PULMONARY EMBOLISM : AN EXPERIMENTAL AND CLINICAL STUDY

THESIS

SUBMITTED FOR THE DEGREE OF

MASTER OF SURGERY

IN

THE UNIVERSITY OF ADELAIDE

BY

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DECLARATION

I declare that this thesis is of my own composition and that it is a true record of original work. It has not been submitted for the award of any degree or diploma in any university.

The experimental work was carried out in Dr. David Sabiston's Surgical Laboratory at the Duke University Medical Center, North Carolina, under the supervision of Dr. Robert Jones.

All of the work was carried out in conjunction with Dr. Andre Duranceau. In Section II of Part I and in Part II, Dr. Duranceau was the principal investigator whilst in all other sections I was the principal investigator.

To the best of my knowledge and belief the thesis contains no material previously published or written by other persons except where due reference is made to such material in the text.

G. G. Jamieson

ACKNOWLEDGEMENTS

The work which is reported in this thesis was carried out while I was a Research Fellow and Instructor in the Department of Surgery, Duke University Medical Center, North Carolina. I am very grateful to Dr. David Sabiston Jr., James B. Duke Professor and Chairman of that Department for providing me with the opportunity to undertake this work and for the encouragement and other support which he provided. Dr. Robert Jones, Assistant Professor of Surgery at Duke supervised the work and was always willing to discuss problems and give practical help when it was needed. Dr. Andre Duranceau, Research Fellow and Instructor at Duke, collaborated with me for much of the work and without him much less would have been achieved and indeed much of the work would have been left unfinished.

Professor John Ludbrook of the University of Adelaide has been most helpful in reading and re-reading the manuscript, and the fact that the final version is not better is not that he ran out of patience but rather that I did.

G. G. Jamieson

PULMONARY EMBOLISM : AN EXPERIMENTAL AND CLINICAL STUDY

PART I : AN EXPERIMENTAL STUDY OF PULMONARY EMBOLISM IN THE DOG.

INTRODUCTION

It has been estimated that pulmonary embolism is the third most frequent cause of death in the United States of America and it is probable that a similar figure obtains for Australia (Dalen and Alpert, 1975).

A very much larger population of patients who are in hospital will sustain a non-fatal pulmonary embolus during the course of their illness.

When pulmonary embolism proves fatal about 50% of patients die within the first hour following the event, 75% of patients are dead within two hours and most of the remaining patients die over the ensuing forty-eight hours (Tibbutt and Chesterman, 1976).

If improvement in treatment is to lower mortality figures then obviously the first hours after the embolic event are the critical ones. This experimental study was undertaken to document the haemodynamic and respiratory changes which take place in this critical period. The effects of two drugs often used in this condition, heparin and isoprenaline, were also studied. The effects of embolism have been well documented previously in animals but the material used has been dissimilar to emboli which occur in man. A model has been developed which produces embolic material closely resembling emboli occurring in man, and the changes produced using this material may more closely mimic the clinical situation in patients.

As a separate but related study we have scrutinised the data from a large group of patients who sustained a pulmonary embolus to try to identify features which may be of diagnostic, and/or prognostic significance. Large groups of such patients have been previously reported but the validity of the conclusions reached in those studies was weakened by the failure to apply an objective

test for pulmonary embolism in all cases. All patients in our study had been objectively tested for pulmonary embolism.

SECTION I (a) A REVIEW OF METHODS USED FOR PRODUCTION OF EXPERIMENTAL THROMBI AND A SURVEY OF MATERIALS USED TO PRODUCE PULMONARY EMBOLISM.

Thrombi which form in man have different characteristics from blood clot.

Under low power magnification blood clot is seen to have a uniform structure while thrombus is composed of two kinds of material which stain differently. At higher magnification the paler of the two materials is seen to consist of agglutinated platelets, fringed by white cells and in between are layers of the other type of material which is mainly red cells. By appropriate staining techniques, fibrin can be demonstrated covering the platelet masses and apparently enmeshing the red cells. Thus a thrombus has been likened to coral with the coral formed by platelets and in the interstices of the coralline structure are red cells held in a tenuous fibrin meshwork. By contrast a clot at high magnification shows no orderly arrangement at all. Red cells, white cells and platelets are distributed at random in a fibrin network of fairly uniform density (Poole and French, 1961; Florey, 1970).

Because of these differences attempts have been made to produce a model of thrombus production in which the product is structurally similar to thrombus found in man.

In 1927 Rowntree and Shionoya published an account of experiments in which blood was made to flow through a shunt from the carotid artery to the jugular vein of a rabbit. The blood passed through a collodion tube and thrombus developed within it. When the thrombus was examined it was found to have similar microscopical structure to that of human thrombus. In 1938 Best et al. also used arteriovenous shunts in rabbits, cats and rhesus monkeys with similar results. Mason and Harrison (1949)

poured heparinized blood through a glass tube which had a side arm plugged with material soaked in tissue extract and again a structure resembling a thrombus in its microscopic appearance was formed. Chandler (1958) later demonstrated that no biological material other than blood was required to form small, thrombus-like structures in a blood-filled rotating plastic tube. This technique has been used to study the microscopic nature of thrombi and other factors in their formation (Poole, 1959; Poole, 1960; Connor et al., 1961; Craig et al., 1973). However this latter technique, or modifications of it, has not been reported as being used for the production of material for embolism into the pulmonary tree. In fact, much of the work for this purpose has been carried out using non biological materials.

Virchow (1846) was the first to use artificial material as pulmonary emboli when he injected muscle into the internal jugular vein of the dog to prove that emboli could travel from the periphera venous system to the pulmonary artery. Since then the dog has been used extensively as an experimental animal for studying the effects of pulmonary embolism, and the nature of the substances used as embolic material has varied widely. Thus, glass beads (Niden and Aviado, 1956; McEvoy et al., 1958), barium sulphate (Halmagyi and Colebatch, 1961), lycopodium spores (Daley et al., 1951), autologous blood clot (Hyman et al., 1964), corn starch granules, lead phosphate agar gel (McEvoy et al., 1958), serum induced blood clot (Wessler et al., 1961), powdered pumice stone and enamel beads (Villaret, 1936) have all been used. Most of the non-blood substances have been used as a means of studying micro-embolism to the lungs, and it has not been suggested that this is the same as the clinical situation in man.

The effect of embolism involving larger pulmonary vessels

has been approached in several ways. Obstruction, by balloon occlusion of major pulmonary arteries (Arramendia et al., 1963; Brofman et al., 1957; Orsorio and Russek, 1962), and occlusion via a screw clamp placed around the outside of the pulmonary artery (Haggart and Walker, 1923; Gibbon, 1932) has been used to study haemodynamic changes taking place rather than to simulate pulmonary embolism as it occurs in man.

The first studies to report the effects of pulmonary embolism with blood clot derived material were those of Love et al. (1938) and de Takats et al. (1939). Love and his co-workers used blood clot coloured with India ink and de Takats used a mixture of blood clot and barium sulphate. Since then, although occasional investigators have reported the use of non-physiological substances in studying major pulmonary embolism (Allison et al., 1960) most investigators have used blood in one form or another. Hyman et al. (1964), Stein et al. (1965), Puckett et al. (1973) and Ozdemir (1974) have reported on autologous blood clot used as emboli, whils Wessler et al. (1961) and Stein et al. (1965) have used autologous blood clot formed in situ in a vein following the injection of specially prepared serum. In situ formation has also been reporte with thrombus and thromboplastin injected directly into the pulmona artery (Olsson et al., 1974).

Sabiston and his co-workers used a technique which involved damaging the intima of the inferior vena cava of the dog so that thrombosis occurred in the vessel over the ensuing days. The thrombus was then removed and used as pulmonary embolic material (Sabiston et al.,1962; Marshall et al., 1963; Sabiston and Wolfe, 1968). This technique has also been used by Vellar and O'Sullivan (1972). Of all the methods reviewed this latter technique is the only one which leads to thrombus production in flowing blood and

thus might be expected to form thrombi with similar characteristics to thrombi formed in man. Production of thrombi by this method has not been used in studying massive pulmonary embolism, as the amounts produced are not large enough. Thus in their 1963 report Marshall et al. found that introduction of these thrombi into the pulmonary artery of the dog did not lead to any acute respiratory or haemodynamic changes.

The method of thrombus production described in Section II similarly aims to form thrombus in flowing blood, but in large enough amounts to be used as massive pulmonary emboli.

SECTION I (b) A REVIEW OF THE HAEMODYNAMIC AND RESPIRATORY CHANGES OCCURRING IN PULMONARY EMBOLISM.

HAEMODYNAMIC CHANGES IN PULMONARY EMBOLISM

In 1889 Cohnheim first reported on the effects in the dog of slowly tightening a ligature around the pulmonary artery. He found that systemic blood pressure and jugular venous pressure did not alter until occlusion passed a critical point when arterial pressure began to fall and venous pressure to rise, leading to rapid death.

Haggart and Walker in 1923 produced graded occlusion of the left main pulmonary artery and the main pulmonary artery by means of a screw clamp applied around those vessels in cats. They found no significant variation in the general circulatory conditio of the animals until from 52 to 62% of the total cross sectional area was occluded. These results were confirmed in 1927 by Moore and Binger and then extended by Gibbon et al. in 1932 who showed that occlusion of up to 60% of the cross sectional area of the pulmonary artery was without significant effect on the arterial and venous pressure, that if 60-85% was obstructed then cardiac output fell whilst obstruction beyond 80% was fatal.

Fineberg and Wiggers (1936) also studied the effects of occluding the pulmonary artery in the dog by mechanical means. They showed a steady rise in pulmonary artery pressure until the right ventricle began to dilate. Then the right heart's contractile force diminished, systolic pressure fell, diastolic pressure rose and death occurred from right heart failure.

In 1939 de Takats et al. studied massive pulmonary embolism in the dog using blood clot mixed with barium sulphate, and they reported pulmonary hypertension to occur prior to death. In 1948 Hellems et al. injected lycopodium spores and measured

pressure increases in the pulmonary artery, and they ascribed some of the pulmonary hypertension to mechanical blockage of vessels and some to reflex vasoconstrictive effects.

The possibility of reflex pulmonary vasoconstriction occurring in pulmonary embolism was put forward by Leriche in 1937 and he advocated stellate ganglion blockade as a means of ameliorating the hypertension. Since then the reflex theory of origin of hypertension has been quite strong in the French literature and has had only intermittent support in the English speaking literature.

Daley et al. in 1951, using lycopodium spores as micro-emboli, stated that the pulmonary hypertension which they produced in dogs was related to mechanical blockage only, as embolizing the materia to one lobe produced no hypertension in the remaining lungs, while generalized embolism did cause pulmonary hypertension which was unaffected by prior sympathectomy and/or vagotomy.

Niden (1956) and Caldini (1965) both used microembolism in isolated dog lungs perfused at a constant rate. They showed that embolism with glass microspheres less than 250 μm in diameter caused an immediate rise in perfusion pressure followed by a secondary further increase, while embolism with larger microsphere caused an immediate rise in pressure without a secondary increase. They believed that mechanical blockage was leading to increased pulmonary artery pressure in both groups but only the smaller spheres caused the secondary increase in pressure, which they attributed to reflex vasoconstriction. Weidner et al. (1958) used plastic microspheres of graded size as microemboli. They found that with spheres greater than 100 μm in diameter a 750 mg dose was required to produce pulmonary hypertension. However with spheres less than 100 μm in diameter a dose of 100 mg was all that was needed to produce pulmonary hypertension. Dexter

et al. (1965) came to similar conclusions about the size of micro-emboli as they found that pulmonary hypertension occurred more rapidly when microspheres less than 170 μm in diameter were injected compared with spheres greater than 170 μm.

The role of the sympathetic nervous system in the causation of reflex vasoconstriction is controversial. As already mentione Leriche thought it vital whilst Daley did not. Price and his co-workers (1955) used barium sulphate as embolizing material in a heart-lung-head preparation of a dog and found that denervating the preparation reversed pulmonary vasoconstriction and therefore pulmonary hypertension and they found that both hexamethonium and sympathectomy had similar reversing actions. Niden et al. (1956) used glass beads as emboli to one lung of a dog whilst the other lung, with its nerve supply intact, was isolated from the circulation and perfused at a constant rate. Pulmonary vasoconstriction occurred in the normal lung following micro-embolism to it, and vasoconstriction also occurred in the vascularly isolated lung following microembolism to the normal lung. McEvoy et al. (1958) using a similar preparation were unable to reproduce these results and further they found pulmonary hypertension to be unaffected by sympathectomy.

Halmagyi et al. in 1961 used Ba SO_4 emboli in sheep and found that pulmonary hypertension was unaffected by antiserotonin and antihistamine type drugs but was reversed by isoprenaline.

It appears therefore that some substances used as micro-emboli in animals may cause reflex vasoconstriction. As well as sympathetic activity other suggested mechanisms for this vasoconstriction have been the direct effect of hypoxaemia (Sasahara, 1967), and the effects of serotonin from platelet aggregation (Comroe et al., 1966; Thomas et al., 1966, Ozdemir, 1974).

With larger vessel occlusion the work of Niden (1956), Weidner (1958) and Caldini (1965) has already been referred to and suggests that the situation may be different.

The early work of Cohnheim (1889), Haggart and Walker (1923), Moore and Binger (1927) and Gibbon (1932) has also been mentioned previously, and Aramendia et al. (1961, 1963) extended this work. They found that ligaturing one main pulmonary artery in the dog did not cause pulmonary hypertension whilst occluding a main pulmonary artery by inflating a balloon within it did lead to pulmonary hypertension. The pulmonary hypertension in this latter circumstance was unaffected by hexamethonium or guanethidin administration or prior sympathectomy but was completely abolished by injection of lignocaine into the region of the pulmonary vessel surrounding the balloon. Orsorio and Russek (1962) also found that distension of a large branch of a pulmonary artery produced pulmonary hypertension in the dog, even when flow was maintained through the distending balloon. Surgical clearance of the hilum of the involved lung prevented hypertension.

In 1963 Hyland and his co-workers again drew attention to the fact that the size of pulmonary vessel embolized was important in regard to the effects produced. They accepted that the evidence for micro-embolism causing reflex vasoconstrictive effects was convincing but found that if embolism was caused by particles which blocked small arteries (rather than arterioles) then the hypertension produced bore a direct relationship to the number of arteries embolized, i.e. the effect was directly related to mechanical blockage.

Daily et al. in 1966 used macerated autologous clot as embolus in a dose of 1.0 ml/kg. They found that this amount of embolus caused pulmonary hypertension and diminished cardiac output and that pre-treatment with isoprenaline, noradrenaline

and atropine had no effect on pulmonary haemodynamic changes, although all the drugs prevented a fall in cardiac output.

Williams et al. (1971), also using massive blood clot embolism, found that when the embolus was allowed to go to the left lung only, then pulmonary hypertension did not occur. When the same amount of embolus was allowed to go to both pulmonary arteries then pulmonary hypertension and often death would occur.

The observation that the unaffected lung was able to accommodate total pulmonary blood flow without difficulty had already been demonstrated by Ebert (1967) who had shown that as much as 75% of the normal lung blood flow could be perfused through only 18% of the pulmonary vasculature.

In spite of these findings several authors recently have suggested that mechanical blockage alone is not enough to explain the degree of pulmonary hypertension which occurs in pulmonary embolism (Levy et al., 1969; Woolverton and Hyman, 1973; Ozdemir et al., 1974). The last authors ruled out neural reflexes as an explanation for pulmonary hypertension by demonstrating similar changes with embolism in dogs who survived lung re-implantations. However pretreatment with reserpine and massive doses of heparin did ameliorate pulmonary hypertension somewhat and they concluded that serotonin release (as first suggested by Comroe in 1953) was the mechanism by which vasoconstriction occurred. Puckett et al. (1973) were unable to confirm these results and found that neither severe platelet depletion, nor reserpine nor heparin pretreatment had any effect on pulmonary hypertension following massive blood clot embolus.

In humans with pulmonary embolism both Leland and Sasahara (1965) and McDonald et al. (1972) reported that the degree of pulmonary hypertension appeared mainly related to the prior

cardiac status and the degree of mechanical obstruction as demonstrated angiographically.

On balance, the work of Niden, Caldini, Weidner et al., Hyland et al. and Dexter et al. makes it likely that micro-emboli to vessels of the size of arterioles or smaller leads to pulmonary hypertension and that reflex vasoconstriction plays a significant role in this hypertension. With larger emboli in animals the work of Hyland et al., Daily et al., Williams et al. and Ebert et al indicates that mechanical blockage is the most important factor in the production of pulmonary hypertension. In man, the clinical studies of Leland and Sasahara, and McDonald et al., indicate that mechanical obstruction is the important factor determining changes in pulmonary haemodynamic and respiratory parameters. Whilst reflex vasoconstriction or hormonal vasoconstriction may contribute to pulmonary hypertension their roles remain controversial.

RESPIRATORY CHANGES IN PULMONARY EMBOLISM

During the 1914-1918 war Dunn (1919) studied the physiologica responses of the airways to pulmonary embolism produced by starch grains in goats. This classic research established that micro-embolism causes rapid, shallow breathing which is abolished by vagotomy. These observations have been confirmed by Whitteridge (1950) and Widdicombe (1964).

Dunn also established that bronchconstriction occurred although this was not dependent on intact vagus nerves. Boyer and Curry in 1944 confirmed this when they observed a transient increase in intra-tracheal pressure and decrease in intra-pleural pressure after experimental pulmonary embolism, suggesting transient bronchoconstriction. Subsequent studies by Halmagyi and Colebatch (1961), Nadel et al. (1964) and Thomas et al. (1964)

established that embolism led to a fall in lung compliance but little change in airways resistance, indicating that broncho-constriction was confined largely to the small peripheral airways. Clarke et al. (1970) and Puckett et al. (1973) have confirmed this by directly measuring the diameter of airways using tantalum bronchograms after pulmonary embolism.

Much of the work establishing the respiratory changes has been carried out using microemboli but it appears that similar changes occur with large emboli from autologous blood clot (Stein et al., 1965; Thomas et al., 1964). Balloon occlusion of one pulmonary artery, both in animals and man, leads to increased pulmonary airways resistance and decreased compliance, functional residual capacity, and anatomic dead space in the occluded lung (Severinghaus et al., 1961, 1962; Swenson et al., 1961). These changes, indicating bronchoconstriction, were prevented by increasing the carbon dioxide content of the air ventilating the ischaemic lung. Bronchoconstriction has also been found to occur in reimplanted dog lungs indicating that the change in airways diameter is not of neural reflex origin (Allgood et al., 1968). Samanek and Aviado (1967), using isolated and denervated but perfused dog lungs, showed that alveolar carbon dioxide concentrations were critical in inducing changes in bronchomotor tone. They showed that hypoxaemia could cause bronchoconstriction by altering the carbon dioxide dissociation curve and thereby lessening alveolar CO_2.

