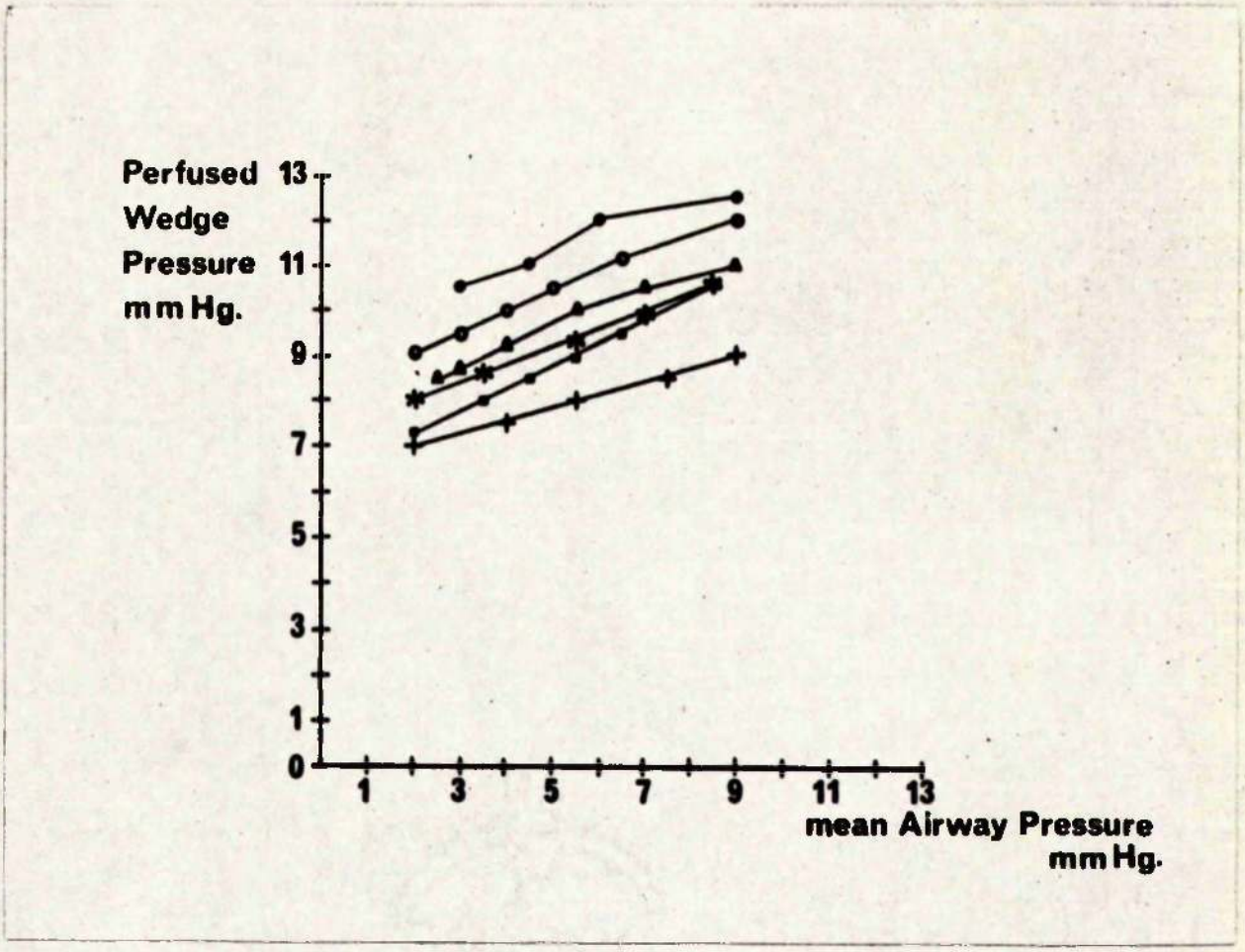


Fig. 74.

A graphic presentation of the results tabulated in Table 39.

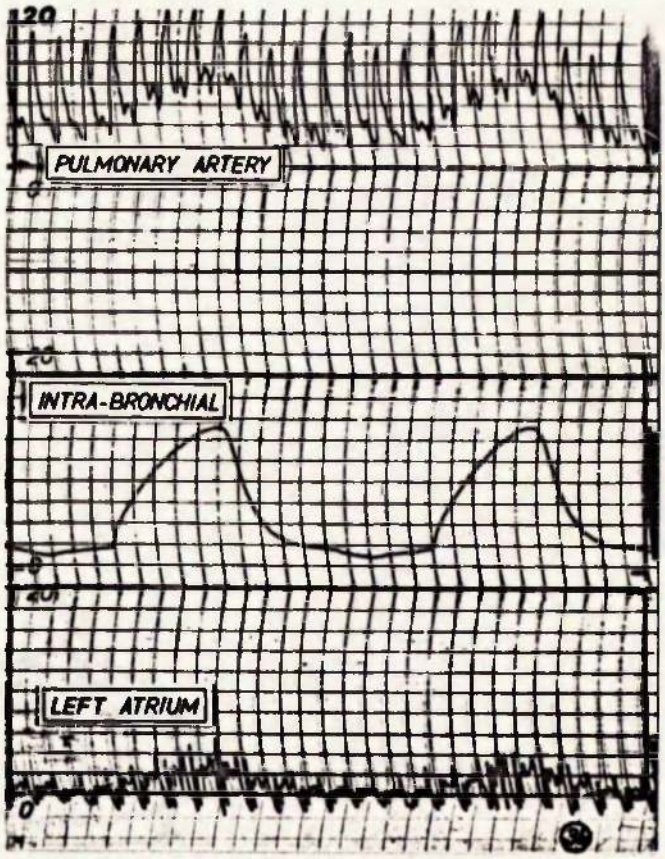


Fig. 75.

Shows the phasic swings in the pulmonary arterial pressure, and left atrial pressure related to intermittent positive pressure ventilation. Attention is drawn to the change in amplitude of the pulse pressures in each tracing.

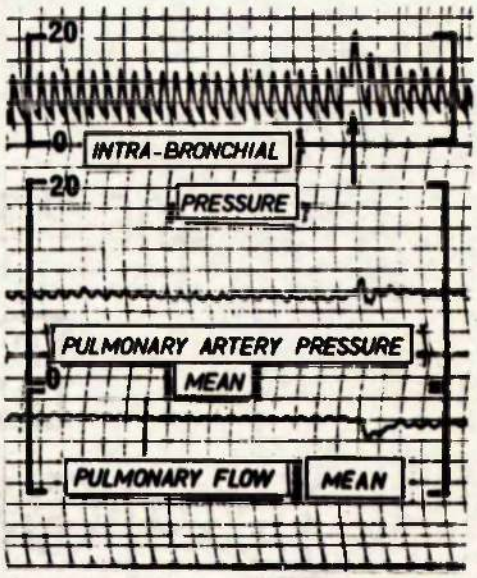


Fig. 76.

The phasic relationship between pulmonary arterial pressure, pulmonary blood flow and intra-bronchial pressure. At the point arrowed, expiration was obstructed so that the subsequent inflation caused a disproportionate increase in airway pressure.