A mechanism other than change in CO_2 concentration causing bronchoconstriction has been suggested by Thomas and his colleagues (1964, 1965, 1966). In a series of experiments in dogs, using autologous blood clot as embolus, they suggested that platelets aggregating on the surface of an embolus released serotonin which led to bronchoconstriction. They found that pre-treatment

with serotonin antagonists or heparin prevented bronchoconstriction However Puckett et al. (1973) when using autologous clot emboli in severely platelet-depleted dogs, or dogs pretreated with serotonin antagonists or using agar emboli on which platelets do not aggregate, were unable to prevent bronchoconstriction occurring.

Therefore it is accepted that terminal airways bronchoconstriction with a fall in lung compliance occurs following pulmonary embolism. The dog lung reimplantation experiments of Samanek and Aviado show that this bronchoconstriction is not a neurally mediated reflex but can be reversed by increasing alveolar carbon dioxide concentration in embolized areas of the lung. The role of serotonin release from platelets in bronchoconstriction remains controversial with Thomas et al. supporting the concept whilst evidence against its importance has been produced by Puckett et al. As with pulmonary vasoconstriction, the role of serotonin in airway changes remains uncertain.

SECTION II A METHOD FOR THROMBUS PRODUCTION

In 1927 Rowntree and Shionoya published an account of experiments in which blood was diverted through a shunt from the carotid artery to the jugular vein of the rabbit. The blood passed through a collodion tube and thrombi having similar microscopic structure to human thrombi developed in the tube. This method of thrombus formation in flowing blood was not used as a source for experimental pulmonary embolism until Sabiston et al. (1962) used the traumatized inferior vena cava of the dog to form thrombi - these being used subsequently to produce pulmonary emboli. This technique did not form large enough thrombi to produce massive pulmonary embolism and for this reason we sought to modify the technique of Rowntree and Shionoya using the dog as the experimental animal.

METHOD

General anaesthesia was induced in mongrel dogs with pentobarbitone sodium and the animals were maintained on positive pressure ventilation using an endotracheal tube. An oblique incision was made in the left side of the neck for isolation of the left common carotid artery. A vertical incision was used in the left inguinal region to expose the left common femoral artery. Using vascular clamps to produce temporary occlusion, a 10 mm woven dacron straight graft (USCI De Bakey graft) was anastomosed end-to-side to the left common femoral artery. A subcutaneous tunnel was then developed along the left thoracoabdominal wall so that the inguinal and neck incisions were in communication. All clot was expressed from the dacron graft which was passed through the subcutaneous tunnel. The graft was then anastomosed to the left common carotid artery in an end to side fashion. The common carotid artery was ligated dista

to the origin of the graft and the left common femoral artery was ligated proximal to the site of graft insertion, to promote brisk flow of blood through the graft (Figure 1).

In the initial part of our study blood flow through grafts was carefully monitored in ten animals. This was done by daily observation of the graft pulse and by serial arteriograms at times ranging from two hours to five days following graft insertion All animals were again anaesthetised within five days of graft insertion and their incisions were reopened. The carotid artery proximal to the graft and the femoral artery distal to the graft were ligated and the graft was removed with attached segments of carotid and femoral arteries. The graft was opened longitudinally (Fig. 2) and its contents were inspected, photographed and weighed. Comparison was made between the contents microscopic structure and the microscopic structure of pulmonary emboli obtained from post mortem examination in humans.

RESULTS

All animals survived graft insertion. In the ten dogs nine grafts remained patent for more than 24 hours. An arteriogram performed two hours after graft insertion in one animal showed early occlusion. Five days after graft insertion all grafts were removed and eight of the ten grafts were occluded at this time with occlusions having occurred between 24 hours and five days except in the one animal already mentioned. The grafts from the two animals in which occlusion had not occurred demonstrated a thick fibrin sleeve lining the interior of the graft, but no thrombus formation.

In the other eight animals thrombus occluded the graft. Microscopically it was found that thrombus which formed near the carotid inflow end of the graft demonstrated the most easily discernible layering of platelets and red cells. Thrombus from

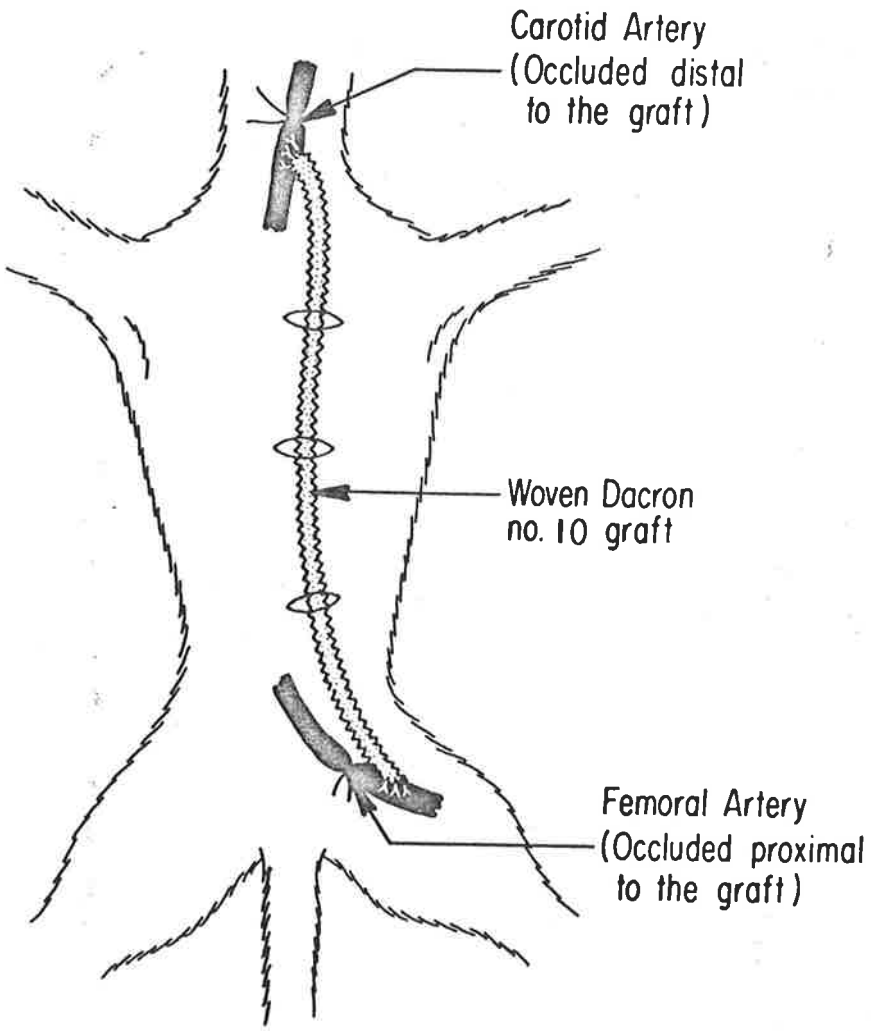


Figure 1

Diagram showing the dacron graft in position.

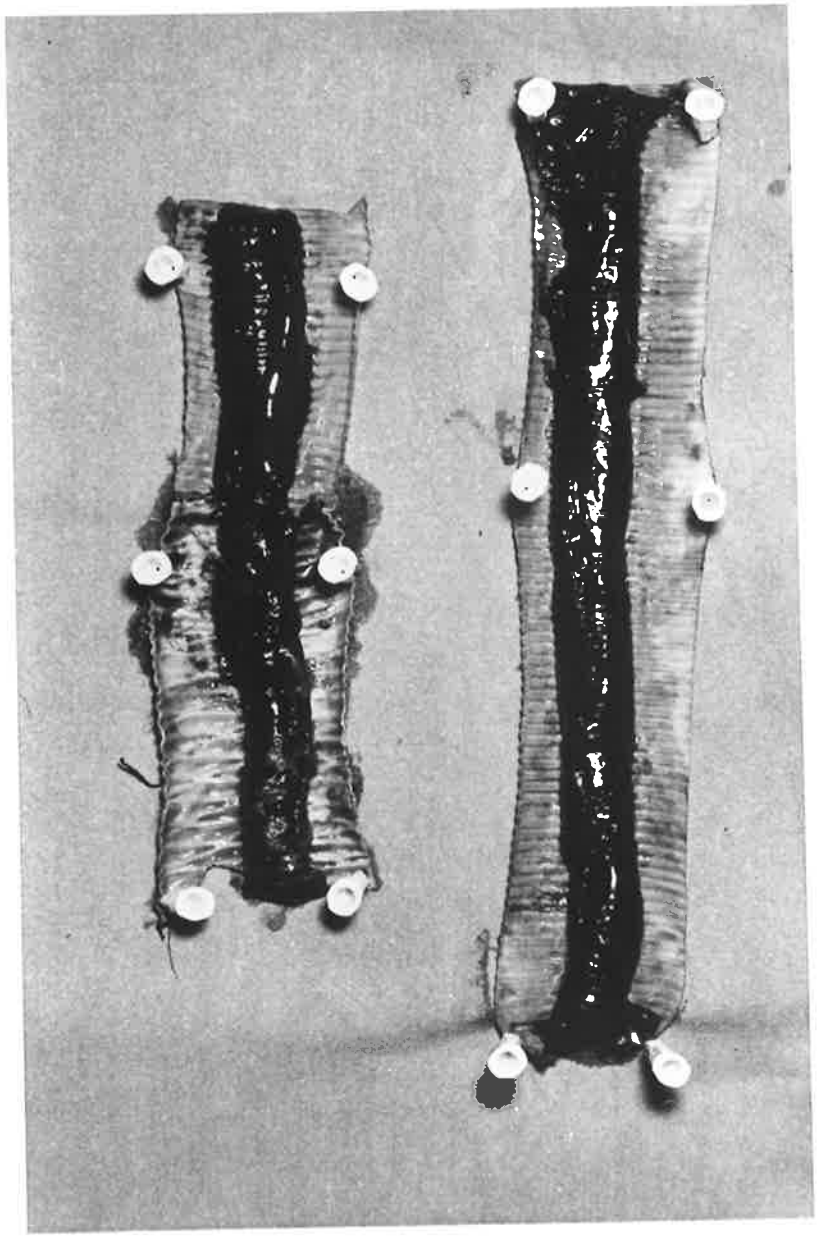


Figure 2

Thrombus shown within the graft with the graft laid open.

the distal portion of the graft frequently was uniform thrombus without obvious structure and in nature this was considered to be propagated clot.

The gross appearance of the thrombi harvested from the grafts was similar to thrombotic material recovered from the veins of patients with venous thrombi and/or pulmonary emboli.

Sufficient formed thrombus was present in all eight dogs with occluded grafts to provide a single intact embolus which was considered large enough to be a massive embolus in the dogs (Fig. 3 This will be discussed in more detail later.

DISCUSSION

Histologic examination of material recovered from pulmonary arteries of patients who die from pulmonary embolism, and of material obtained from veins of the legs of such patients, typicall demonstrates a thrombus which is organised into layers of fibrin with platelets and red cells enmeshed between (Fig. 4A). Interspersed with organised thrombus may be areas of less organised clot which commonly appear as aggregates of red cells (Poole and French, 1961; Florey, 1970).

Fresh clot formed in the absence of blood flow fails to demonstrate an organised arrangement and all blood components are distributed in a random uniform fashion (Fig. 5B). Histologic examination of thrombus formed in grafts implanted in these dogs showed a structure suggesting sequential layering of platelets, fibrin and blood cells which appears similar to the structure of human thrombi (Figs. 4C and 5D).

CONCLUSION

It was concluded that this preparation produced thrombi of similar microscopic structure to venous thrombi in humans and thus it seemed appropriate to use these as embolic material for the study of pulmonary embolism in the dog.

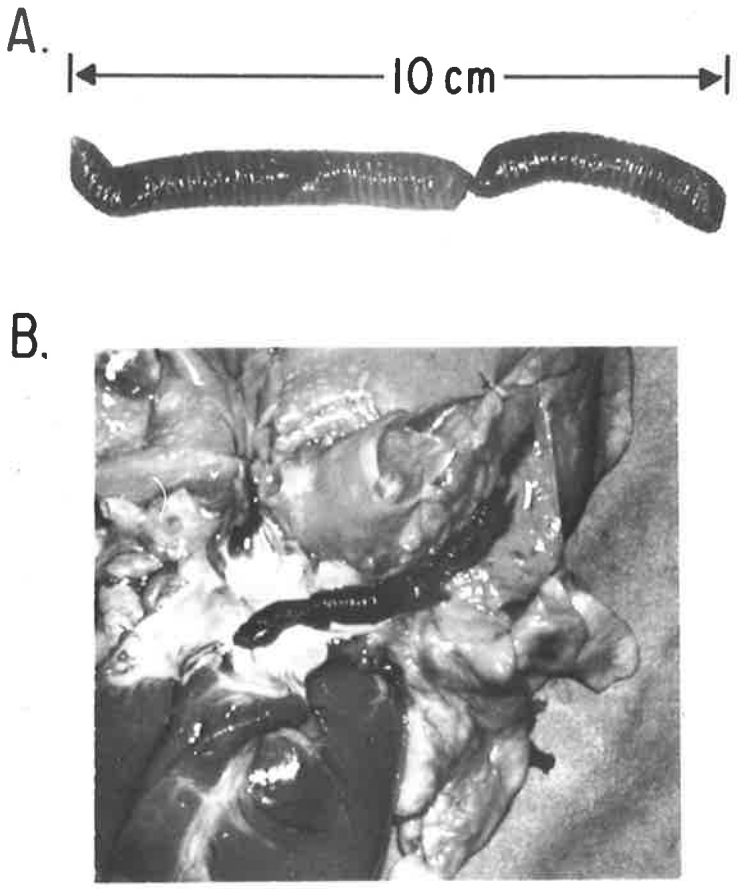
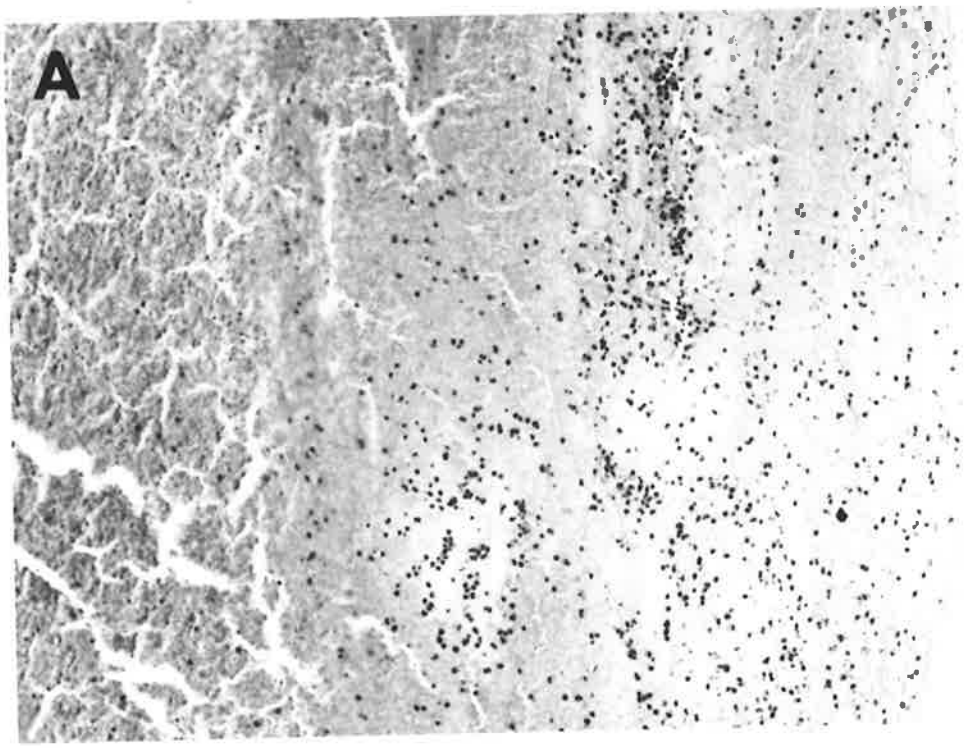


Figure 3

Graft induced thrombus (at top) and in situ in the main pulmonary artery and left pulmonary artery following embolism.



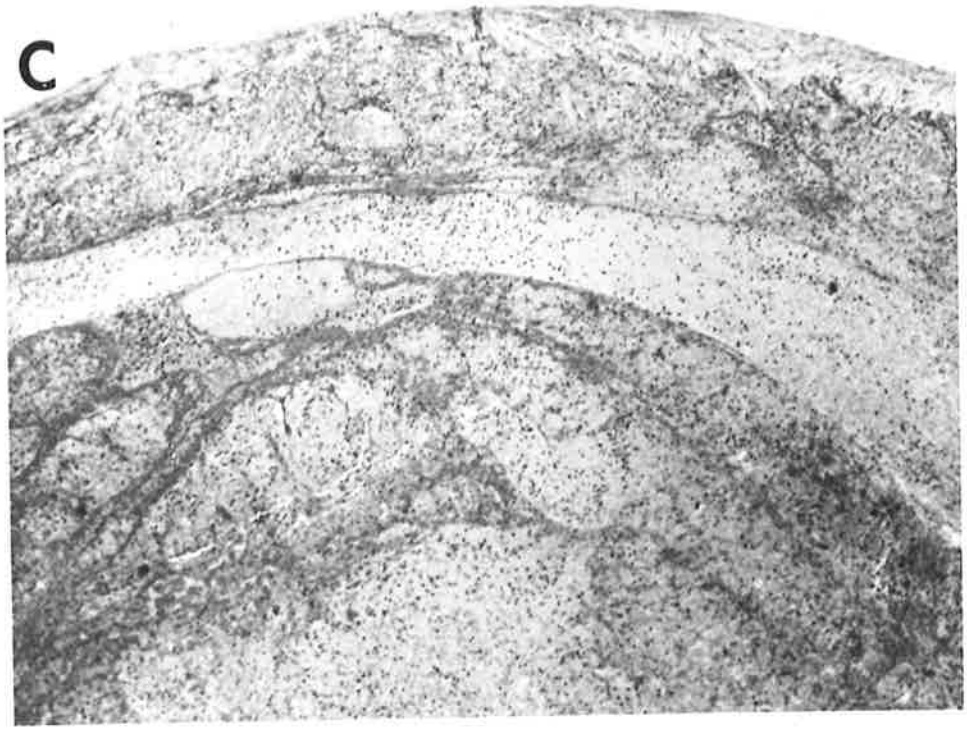


Figure 4

A Microscopic structure of pulmonary embolus from a patient. It shows fibrin layering, best seen on the right edge of the photograph (40x)

C Microscopic structure of graft induced thrombus showing coralline structure from fibrin bands (40x)

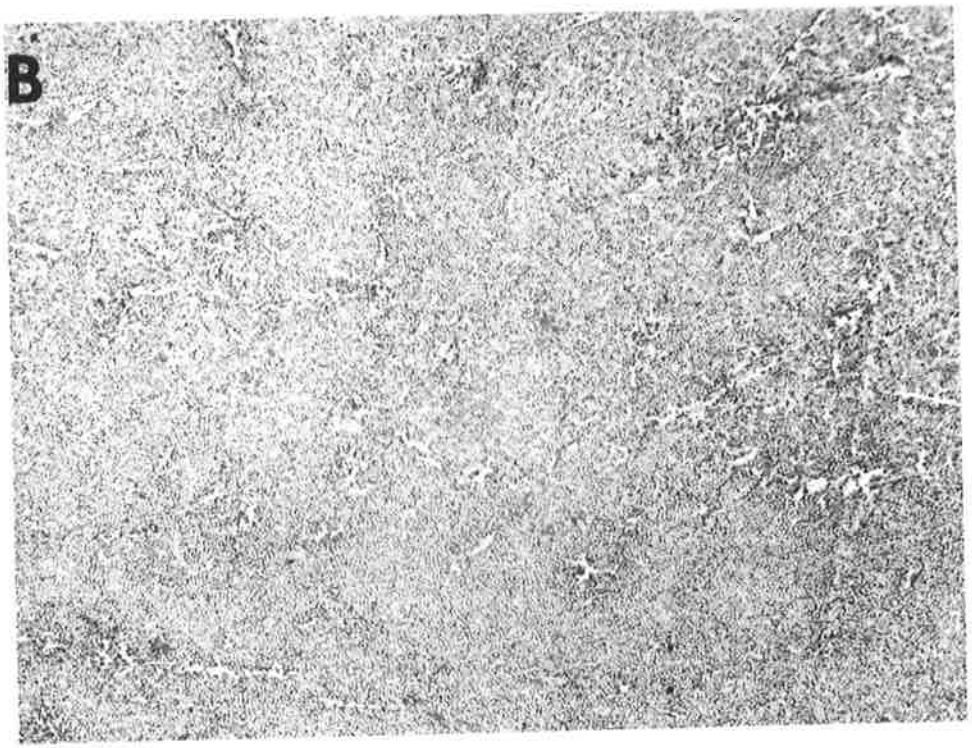


Figure 5

B Microscopic structure of blood clot showing the complete absence of any form or framework. (40x)

D Microscopic structure of graft induced thrombus showing fibrin layering. (40x)

SECTION III A STUDY OF PULMONARY EMBOLISM COMPARING AUTOLOGOUS BLOOD CLOT AND GRAFT INDUCED THROMBUS

Autologous blood clot has been widely used as material for studying the effects of pulmonary embolism (Wessler et al., 1961; Stein et al., 1965; Bloor et al., 1970; Puckett et al., 1973; Kimbel et al., 1973; Heimbecker et al., 1973; and Olsson et al., 1974).

We therefore compared the effect of autologous blood clot with graft induced thrombus when both were used as pulmonary emboli.

METHODS

Two groups of adult mongrel dogs were used. The animals were free of heart worms, their weights ranged from 16-25 kg and there were ten animals in each group.

The first group of ten animals had a graft inserted as described in the previous section, and then the graft was removed on the fifth postoperative day and thrombus was removed from the graft, weighed and placed in normal saline. The second group of ten animals had autologous clot prepared by taking 50 ml of venous blood from each animal and placing it in polyethylene tubes with an internal diameter of 10 mm. To this blood 30 units of bovine thrombin was added. Clotting occurred rapidly in the tube and incubation of the clot at room temperature for 90 minutes allowed clot retraction to occur. Serum was then decanted from the tube and the retracted clot was weighed and placed in normal saline, awaiting use.

The ten dogs used in the autologous clot part of the study were further subdivided into two groups of five. In one group a graft was inserted in the usual way but this was discarded on

removal five days later. The other group of five dogs had no such graft insertion and they were used in the experiments without any prior operative procedure having taken place.

All animals were anaesthetised with pentobarbitone sodium and maintained on positive pressure ventilation using an endotracheal tube. In animals which had previously had a graft insertio the first step was to remove the graft and if necessary harvest the thrombus. A polyethylene cannula was inserted into the right femoral artery for continuous monitoring of systemic blood pressure A left thoracotomy was performed, the pericardium opened and a polyethylene catheter (RACATH, 8F, USCI, 10616) was inserted into the left atrium through the left atrial appendage. A catheter (RACATH 8F, USCI, 10616) was also placed directly into the pulmonar artery and an appropriately sized micron RC1000 electromagnetic flow probe was positioned about the pulmonary artery. Thus pressure measurements were obtained from the left atrium, pulmonary artery and right femoral artery, using P23DB pressure transducers the signal from which was amplified and continuously recorded on a Hewlett-Packard 7,700 8-channel heat stylus recorder. The signal from the flowmeter was continuously recorded on the Hewlett-Packard instrument. Calibration of flow measurements had been previously validated by direct determination of saline flow through tubes constructed from fine rubber membrane. In addition to these measurements endotracheal pressure was also monitored using a small catheter passing internally in the endotracheal tube and connected to a Statham P23DB pressure transducer. A chest tube was inserted and connected to an underwater seal drain and the thoracotomy wound was then closed. During the course of the experiment 500-1000 ml of normal saline was administered intravenously at a slow rate (Fig. 1).

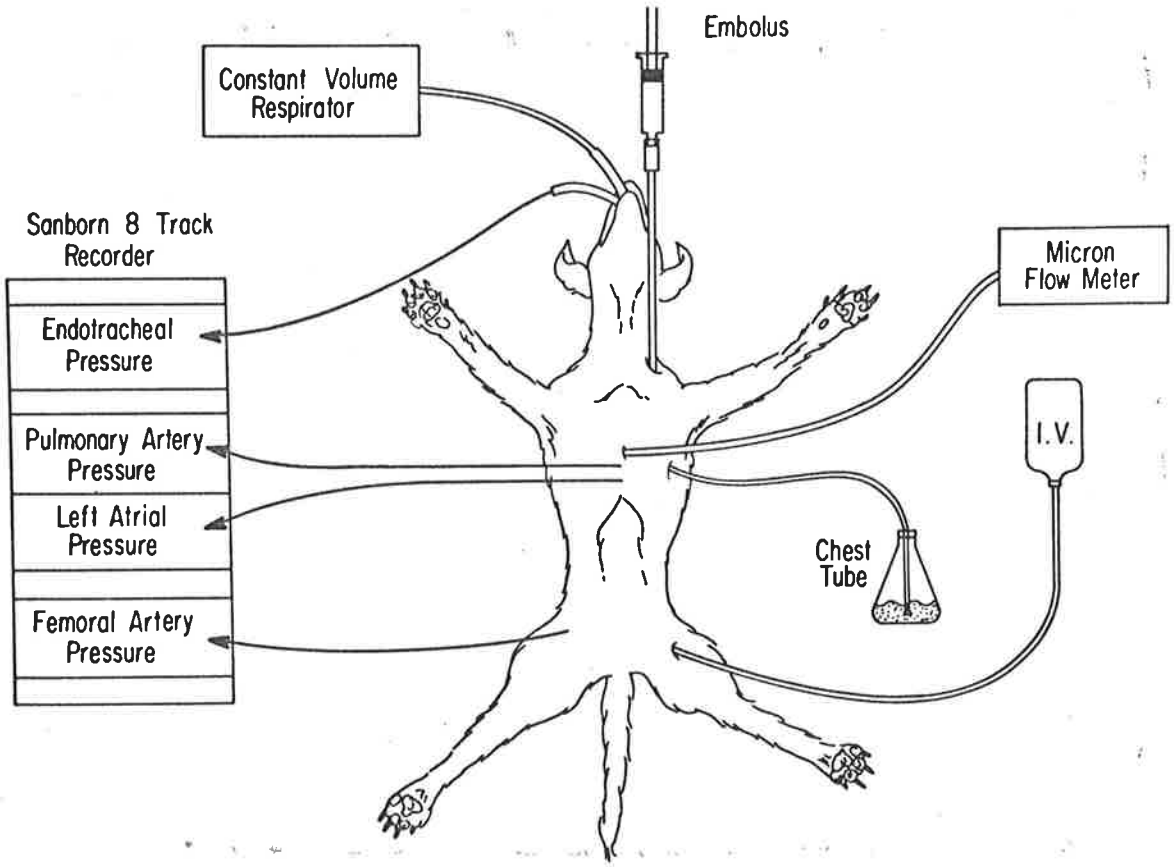


Figure 1

Diagrammatic representation of the measurements made during the study.

A weighed embolus of 0.2g/kg animal weight of retracted autologous clot or graft induced thrombus was suspended in saline and placed in a rigid plastic tube with an internal diameter just greater than 10 mm. A plunger was adapted to the tubing to aid introduction of the clot into a vein. Haemodynamic and ventilatory measurements were obtained during a stable control period following which an embolus was introduced through the previously exposed internal jugular vein.

Haemodynamic measurements were made continuously during introduction of the embolus and for a 120 minute period following embolism. Using a calibrated fixed volume respirator endotracheal pressure was determined immediately before and after cessation of air flow at tidal volumes of 100, 200, 300, 400, 500 ml respectively. The dynamic and static compliance at each of these volumes was calculated and the five values were then averaged (Comroe et al., 1971).

In both groups of ten dogs, one dog died or was killed at 20 minutes following embolism, three dogs died or were killed 60 minutes following embolism and six dogs died or were killed at 120 minutes following embolism. Each animal was systemically heparinised at the end of the study and following death the heart and lungs were removed en bloc. The heart was opened and examined for thrombus. The main pulmonary artery and all branches of sufficient size to be examined by gross dissection were opened and the distribution of thrombi recorded.

The total quantity of embolic material recovered from the heart and lungs was weighed. From the continuously recorded haemodynamic data, determinations of mean pulmonary blood flow and pressure, mean left atrial pressure and systolic and diastolic systemic pressure were obtained at -40, -5, 5, 20, 40, 60, 90, 120

minutes relative to the time of pulmonary embolism. Pulmonary vascular resistance was calculated from the difference between the mean pulmonary pressure and the mean left atrial pressure divided by pulmonary blood flow. A statistical analysis of data was performed within and between groups using a two tailed Student t test.

RESULTS

The average weight of recovered embolic material in 10 animals that received fresh clot was 26.6 ± 12.8% and in 10 animals receiving graft induced thrombus was 60.3 ± 18.2% of the original weight of embolic material injected. There was no tendency for either type of embolus to fragment.

Systolic and diastolic blood pressure did not change systematically following either type of pulmonary embolism (Fig. 2) although two animals died in the thrombus group at 20 minutes and 58 minutes respectively after the embolus and a further two sustained a transient hypotension in the thrombus group.

Pulmonary artery pressure increased following embolism in both groups and the magnitude of increase was greater in the thrombus group compared to the clot group ($p < .01$) (Fig. 3). Within 60 minutes of embolism the pulmonary artery pressure returned to pre-embolic levels in the clot group. Although pulmonary artery pressure did decrease over the same period of time in the thrombus group, the pressure remained above pre-embolic levels throughout the period of the studies (p always $< .01$).

Pulmonary blood flow decreased slightly in the dogs embolised with clot ($p > .05 < .10$) but again this was much more marked in the dogs embolised with thrombus ($p < .01$) (Fig. 4).

Calculation of pulmonary vascular resistance from pulmonary blood flow and pulmonary and left atrial pressure measurements

Note: In this and following figures points represent a mean value They are accompanied by the positive and/or negative value of the standard error for that mean.

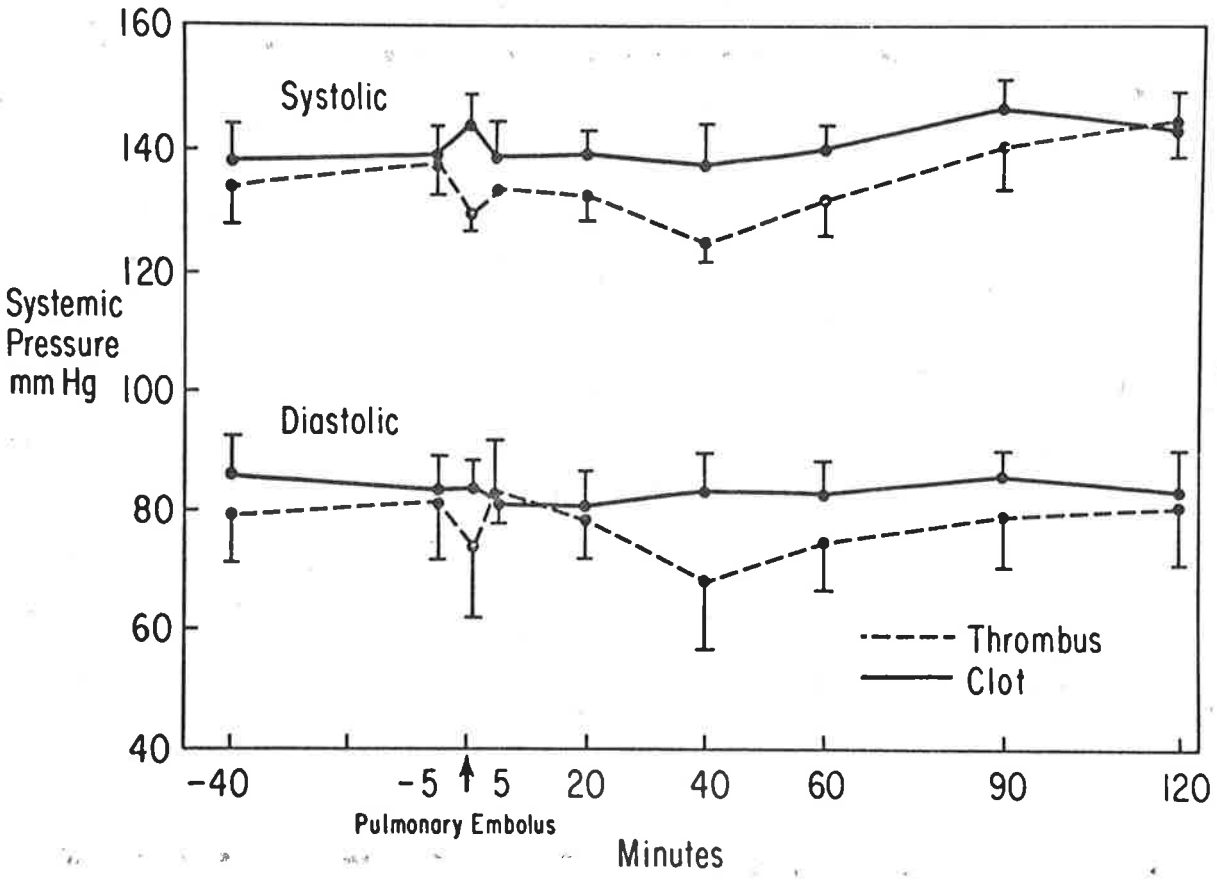


Figure 2

Systemic blood pressure following pulmonary embolism.

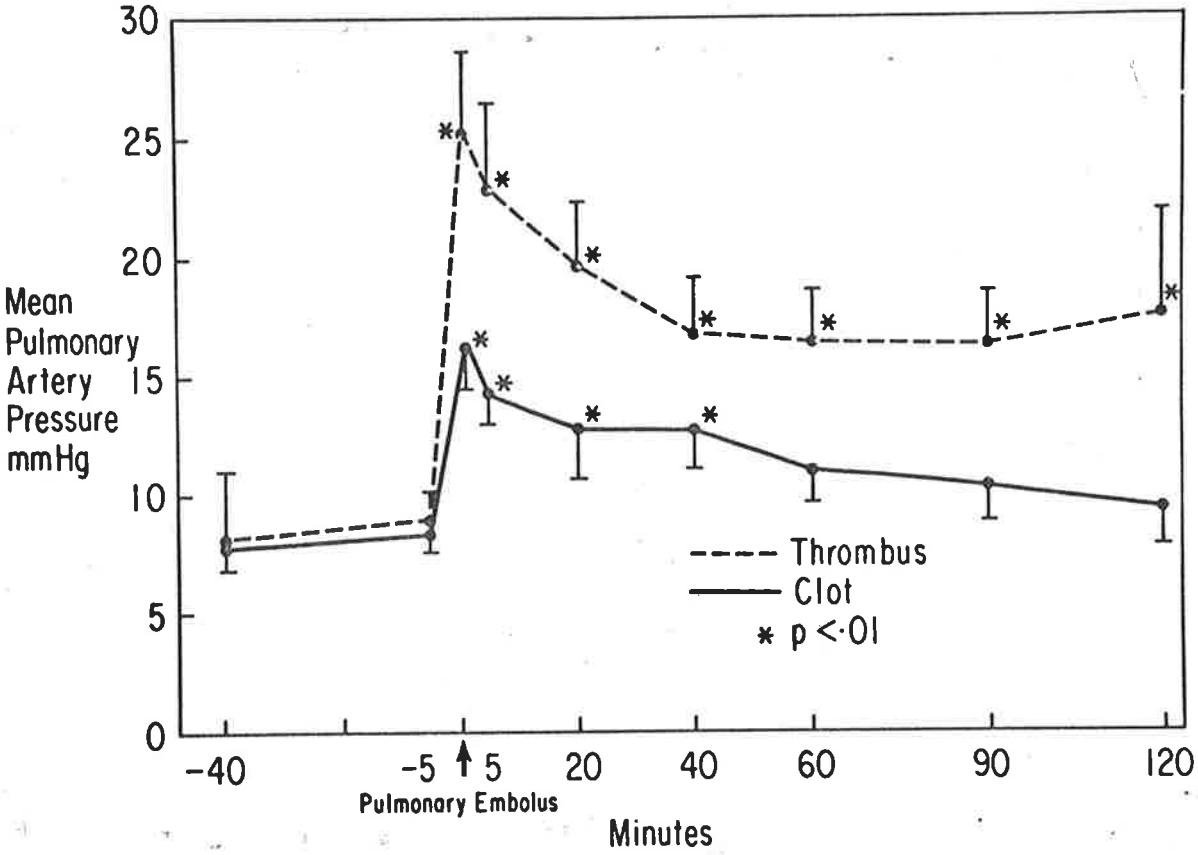


Figure 3

Mean pulmonary artery pressure following pulmonary embolism. The significance values refer to the pre-embolic levels in the respective groups.

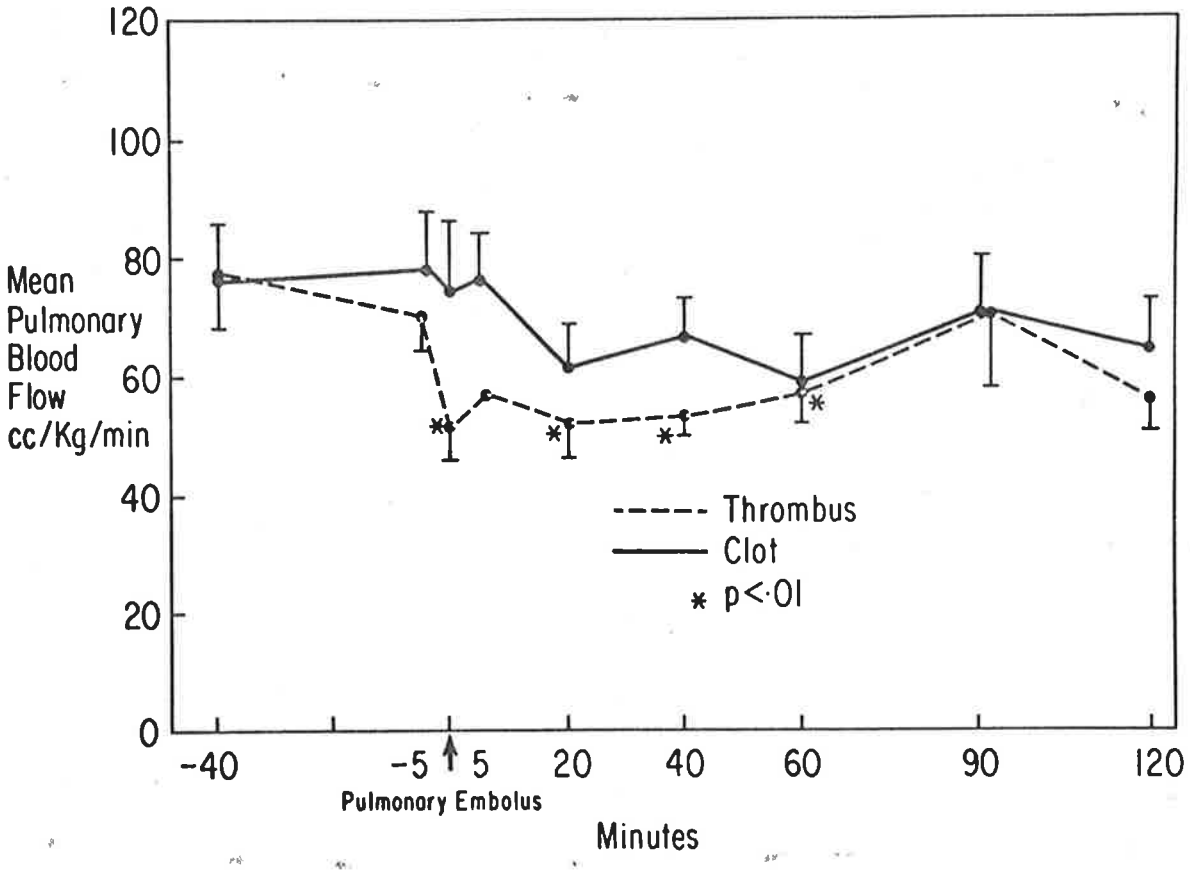


Figure 4

Mean pulmonary blood flow following pulmonary embolism. The significance values of the various points are in reference to the pre-embolic blood flows in the respective groups.

reflected the alterations already alluded to in these measurements (Fig. 5). Pulmonary vascular resistance remained elevated for only 20 min in dogs embolised with clot whereas the resistance remained elevated for the entire period of study in animals embolised with thrombus. The pulmonary vascular resistance increase was almost three-fold greater in the latter group of dogs.

Left atrial pressure increases following embolism were small in both groups - but again the increases were only at the 1% level of significance in the thrombus group (Fig. 6).

Graft induced thrombus caused substantial decreases in static and dynamic lung compliances ($p < .01$) whilst fresh clot produced smaller and less sustained falls (Fig. 7).

DISCUSSION

Many studies in pulmonary embolism have used autologous clot either formed in situ or outside the animal, the clot being used as the embolising agent. However clot which forms in a static column of blood has different characteristics from thrombus formed in situ (Poole and French, 1961) and so it is perhaps not surprising that autologous blood clot will differ from thrombus when used as a pulmonary embolus. This study indicates that graft-induced thrombus is a much more severe insult to the pulmonary vasculature than autologous clot when a similar weight of embolic material is used.

Two out of the ten dogs in the thrombus group died following embolism and two more developed transient hypotension. No such findings occurred in the autologous clot group and there was no change in their blood pressure immediately following embolism or subsequently.

In spite of the massive nature of the pulmonary emboli as shown in Fig. 8 there was no sustained fall in mean blood pressure

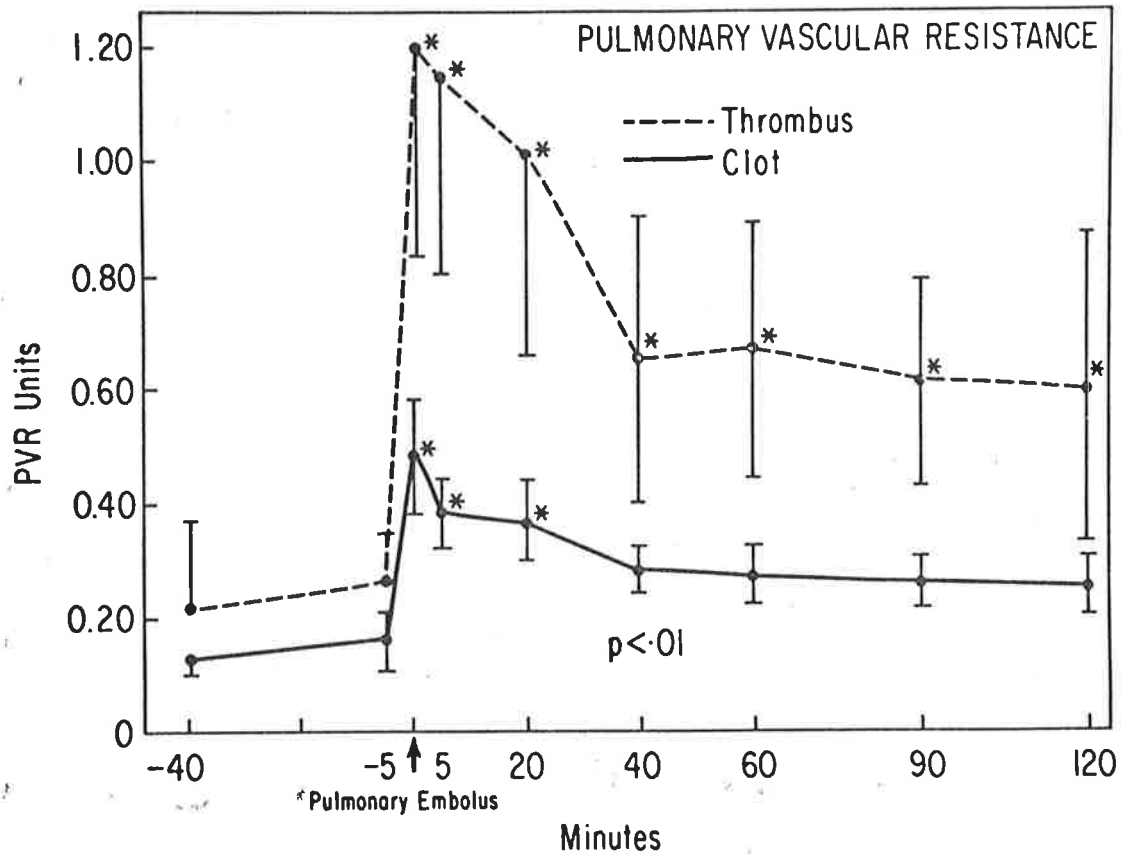


Figure 5

Pulmonary vascular resistance following pulmonary embolism. (Resistance units are arbitrary units used when pressure is measured as mmHg instead of dynes/cm^2).

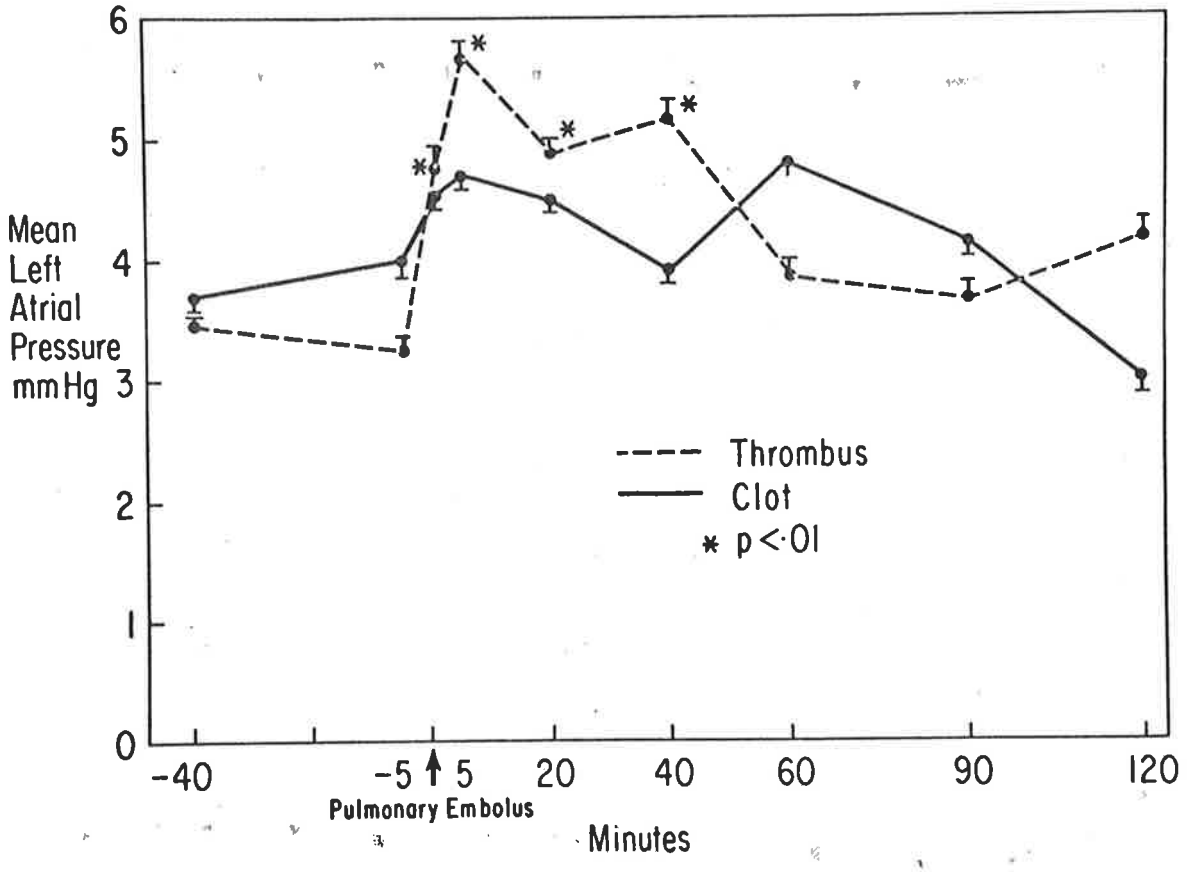
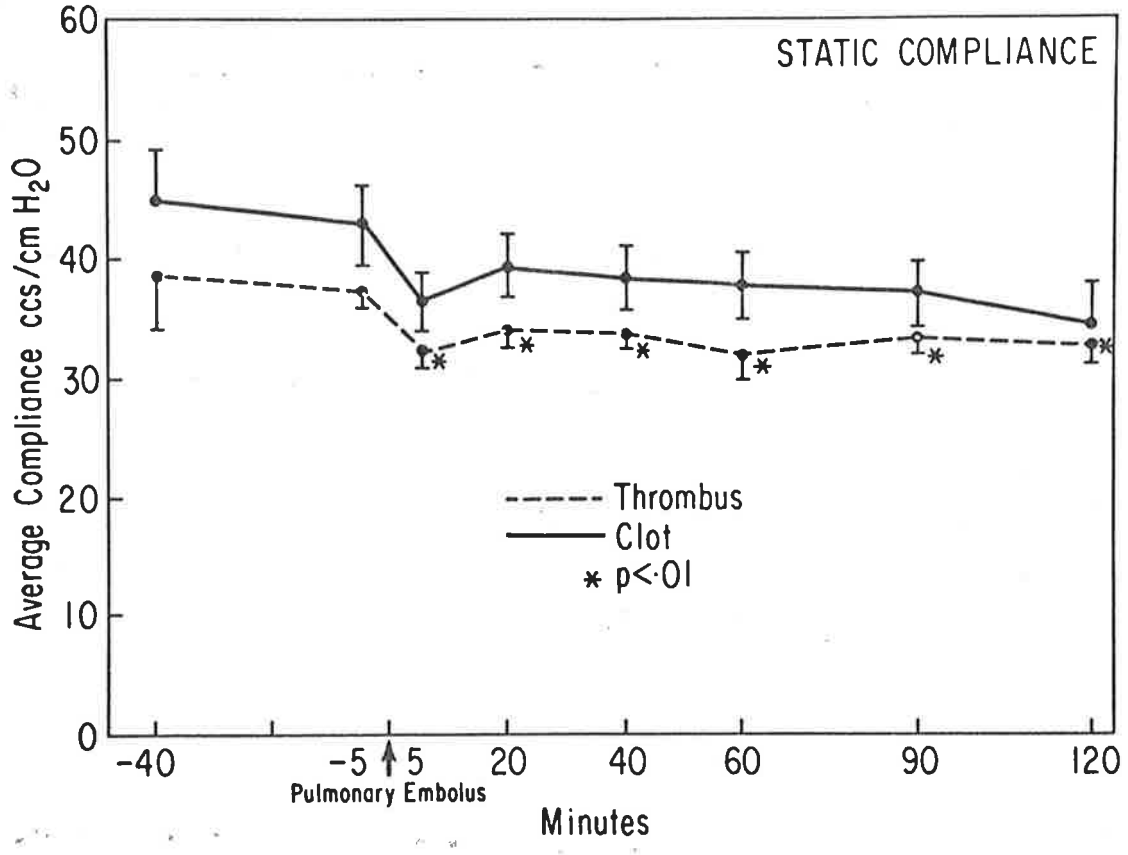


Figure 6

Mean left atrial pressure following pulmonary embolism.



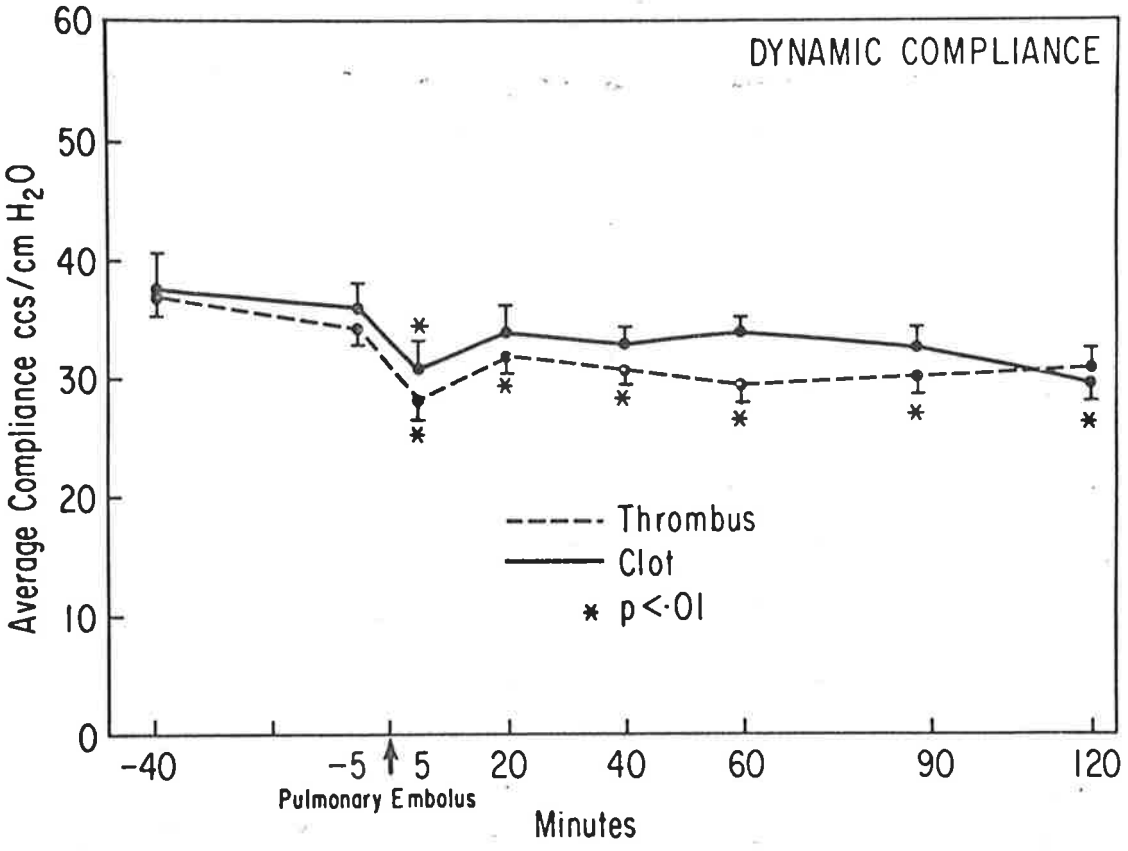


Figure 7

Static and dynamic lung compliance following pulmonary embolism.

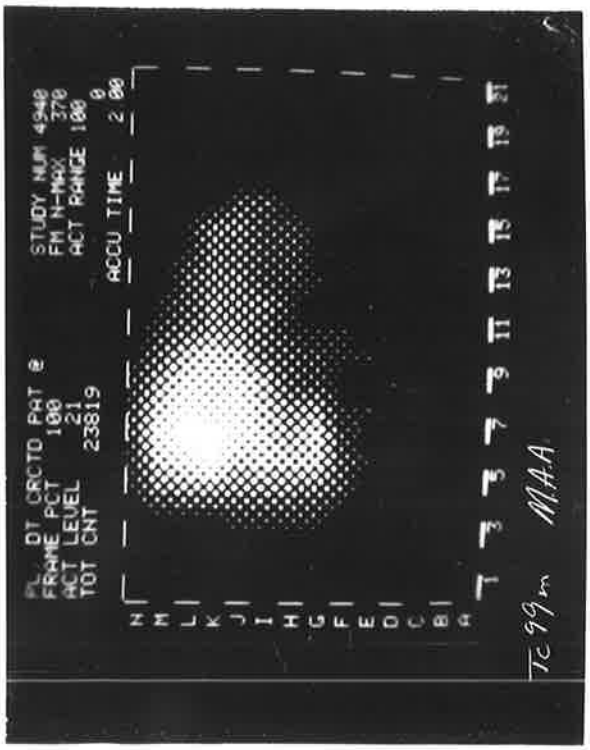


Figure 8. This shows a perfusion lung scan in a dog following a massive pulmonary embolism (which is shown at autopsy) demonstrating the large amount of blood flow which can take place around an embolus.

in either of the two groups following embolism (with the exception of the two dogs which died and whose measurements have been excluded from the blood pressure study). As pulmonary blood flow and therefore by inference, cardiac output, fell substantially in both groups it is evident that an increase in peripheral resistance occurred to maintain blood pressure.

Pulmonary blood flow returned toward normal in both groups - this in spite of the large emboli found at autopsy. This means that either the unobstructed pulmonary bed conducted a much greater amount of blood than prior to embolisation or that blood was able to flow around the embolus. That the latter can occur is shown in Fig. 8, which shows a massive pulmonary embolus and a perfusion lung scan taken following embolism in the animal. It is evident that in spite of the large embolus in the pulmonary artery considerable perfusion of the lungs was taking place. Furthermore, it has previously been demonstrated that total occlusion of one main pulmonary artery does not necessarily alter pulmonary blood flow (Brandfonbrener et al., 1958) indicating that unobstructed pulmonary vasculature can greatly increase the amount of blood flowing through it.

The steep rise in pulmonary artery pressure after autologous blood clot embolism is evanescent and this has previously been noted (Bloor et al., 1960; Puckett et al., 1973; Kimbel et al., 1973). With autologous thrombus the rise in pulmonary artery pressure is much greater and although it falls from the very high levels which occurred immediately after embolism it remained elevated above pre-embolism levels for the duration of the study.

The reason for the elevation in left atrial pressure is obscure. As there was no systematic increase in systolic pressure the elevation was not due to increased afterload. Perhaps the

momentary fall in right to left blood flow leads to hypoxic depression of the left ventricle and left ventricular failure of short duration. Once again it was only in the graft induced thrombus group of dogs that significant left atrial pressure elevation occurred.

Pulmonary vascular resistance increased greatly in both groups with the increase being greater in the thrombus group. Autopsy examination showed there was little tendency for the embolus to fragment in either group and so the increased vascular resistance at least in part was directly related to the mechanical blockage by the embolus. With time an important added factor leading to a fall from the high levels immediately following embolism would be the diminution in size of the embolus by lysis.

A fall in static lung compliance following pulmonary embolism has been noted previously (Halmagyi and Colebatch, 1961; Thomas et al., 1964; Stein et al., 1973) and occurred in both groups of dogs although the fall was only significant at the 1% level in the graft induced thrombus group. The same authors also noted changes in dynamic compliance and in this study dynamic compliance fell with changes again being greater in the graft induced thrombus group.

Perhaps the finding which most highlights the difference between the two types of emboli is the reduction in their size which occurred over the two hours of the study. Only about a quarter of an autologous clot embolus was recoverable whilst about three-quarters of a thrombus embolus was usually found (Figs. 9, 10). This reduction in size is a ready explanation for the longer term changes induced by embolism in the graft induced thrombus group of animals, but the reasons why the acute changes should be more severe in the thrombus group are not quite so readily apparent. Perhaps the softer autologous clot emboli

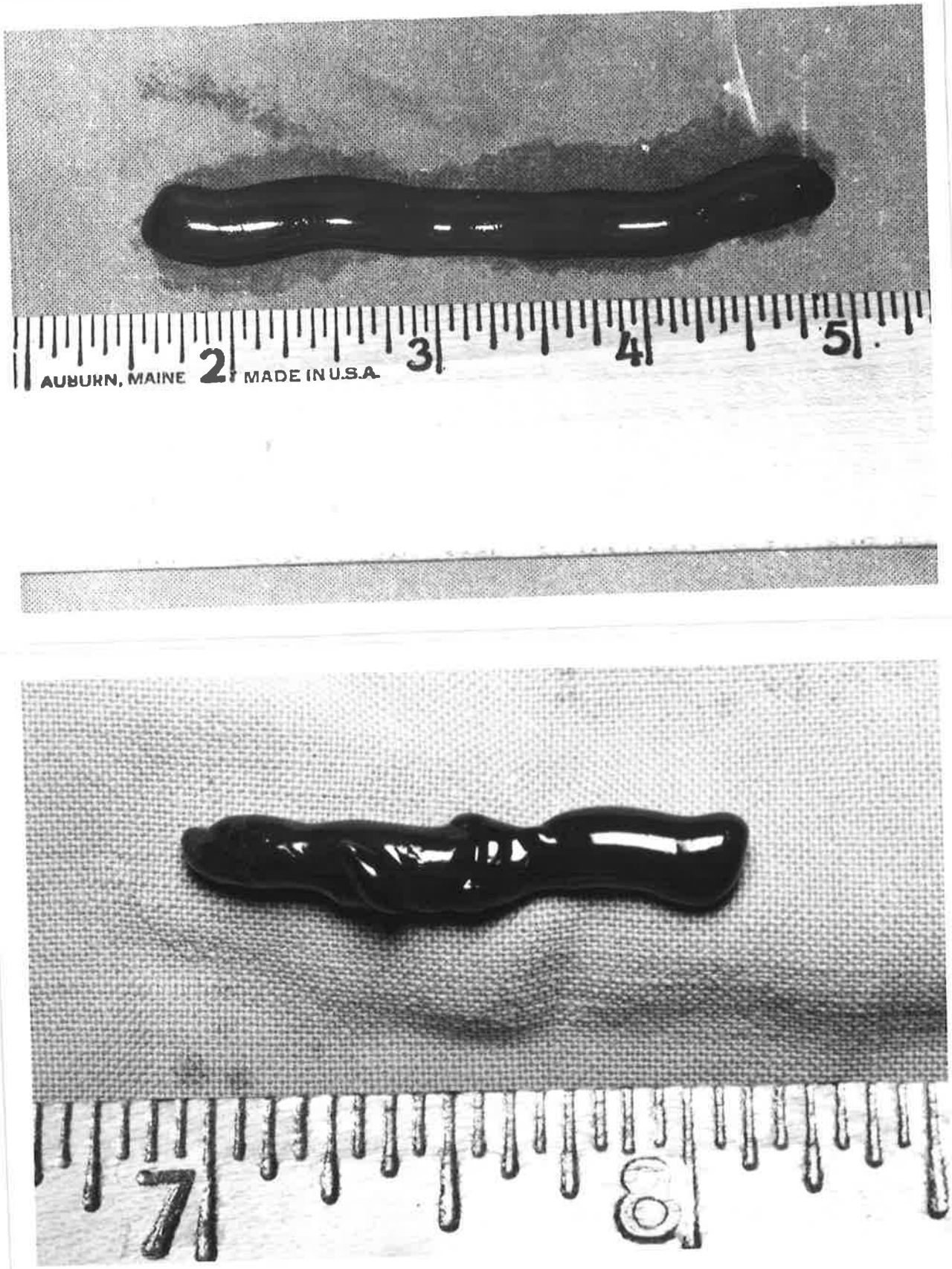


Figure 9

Autologous blood clot embolus before and after embolisation.

Top photograph : Before = 5 gm

Bottom photograph : After = 1.2 gm

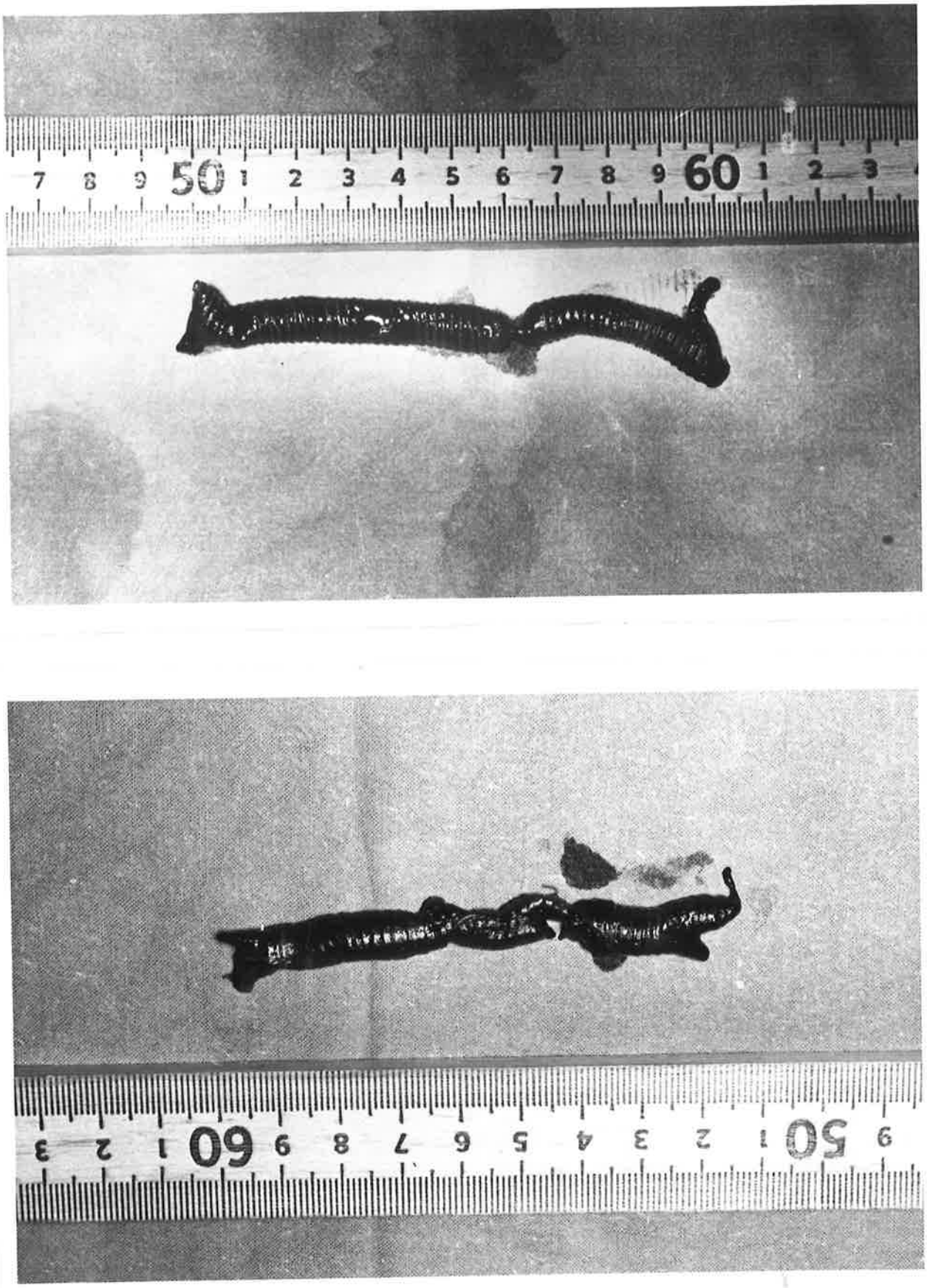


Figure 10

Graft induced thrombus before and after embolisation.

Top photograph : Before = 4.8 gm

After = 4.0 gm

allowed more blood to flow around them.

This study indicates that thrombus formed in flowing blood when used as a pulmonary embolus in dogs is a much more severe event than is autologous clot used in a similar manner. Use of this preparation for the production of pulmonary emboli may more accurately reflect the changes of massive and potentially fatal emboli in man, than other models which have been used.

SECTION IV THE INFLUENCE OF HEPARIN AND ISOPRENALINE ON THE CHANGES PRODUCED BY PULMONARY EMBOLISM

As mentioned in the introduction the majority of patients who die as a result of pulmonary embolism do so within two hours of the embolus occurring.

We have seen that graft induced thrombus induces marked changes in haemodynamic and respiratory function when embolised into the pulmonary artery of the dog.

Heparin is a drug which is in widespread use in pulmonary embolism and its place has been largely unchallenged since the small prospective study of Barritt et al. (1960) showed that 5 of 19 untreated patients died of a further pulmonary embolus and a further 5 had a non-fatal embolus whilst only one patient died in 16 patients who were heparinised - and that patient died of gastro-intestinal bleeding - and there were no recurrent emboli in the treated group.

However heparin is often not given for some hours after embolism has occurred (whilst the diagnosis is being established) and during this time the patient may die. The purpose of this study was to see in what way heparin modified the acute embolic effects in the crucial first hours after embolisation.

McDonald et al. (1968) have reported favourably on the use of isoprenaline in acute massive pulmonary embolism and yet in spite of their report it is not used as frequently as heparin. In this study we also observed its effects in the first two hours following embolism.

METHOD

Thirtytwo adult mongrel dogs free of heart worms and weighing between 14-24 kg were used in this part of the study. One group of 11 dogs served as controls, 11 dogs receiving isoprenaline

and 10 dogs heparin - beginning 30 minutes after embolism.

The previously described technique for thrombus generation, using a 10 mm dacron graft between the left carotid and left femoral artery was used to produce thrombus in all animals.

Experimental pulmonary embolism was induced as described previously and systemic blood pressure, left atrial pressure, pulmonary artery pressure, endotracheal pressure, and pulmonary artery blood flow were all monitored throughout the study.

Haemodynamic and ventilatory measurements were documented for a stable control period prior to introduction of the embolus through the internal jugular vein and then for a 120 minute period following embolism. Pulmonary vascular resistance was calculated from mean pulmonary pressure, left atrial pressure and pulmonary blood flow. The respirator was calibrated as described previously for the measurement of static and dynamic compliance. Arterial blood gases were determined at 20 minute intervals throughout the study with animals breathing room air.

An arteriovenous shunt fraction was calculated by having the animals breath 100% oxygen for a period of 20 minutes before embolism and again just prior to completion of the study, with blood samples taken at appropriate times. All animals received a slow saline infusion throughout the study. The control animals received nothing further. In the second group of dogs isoprenaline infusion was begun 30 minutes after embolism beginning at a dose of 1 µg per minute and slowly increasing the dosage until cardiac arrhythmia occurred, or until a rate of 2 µg per minute was reached. Most animals tolerated this rate without developing arrhythmias. The third group of animals were heparinised by giving a single intravenous dose of heparin of 500 u/kg 30 minutes after embolism.

Observations were terminated 120 minutes following embolism and the control and isoprenaline treated animals were heparinised. All animals were then killed and the heart and lungs were removed en bloc. The cardiac chambers, main pulmonary artery and all pulmonary branches with sufficient size to be examined by gross dissection were opened to determine the distribution and total weight of thrombus. All data were subjected to statistical analysis within and between groups using a two tailed Student t test. Means are usually accompanied by the positive and negative standard error.

RESULTS

The weight of recovered embolic material in the control animals was 69.2 ± 8.2%, and in the isoprenaline treated dogs 71.4 ± 12.6%. In the heparin treated group recovered weight was 52.0 ± 10.7% and this was significantly less than the other two groups ($p < .05$).

The shunt fraction rose from 25.5 ± 8.4% to 28.3 ± 6.1% in the control group, from 38.6 ± 13.4% to 41.8 ± 15.8% in the isoprenaline treated group and 35.5 ± 16.1% to 41.8 ± 15.9% in the heparin group. P was > .05 in regard to these differences.

Systemic blood pressure did not decrease significantly in any of the groups and an increase occurred in the animals treated with isoprenaline after perfusion was begun. Pulmonary artery pressure increased following embolism and remained elevated for the duration of the study in all groups ($p < .01$) (Fig. 1).

Pulmonary blood flow decreased after embolism in all groups. However, it was only in the isoprenaline treated group that rapid return of blood flow towards normal occurred (Fig. 2). Pulmonary vascular resistance remained greatly elevated throughout the study in all groups (p always < .01) (Fig. 3).

Static and dynamic lung compliance fell in all animals following embolism ($p < .01$) and remained low in the control and

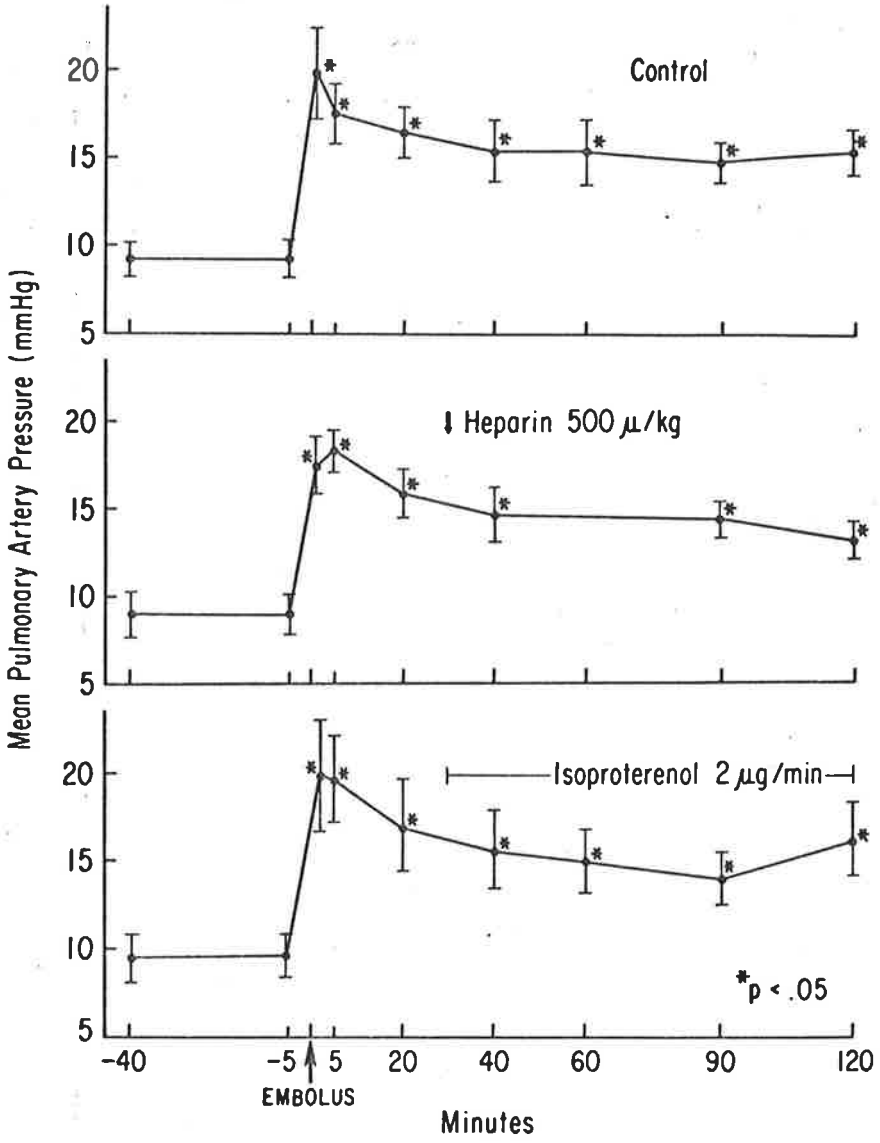


Figure 1

Mean pulmonary artery pressure following pulmonary embolism in control, heparin treated and isoprenaline (isoproterenol) treated groups of dogs.

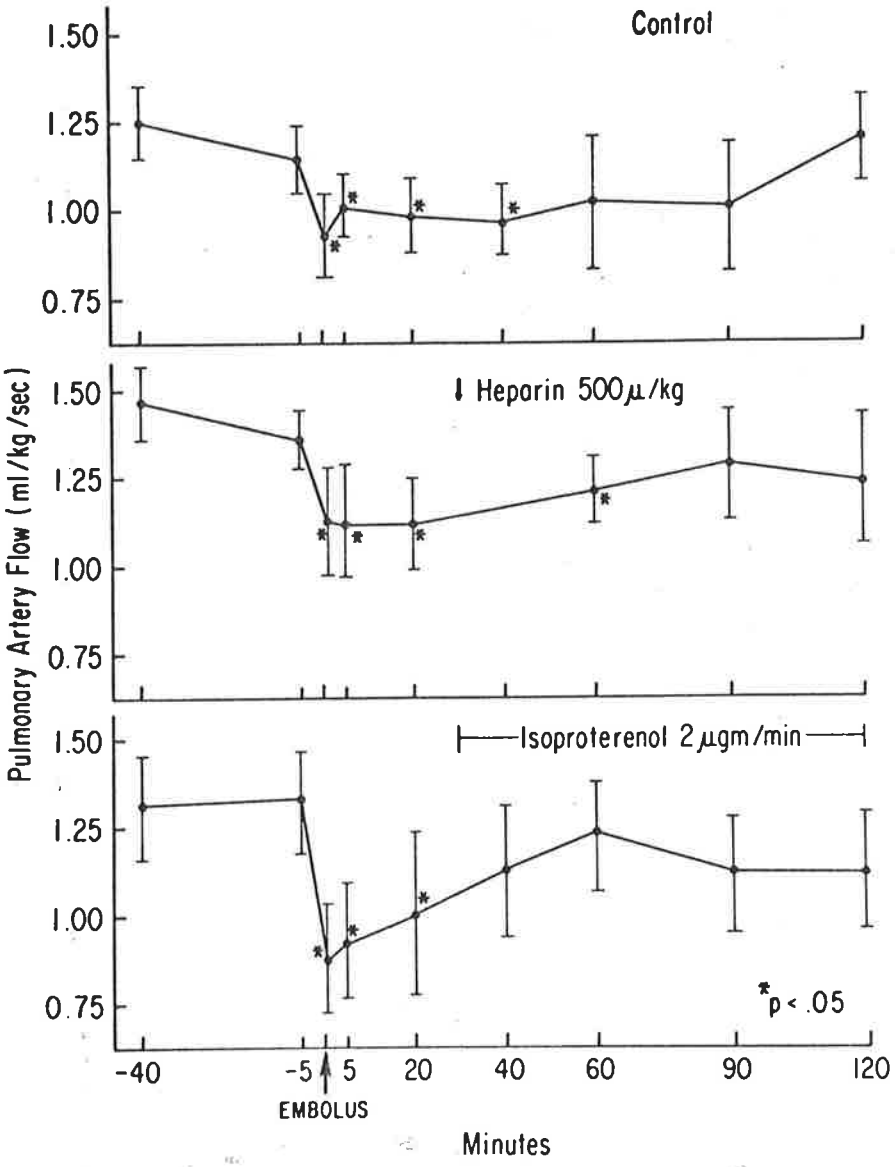


Figure 2

Mean pulmonary blood flow following pulmonary embolism in control, heparin treated and isoprenaline (isoproterenol) treated groups of dogs.

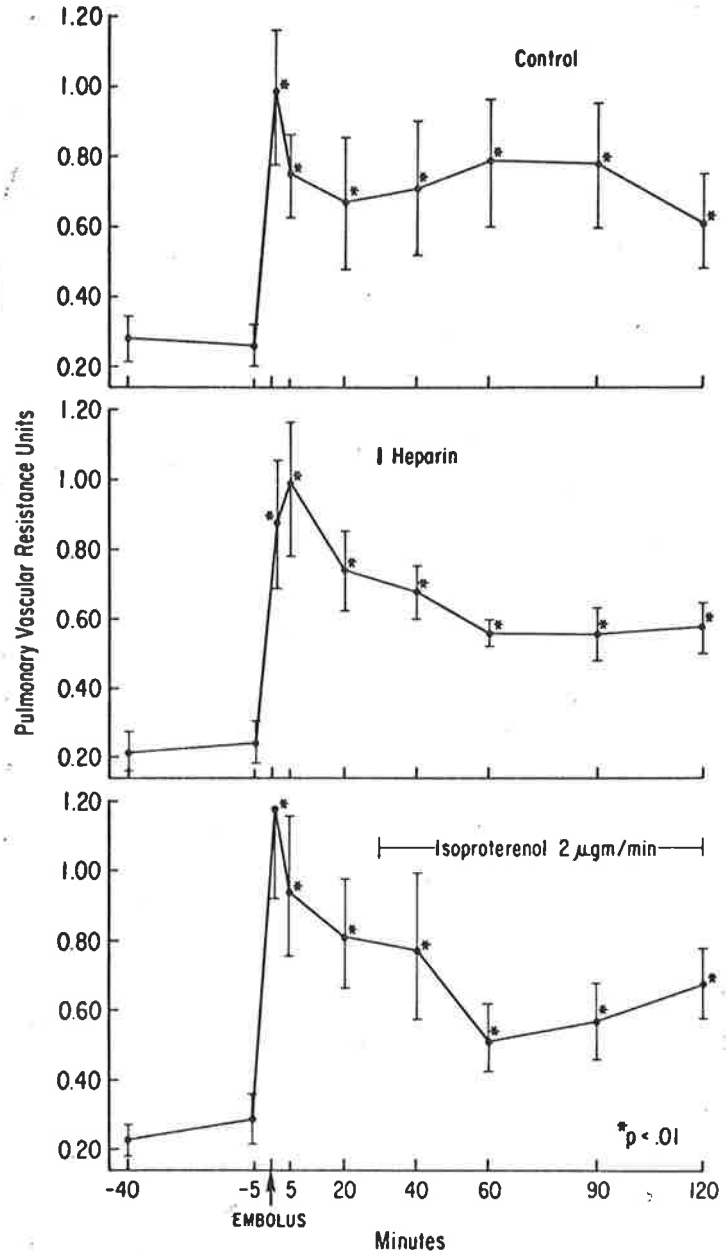


Figure 3

Pulmonary vascular resistance following pulmonary embolism in control, heparin treated and isoprenaline (isoproterenol) treated groups of dogs.

heparin treated animals ($p < .01$). However in the isoprenaline treated animals lung compliances returned to control levels (Figs. 4, 5).

The arterial $P O_2$ levels with all groups included fell significantly after embolism ($p < .01$). Individually the fall was only significant in the heparin group. In the control animals the fall in Pa O_2 continued slowly whilst in the two other groups the falling trend was reversed - although without reaching a level of significance ($p > .05$). The rise in Pa CO_2 levels were small with $p < .01$ however (Table 1).

DISCUSSION

Recovered embolus weight was significantly lower in the heparin treated group after two hours and this is similar to a finding made in a study by Vellar and Sullivan (1972) in which heparin induced a greater weight loss in emboli formed in flowing blood than in untreated animals with similar emboli. It has been postulated (Moser et al., 1973) that heparin acts by preventing fibrin deposition on emboli thus allowing fibrinolytic mechanisms to proceed unimpeded.

Pulmonary artery pressure rose steeply following embolism and remained elevated above normal throughout the study in all three groups. Neither heparin nor isoprenaline had any consistent effect on pulmonary artery pressure. Isoprenaline has previously been reported to abolish pulmonary hypertension induced by microemboli such as $BaSO_4$ (Halmagyi and Colebatch, 1961) and glass microspheres (Caldini, 1965). However, pre-treatment of dogs with isoprenaline before embolisation with macerated autologous thrombus did not prevent pulmonary hypertension (Hyman et al., 1964) and nor did the use of isoprenaline in patients following massive pulmonary embolism (McDonald et

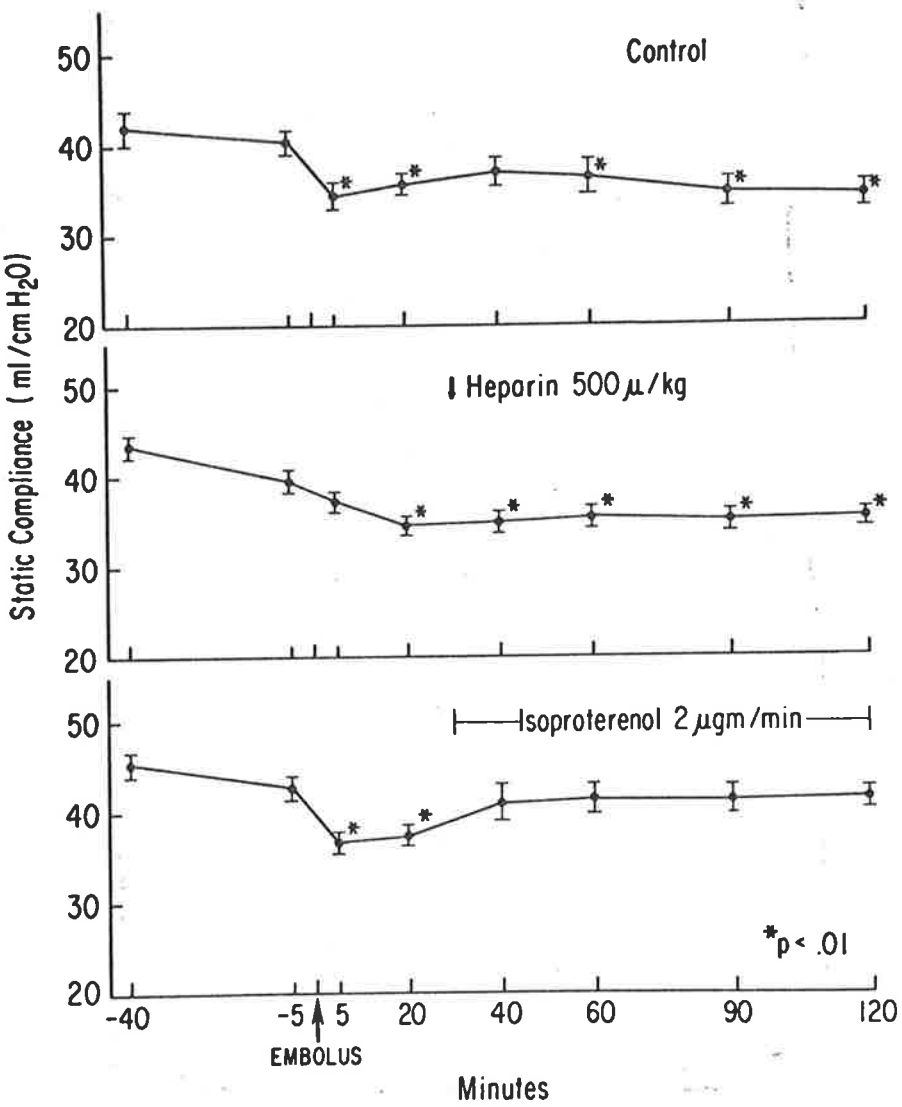


Figure 4

Static lung compliance following pulmonary embolism in control, heparin treated and isoprenaline (isoproterenol) treated groups of animals.

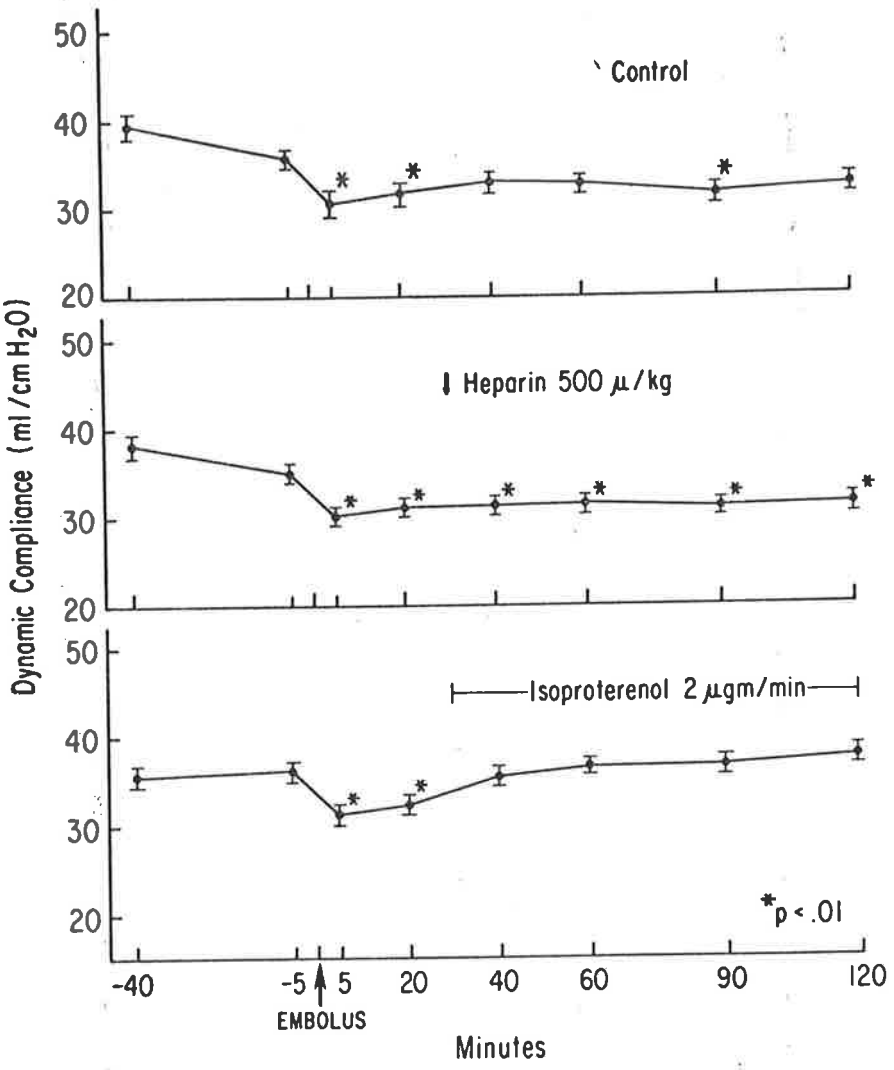


Figure 5

Dynamic lung compliance following pulmonary embolism in control, heparin treated and isoprenaline (isoproterenol) treated groups of animals.

TABLE 1. BLOOD GASES IN EXPERIMENTAL PULMONARY EMBOLISM (mmHg)

	40 min Pre-embolism Period		5 min Pre-embolism Period		5 min Post-embolism Period		40 min Post-embolism Period		90-120 min Post-embolism Period	
	Pa O_2	Pa CO_2	Pa O_2	Pa CO_2	Pa O_2	Pa CO_2	Pa O_2	Pa CO_2	Pa O_2	Pa CO_2
Control Group	71.8	35.1	-	33.5	71.5	32.0	69.0	33.5	67.9	35.1
Isoprenaline Group	74.5	34.0	-	32.5	67.7	34.6	64.6	35.4	67.9	38.7
Heparinized Group	79.4	29.1	-	27.6	61.9	34.1	60.3	33.0	65.9	34.4

Pa O_2 at 5 minutes pre-embolism and 120 minutes post embolism not shown as the animals had been breathing 100% O_2 as part of the protocol for estimation of shunt fraction.

al., 1968) abolish pulmonary hypertension. Our findings lend support to the concept that the degree of pulmonary hypertension is related more to the degree of mechanical blockage than to reflex or hormonally induced vasoconstriction. It perhaps should be pointed out, though, that the reduction in size of the embolus after heparin has not led to appreciable changes in haemodynamic or respiratory parameters.

Pulmonary embolism caused a profound fall in pulmonary blood flow in all groups and flow only slowly returned to normal, reaching pre-embolism levels towards the end of the study in untreated controls and the heparin treated group. Isoprenaline infusion on the other hand was followed by a rapid return of pulmonary blood flow towards normal. Two studies in humans, one in normal patients (Whalen et al., 1963) and the other in patients following embolism (McDonald et al., 1968) both reported that isoprenaline increases pulmonary blood flow. This return of blood flow towards normal may be due to dilatation of the unobstructed pulmonary vascular bed (Lockhart et al., 1967), and also increased ventricular contractility induced by isoprenaline (Whalen et al., 1963; Hyman et al., 1964; McDonald et al., 1968).

Pulmonary vascular resistance fell from its initial high levels after embolism but remained elevated in all groups throughou the study probably reflecting the large degree of mechanical obstruction present. Static and dynamic lung compliance fell significantly in each group of animals after embolisation and although heparin had no effect compared with the untreated control isoprenaline caused compliance to return to pre-embolisation level Contraction of terminal bronchiolar smooth muscle leading to decreased compliance in both microembolism (Nadel, 1973), and in macroembolism as shown previously in this thesis, remains a phenomenon without a definitive explanation. However the ability

of isoprenaline to reverse the changes has been previously reported (Nadel, 1973; Halmagyi et al., 1961). It has been suggested that serotonin released from platelets aggregating on the surface of the embolus is responsible for the changes in compliance (Stein et al., 1965). However in as much as heparin prevents platelet aggregation this study does not support that concept, and tends to reinforce a recent study questioning the role of serotonin in pulmonary embolism (Puckett et al., 1973).

The high values for shunt fraction in all groups are indicative of the degree of operative trauma which occurred presumably leading to ventilation-perfusion mismatch which worsened with time. Whether this worsening was due to embolisation or not cannot be answered, as we did not study a control group who had similar procedures carried out, with the same length of anaesthesia and yet were not embolised.

In the pooled data from the groups Pa O_2 fell significantly five minutes after pulmonary embolisation. For reasons which are uncertain there was a larger fall in the heparinised group than in the other animals and this is presumed to be a chance finding ($p < .05$). In following the course of the blood gases in the individual groups there were no changes which reached the level of significance of $p < .01$. However it is of interest that the Pa O_2 level tended to fall slowly in the control group whilst in the heparin and isoprenaline treated groups the Pa O_2 actually rose by the end of the study. As with shunt fraction so also with the bloo gases we cannot be certain that the fall in Pa O_2 was due to the embolus - it may have represented worsening atelectasis as a result of operative trauma and lengthy anaesthesia or indeed pulmonary embolism may have added to the worsening ventilation. Sabiston an Wolfe (1968) using ventilation and perfusion lung scans did not fin measurable ventilatory changes attributable to pulmonary embolism occurring until four hours had elapsed from the time of embolism.

In humans in whom embolism has occurred arterial oxygen nearly always falls, even with as little as 13% obstruction angio-

graphically (McIntyre & Sasahara, 1971). However the time course of this fall has not been well documented. Blood gas estimations are often taken some hours after the embolic event and so the time when a fall in Pa O_2 begins is not known. The reason why arterial oxygen tension should fall at all in pulmonary embolism remains controversial. Theoretically we have an example of an unperfused but normally ventilated area of lung when an embolus occurs and this should lead to no change in blood gases. $^{Va}/_{Q}$ imbalance (Kafer, 1969; Robin, 1965) atelectasis (Wilson et al., 1971), the opening of A-V anastomoses (Niden & Aviado, 1956; Deal et al., 1970) and pulmonary oedema (Swenson et al., 1963) are some of the mechanisms which have been suggested for this phenomenon.

Hyperventilation has been a commonly recorded event following pulmonary embolism since the classic studies of Dunn in 1918. This inevitably leads to a fall in Pa CO_2 and this has been shown in both man (Sasahara et al., 1967) and animals (Stein et al., 1960). As our animals were on a fixed volume respirator they were unable to increase their respiratory rate which probably explains why the Pa CO_2 did not fall and indeed rose slightly - a finding noted by others (Stein & Kimbel, 1973).

If total mechanical blockage of the pulmonary outflow tract by embolism occurs then it is obvious that almost instant death will ensue. However when obstruction is not total then any improvement in respiratory and haemodynamic function may be critical for the survival of the patient. It has long been thought that pulmonary hypertension leading to right heart failure is a probable cause of death in pulmonary embolism (Haggart et al., 1923; Gibbon et al., 1936), and unfortunately neither heparin nor isoprenaline has any dramatic effect on pulmonary hypertension in the critical time immediately after embolism

has occurred.

Heparin in the very large doses used did lessen the size of the embolus and on first principles it would seem that eventually this would lead to an increase in pulmonary artery flow. Isoprenaline increased lung compliance and increased pulmonary blood flow, and as pulmonary blood flow rather than pulmonary hypertension per se is probably the most critical factor in pulmonary embolism, this study supports the use of both heparin and isoprenaline as early as possible in this disease.

SECTION V THE USE OF VENTILATION AND PERFUSION LUNG SCANS TO DOCUMENT CHANGES FOLLOWING PULMONARY EMBOLISM

Since the introduction of pulmonary perfusion scans by Wagner and his colleagues (1964) this technique has been widely used in the diagnosis of pulmonary embolism. Perfusion lung scans, when interpreted with other clinical and laboratory evidence are now regarded as highly accurate in demonstrating pulmonary perfusion defects caused by pulmonary emboli (Szucs, 1971). Nevertheless, one common source of difficulty in interpreting a pulmonary perfusion scan is the fact that many pulmonary parenchymal diseases also cause differential reduction in blood flow to areas of the lung (Bryant et al., 1968). Radionuclide ventilation lung scans have thus been introduced (Loken & Westgate, 1967) and used with perfusion scanning in the evaluation of patients so that perfusion abnormalities resulting from parenchymal disease can in most cases be distinguished from those caused by vascular disorders such as pulmonary embolism.

Respiratory changes occur rapidly after pulmonary embolism as previously documented in this thesis. How much atelectasis contributes to the blood gas changes is uncertain as was mentioned in the previous section. Using combined ventilation perfusion lung scans in dogs Wolfe & Sabiston (1968) showed areas of decreased perfusion and ventilation in regions of autologous clot emboli. The ventilatory changes were first seen four hours after embolism and returned to normal by fortyeight hours. However in a clinical study Bass et al. (1967) using ^{133}Xenon for ventilation scans were unable to confirm a shift in ventilation away from areas in which the pulmonary blood flow had been reduced by thromboembolic disease.

By using both ventilation and perfusion lung scans it was our aim to look further at changes in ventilation and their time course and also to shed further light on whether increases in pulmonary blood flow following isoprenaline occurred only in non-embolised areas of the lung and whether reduction in thrombus size by heparin led to any significant increased flow to embolised areas of the lung.

METHOD

Thrombus for use as embolus in the dog was formed in the same way as described previously. The technique used for ventilation and perfusion lung scans has been reported by Jones et al. (1967, 1971). Briefly it consists of injecting IV ^{133}Xenon dissolved in saline and then measuring counts over the chest of the animal by means of a scintillation counter. The major part of the injected ^{133}Xenon passes from the pulmonary capillary blood into the alveolar spaces and is then removed by normal ventilation. The ^{133}Xenon therefore is distributed throughout the lung in proportion to the regional perfusion and so relative count densities over the chest during the time of greatest concentration of this agent in the lungs can be used to quantitate the distribution of pulmonary blood flow.

Ventilation scans were obtained by the animal rebreathing an air and ^{133}Xenon mixture for a two to three minute period followed by subsequent air breathing. Counts over the chest after a period of re-breathing provide a relative index of aerated lung volume.

Animals were divided into three groups of 10. Following pulmonary embolism one group was not treated and acted as a control group. The second group received intravenous heparin (500 u/kg) 30 minutes after embolism was induced. The last group received an intravenous isoprenaline infusion (2 µg/min) from 30

minutes after embolism until the conclusion of the study.

Pulmonary haemodynamic function and respiratory function was monitored as in the previous studies.

Radioactive counts were monitored by a Baird-Atomic System Seventy Scanning Gamma Camera which is basically a matrix of 294 NaI scintillation crystals interfaced directly into a small computer This camera has proven capable of recording counting rates up to 200,000 counts per sec with a high degree of accuracy in static and dynamic studies (Jones et al., 1973). Images of ventilation and perfusion lung scans were interpreted with the knowledge of the distribution of emboli found at autopsy so that it became possible to divide the lungs into regions affected and regions unaffected by emboli.

RESULTS

Total alveolar ventilation fell following pulmonary embolism ($p < .001$) (Table 1). In the areas unaffected by embolism this fall amounted to a 15.4 ± 21.9% drop whilst in areas affected by embolism the fall was 20.8 ± 25.2% measured 15 minutes after embolism.

In the individual groups the fall in alveolar ventilation did not reach the 1% level of significance except at 60 minutes post embolus in the control group and neither heparin nor isoprenaline had any obvious effect on either total or regional ventilation up to two hours post-embolus (Tables 2, 3).

There was a large fall in pulmonary blood flow 15 minutes following embolism and this was made up of a fall of 14.1 ± 29.7% to areas not affected by emboli and 55.1 ± 38.7% to areas which had been affected by emboli (Table 1). In the individual groups the total blood flow and the regional blood flow to the embolised areas remained depressed ($p < .01$) in both the control and heparin treated groups. However, in the isoprenaline treated group blood

TABLE 1

Acute Changes after Pulmonary Embolism in 29 Dogs

	15 min BEFORE EMBOLISM	15 min AFTER EMBOLISM		% change
VENTILATION				
Regional Areas Not Embolized	1370	1160	$p < .001$	15.4 fall
Regional Areas Embolized	934	740	$p < .001$	20.8 fall
PERFUSION				
Regional Areas Not Embolized	1071	921	$p < .05$	14.1 fall
Regional Areas Embolized	799	359	$p < .001$	55.1 fall

Treatment was not begun for 30 minutes after embolism so that these changes occurred in 29 untreated animals.

TABLE 2

Alveolar Ventilation Following Experimental Pulmonary Embolism (ml/min)

		Pre-embolism Period		15 min Post-embolism Period		60 min Post-embolism Period		120 min Post-embolism Period	
Untreated	Total	2202	100%	1797	81.6%	1613	73.3%	1717	77.9%
	Embolic Region	899	100%	681	75.6%	679	75.5%	691	76.9%
Heparin	Total	2075	100%	1695	81.7%	1685	81.2%	1480	71.3%
	Embolic Region	873	100%	709	81.2%	691	79.1%	606	69.4%
Isoprenaline	Total	2637	100%	2208	83.7%	2289	86.8%	2321	88.0%
	Embolic Region	1030	100%	830	80.6%	834	80.9%	841	81.6%

TABLE 3

Percentage Contribution of Embolised Areas to Total Ventilation

	Pre-embolism Period	15 min Post-embolism	60 min Post-embolism	120 min Post-embolism
Untreated	40.8%	37.9%	42.1%	40.2%
Heparin	42.1%	41.8%	41.0%	40.9%
Isoprenaline	39.1%	37.6%	36.4%	36.2%

flow returned towards normal with a greatly increased flow in the non-embolised areas of the lung and a smaller increase in flow in the area of lung which had been embolised (Tables 4, 5). This latter may represent increased bronchial rather than increased pulmonary blood flow. A representative study showing ventilation and perfusion lung scans is shown in Figs. 1, 2, 3.

DISCUSSION

Whilst reflex activity in the vascular system in pulmonary embolism remains controversial there is little doubt that there are changes in the airways in which reflexes are involved (Widdicombe, 1972; Stein et al., 1973). A fall in alveolar ventilation has previously been described following pulmonary embolism in the dog (Severinghaus et al.,1961; Wolfe & Sabiston, 1968a) and its mechanism remains speculative. There is little doubt that terminal bronchiolar constriction occurs either through vagally mediated reflexes (Nadel, 1973; Stein et al., 1973), from serotonin released from platelets (Levy & Simmons, 1975), and/or from changes in alveolar CO_2 concentration (Severinghaus et al., 1961, 1962; Samanek & Aviado, 1967). However, isoprenaline, which reverses the bronchiolar constriction (as shown by the reversal of compliance changes) does not reverse the fall in alveolar ventilation. This suggests that some additional factor is responsible for the fall in alveolar ventilation. It has been reported that changes in lung compliance and alveolar ventilation after embolism are abolished by cervical vagotomy (Macklem, 1970) and this taken with the lack of effect of heparin is against the explanation that serotonin is involved. On the other hand pulmonary embolism induces hypocarbia in the affected alveoli and this leads to bronchiolar and then alveolar constriction and collapse (Samanek & Aviado, 1967; Swenson et al., 1961), and this

TABLE 4

Pulmonary Blood Flow Following Experimental Pulmonary Embolism (ml/min)

		Pre-embolism Period		15 min Post-embolism Period		60 min Post-embolism Period		120 min Post-embolism Period	
Untreated	Total	1675	100%	1305	77.9%	1290	77.0%	1329	79.3%
	Embolic Region	717	100%	387	53.9%	420	58.6%	367	51.2%
Heparin	Total	1953	100%	1444	73.9%	1490	76.3%	1502	76.9%
	Embolic Region	830	100%	358	43.1%	378	45.0%	372	44.8%
Isoprenaline	Total	1990	100%	1108	55.6%	1649	82.9%	1670	83.9%
	Embolic Region	852	100%	332	38.9%	470	55.1%	486	57.0%

TABLE 5

Percentage Contribution of Embolised Areas to Total Perfusion

	Pre-embolism Period	15 min Post-embolism Period	60 min Post-embolism Period	120 min Post-embolism Period
Untreated	42.8%	29.6%	32.5%	27.6%
Heparin	42.5%	24.8%	25.4%	24.7%
Isoprenaline	42.8%	29.9%	28.5%	29.1%

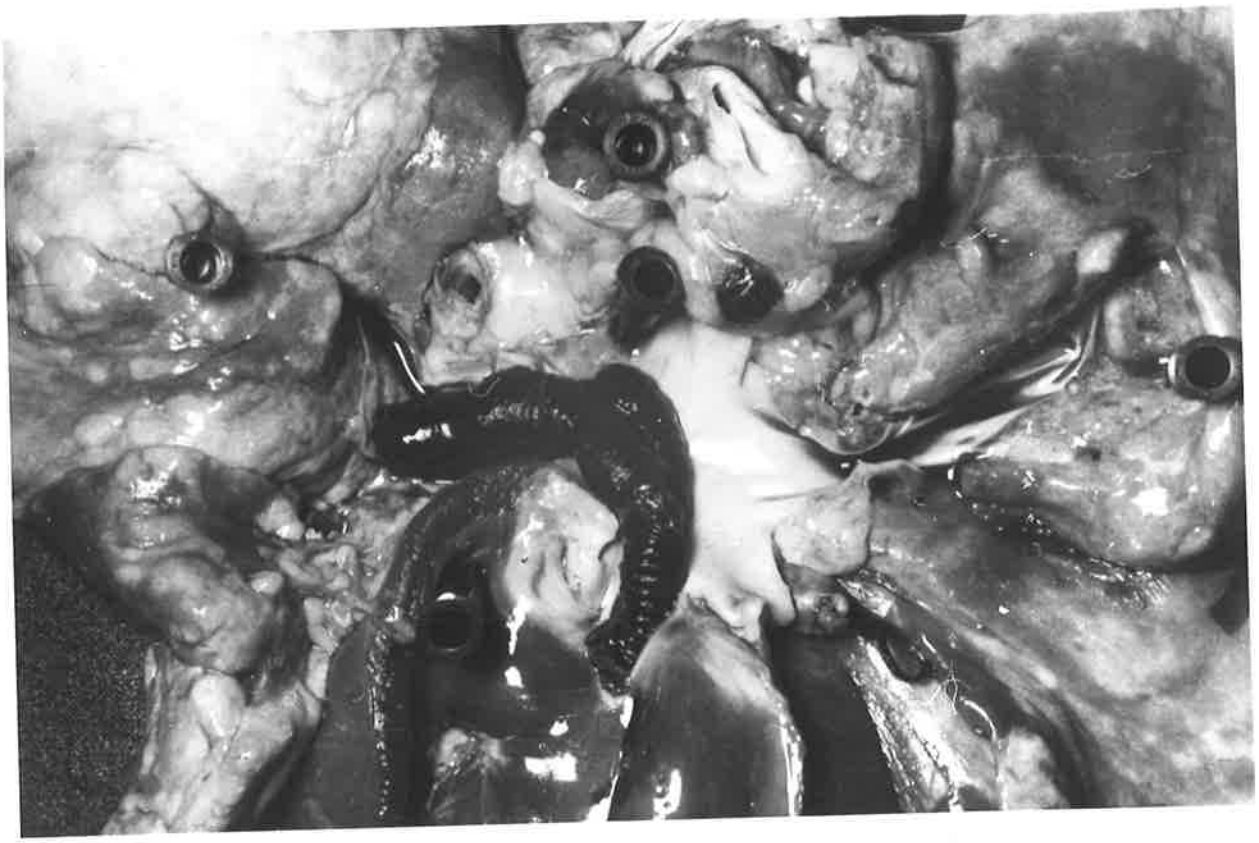


Figure 1

Pulmonary embolus in situ in the main pulmonary artery and extending into the right pulmonary artery. The ventilation and perfusion scans from this study are shown in Figures 2, 3.

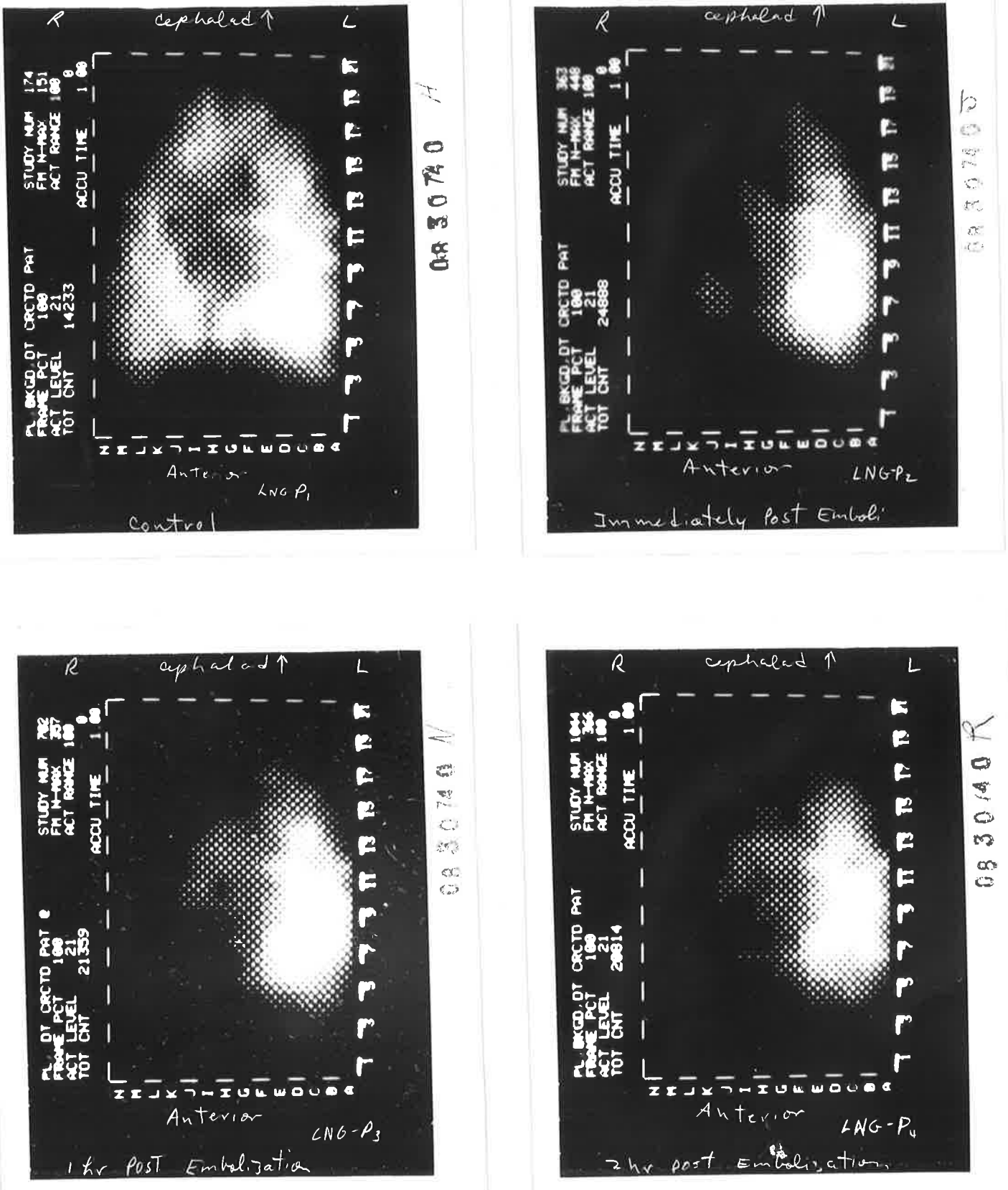


Figure 2.

Perfusion lung scans taken before (top left) and then at 15 minutes (top right), 60 minutes (bottom left) and 120 minutes (bottom right) after pulmonary embolism shown in Figure 1.

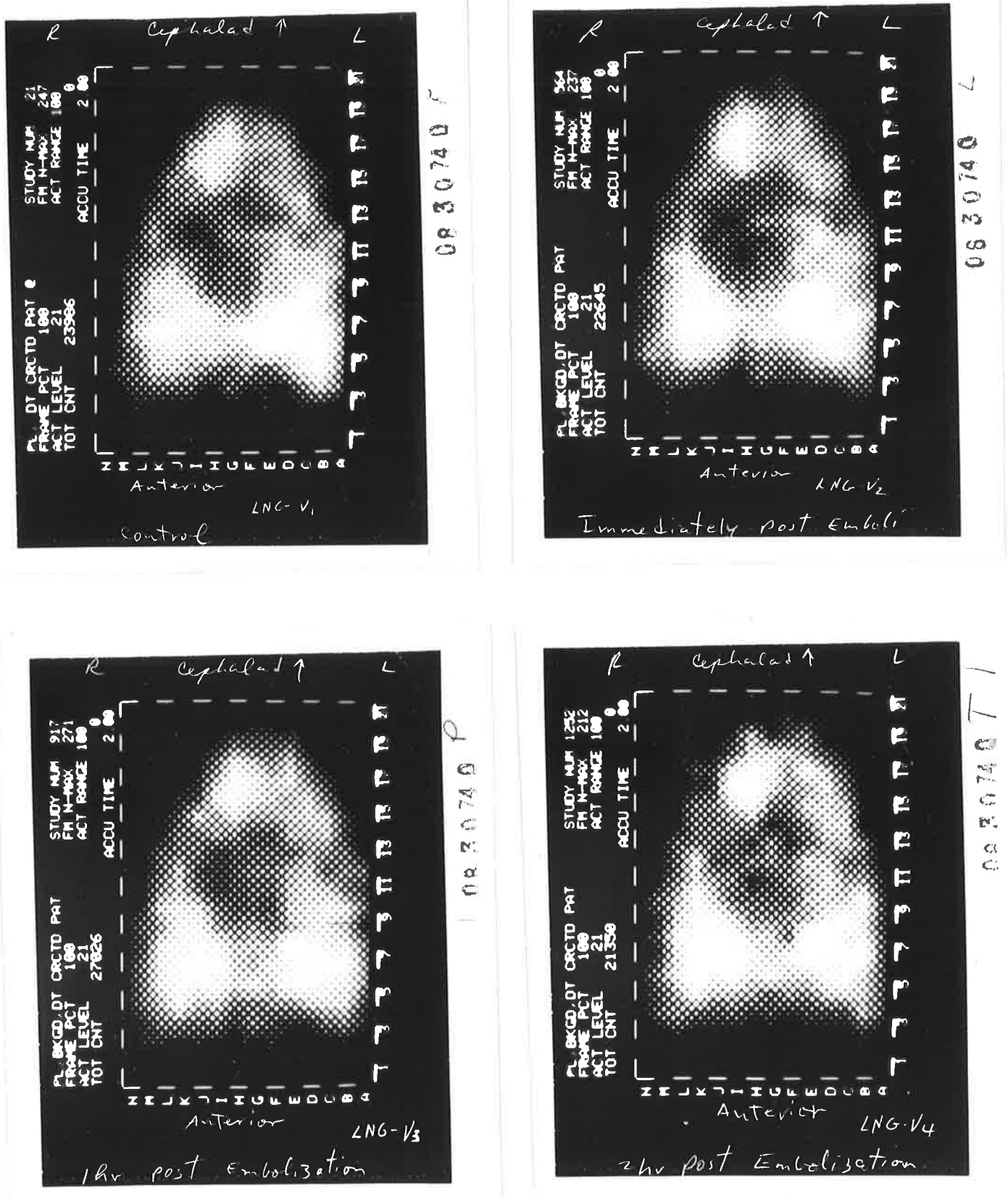


Figure 3

Ventilation lung scans taken before (top left) and then at 15 minutes (top right), 60 minutes (bottom left) and 120 minutes (bottom right) after pulmonary embolism shown in Figure 1.

latter situation is not reversed by isoprenaline. Isoprenaline can, therefore, block or reverse the reflex effects of vagal bronchoconstriction, but cannot reverse alveolar duct constriction and alveolar collapse because of the direct action of continuing hypocarbia. It should be noted here again that we cannot be certain in our study how much of the fall in alveolar ventilation was due to prolonged anaesthesia per se as we did not study an unembolised group. Further, although ventilation fell to a greater degree in the embolised areas of the lung this was not significantly different from the unembolised areas of the lung. The work of Sabiston & Wolfe (1967) indicates that had we continued the study for a longer period of time this trend may have become significant. A reasonable interpretation of these findings is that prolonged anaesthesia induces alveolar collapse and worsening alveolar ventilation. Pulmonary embolism leads to bronchiolar constriction by reflex effects and by changes in CO_2 concentration within the alveoli. The CO_2 changes also lead to further alveolar collapse but this process takes some hours to develop fully, perhaps related to slowly developing changes in surfactant (Wolfe and Sabiston, 1968b).

The role of reflexes and vasoconstriction in pulmonary embolism is even less well resolved than with bronchoconstriction although most workers regard it as of minor import compared to the effect of mechanical blockage of the pulmonary artery or one of its main branches by an embolus (McIntyre et al., 1972; Puckett et al., 1973).

The pulmonary blood flow data are on the whole similar to the findings in the study reported in Section IV. Several points of interest can be noted however. Firstly, there is the degree of perfusion that can take place around an embolus. Figure 4 shows a photograph taken at autopsy of a large embolus with the

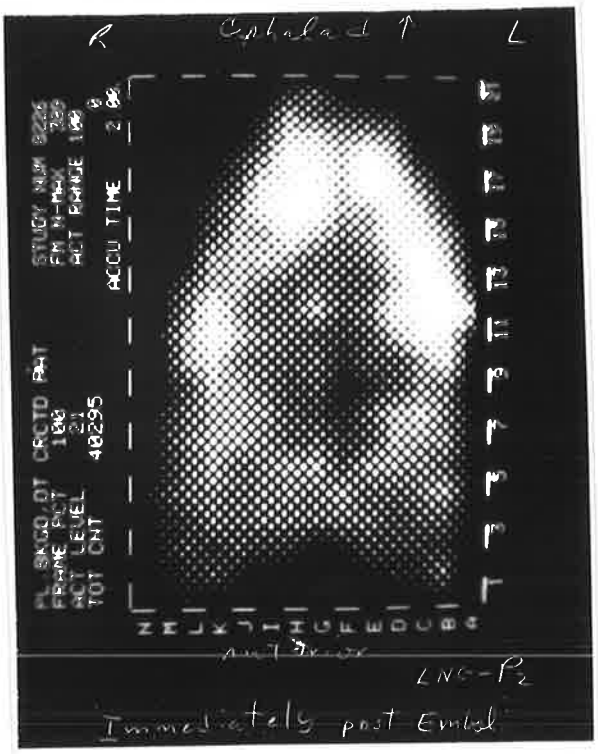


Figure 4. Embolus seemingly totally occluding the main pulmonary artery (above) and yet lung scan taken 15 minutes post embolus reveals a large amount of blood flow to the lungs still occurring. (obtained just prior to killing the animal)

bulk of it appearing to be in the main pulmonary artery. However the lung scans taken before death in this animal show remarkably good perfusion of the lungs. In each of the studies performed the embolus was considered a massive one and usually seemed to occlude at least one of the right or left pulmonary arteries and/or often the main pulmonary artery at autopsy. In spite of this the mean fall in blood flow to the affected areas was only of the order of 55% of the flow prior to embolisation and so again it reiterates the point of how much blood can flow around a large embolus.

The isoprenaline infusion caused blood flow to increase mainly in the areas unaffected by embolism. It is possible that the smaller increases in flow in the embolised areas was due to bronchiolar arterial dilatation. There have been other studies in both animals (Halmagyi and Colebatch, 1961) and man (McDonald et al., 1968), which show that isoprenaline increases cardiac contractility and causes pulmonary arterial dilatation.

This part of the study, therefore, further supports the use of isoprenaline as early as possible following a massive pulmonary embolism.

PART II : CLINICAL REVIEW OF ONE THOUSAND PATIENTS WITH PULMONARY EMBOLISM.

In the past, objective study of the problem of pulmonary embolism has been bedevilled by the difficulty of making a definitive diagnosis of the condition without resorting to pulmonary angiography.

Since the introduction of lung scans (Wagner et al., 1964), this technique has been increasingly used in the diagnosis of pulmonary embolism. Data from pulmonary angiograms and lung scans in the Urokinase Pulmonary Embolism Trial were compared and the correlation between angiographic and lung scanning methods of analysis was very good (UPET 1973).

In this review the aim was to study a large group of patients in whom the diagnosis of pulmonary embolism had been established beyond clinical diagnosis alone. This report summarises the total ten year experience with pulmonary embolism at the Duke University Medical Center, Durham, North Carolina. There was no uniformity in approach to diagnosis and management and so the observations recorded reflect typical experience with several different approaches to the management of pulmonary embolism.

METHODS

Clinical records were reviewed of 1,596 patients with the diagnosis of pulmonary embolism hospitalised between January 1965 and December 1974 at Duke University Medical Center. The record coding procedures of the hospital are such that we were able to review all patients with the diagnosis of pulmonary embolism made by autopsy, pulmonary arteriogram, lung scan, or clinical findings. A group of 411 patients were eliminated from study following initia review either because post-mortem examination failed to confirm the clinical diagnosis of pulmonary embolism or because clinical evidence appeared insufficient to support the diagnosis of pulmonary embolism. An additional 185 patients bearing the

clinical diagnosis of pulmonary embolism demonstrated a syndrome suggestive of pulmonary embolism on review of the record, but appropriate diagnostic tests were not completed to substantiate the diagnosis and they were excluded from this study. Clinical information was retained on this group however to insure a thorough evaluation of all patients who succumbed to pulmonary embolism during the past decade.

Primary attention was devoted to the study of 1,000 patients with an objective diagnosis of pulmonary embolism confirmed by lung scan, pulmonary arteriogram, post-mortem examination or combinations of these three studies. All available data from individual patient records was retrospectively reviewed and objectively tabulated in a standard form. All charts were reviewed by at least one physician and at least two physicians conferred on information requiring subjective decisions for categorisation such as the cause of death. Laboratory data were recorded as reported in patient charts without further confirmation of the accuracy of these reports. Lung scans were interpreted by practitioners in nuclear medicine and pulmonary arteriograms were evaluated by vascular radiologists. Readings of radiographs, lung scans, and pulmonary arteriograms were recorded as initially reported without further review. Pathologic data were obtained by review of complete autopsy protocols including the available diagrams and photographs of pathologic material.

Patients who died were arbitrarily classified into four groups by thorough review of all recorded information with strong emphasis given to the opinion of the clinicians and pathologists initially responsible for each patient. Group I (pulmonary embolism causing death) included 77 patients in whom the pulmonary

embolism appeared to represent the most likely cause of death irrespective of the severity of other associated diseases. Group II (pulmonary embolism associated with death) included 124 patients in whom manifestations of a significant primary disease hindered accurate assessment of the influence of pulmonary embolism but in whom circumstances at the time of death did not appear to result only from pulmonary embolism. Group III (pulmonary embolism probably unrelated to death) included 124 patients without documentation of a definite cause of death but with pulmonary embolism appearing unrelated because of the remoteness in time of the event or the nature of the clinical syndrome. Group IV (pulmonary embolism unrelated to death) included 55 patients documented to die from causes other than pulmonary embolism and with evidence suggestive that the pulmonary embolism played no significant role in death.

A degree of subjectivity is inherent in these classifications but in equivocal situations patients were consistently entered into the category which suggested the greater influence of embolism in causing death.

RESULTS

Patient population

The 1,000 patients with documented pulmonary embolism represent 0.4% of the 248,743 admissions to Duke University Medical Center during the period of study. Comparison of the yearly incidence of the diagnosis of pulmonary embolism shows a sharp increase after 1965 which is proportionally greater than the increase in total admissions (Fig. 1). This period of rapid increase in incidence of diagnosis occurred soon after the introduction of lung scanning at this institution. During the last five years of study, the frequency of diagnosis of

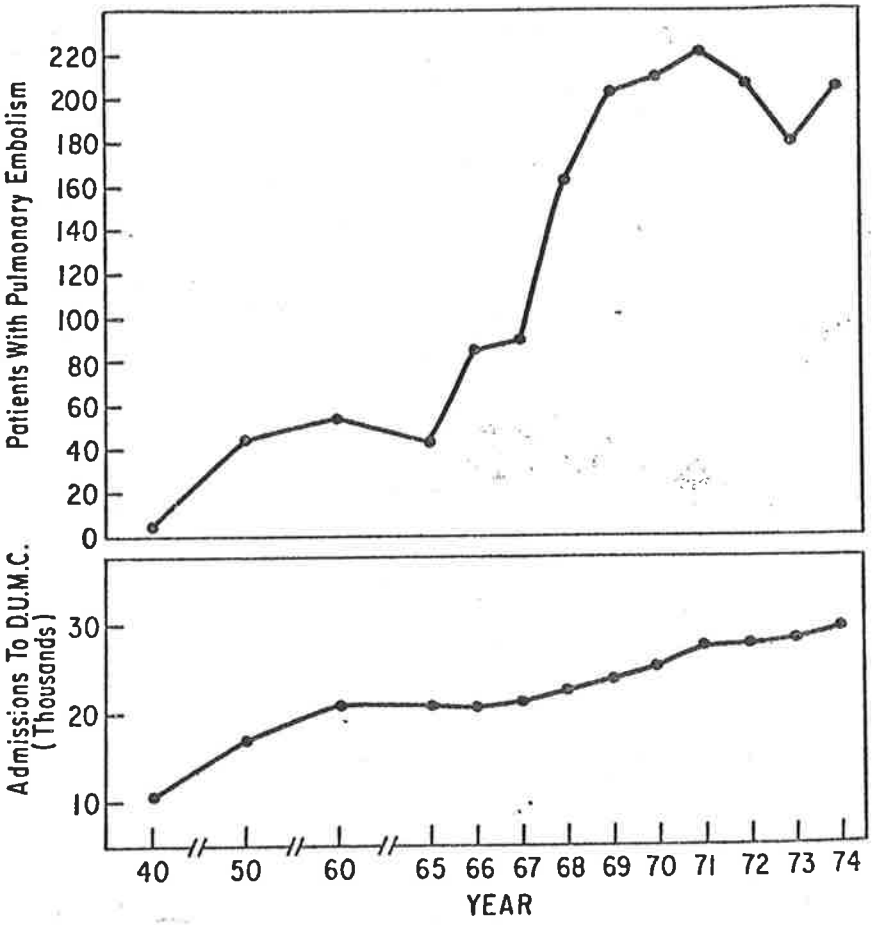


Figure 1. Admission to Duke University Medical Centre and the incidence of pulmonary embolism.

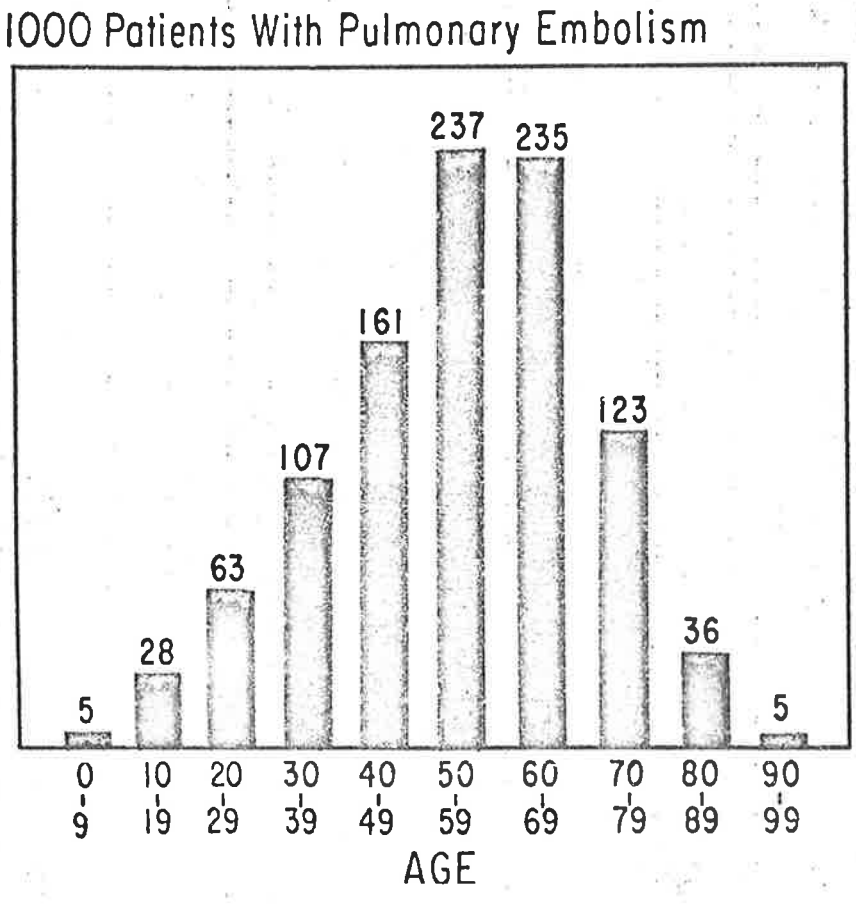


Figure 2. Age distribution of patients with pulmonary embolism.

pulmonary embolism did not change significantly. The race and sex distribution of patients with pulmonary embolism appeared similar to the distribution observed in the entire population of hospital admissions. Older patients proved more susceptible to pulmonary embolism and a majority of patients with the disorder were greater than 50 years of age (Fig. 2). However, more than 200 patients under the age of 40 sustained pulmonary embolism and the youngest was a 2 day old infant who died with a massive pulmonary embolism originating in an umbilical vein.

Predisposing factors (Table 1)

In all but 17 of the 1,000 patients a primary disorder was recognised which appeared interrelated to the episode of pulmonary embolism. Cardiac failure which represented the most prominent associated disease was recognised in 441 patients prior to the time of pulmonary embolism. In 420 patients recent operations or trauma appeared to predispose to pulmonary embolism. In 218 patients of this group, the interval between the surgical procedure and the pulmonary embolus was documented to be less than 30 days. The earliest pulmonary embolism occurred intraoperatively, but the average time between surgery or trauma and the onset of the embolus was 9.8 days. A malignancy was diagnosed in 190 of the 1,000 patients with pulmonary embolism. Chronic lung disease occurred concurrently with pulmonary embolism in 150 patients. Oral contraceptive use or pregnancy was recognised in 33 of the 1,000 patients. Prolonged immobility represented a major factor in the majority of other conditions associated with pulmonary embolism.

TABLE 1. Predisposing factors and associated diseases in 1,000 patients with pulmonary embolism.

Cardiac failure	441
Deep venous thrombosis	346
Prior operation	316
Obesity	217
Malignancy	190
Hypertension	185
Chronic lung disease	150
Diabetes	128
Trauma	104
CNS disease	84
Prolonged immobilisation	78
Debility	65
Renal failure	56
Alcoholism	36
Pregnancy and contraceptive pill	33
Polycythaemia	8
Miscellaneous disorders	369
No predisposing factor or associated disease	17

Clinical manifestations (Table 2)

Signs and symptoms associated with pulmonary embolism are often vague and serve only to suggest the diagnosis. Dyspnoea which was the most common symptom was observed in 77% of the patients. Chest pain occurred in over one half of the patients and typically was of a pleuritic nature. Chest pain clearly of an anginal nature was observed in 76 patients at the time of embolism. Haemoptysis occurred in only 26% of the patients and the triad (often considered specific for pulmonary embolism) of dyspnoea, pleuritic pain, and haemoptysis occurred in only 14% of the patients. A decreased alertness was noted in 228 patients. The 112 patients who developed syncope usually were found to have massive pulmonary embolism on further study.

Tachycardia occurred commonly and was usually 10 to 20 beats/min more rapid than pulse rates recorded before embolism. Most patients had no change in systemic blood pressure, but 110 patients with massive pulmonary embolism developed shock. A recent temperature elevation was observed retrospectively in almost one half of the patients. The jugular venous pressure recorded was normal in most patients and was elevated in only 177 patients. Examination of the lungs rarely showed specific signs suggesting pulmonary embolism. Rales and other pulmonary abnormalities observed often appeared related to pre-existing lung or cardiac disease. Tachypnoea was another non-specific sign which was frequently documented. Less than one quarter of the patients had leg oedema, tenderness or other physical signs suggestive of venous thrombosis. Approximately 11% of patients had an accentuated pulmonary second heart sound associated with acute pulmonary hypertension and only 9% of the patients appeared cyanotic at the time of embolism. A pleural friction rub was observed in only 8% of the patients.

TABLE 2 Clinical manifestations in 1,000 patients with pulmonary embolism.

SYMPTOMS	
Dyspnoea	772
Chest pain	626
Haemoptysis	262
Altered mental status	228
Dyspnoea, chest pain, haemoptysis	144

SIGNS	
Tachycardia	588
Recent fever	426
Rales	418
Tachypnoea	380
Leg oegema and tenderness	234
Elevated venous pressure	177
Shock	110
Accentuated P_2	107
Cyanosis	89
Pleural friction rub	81

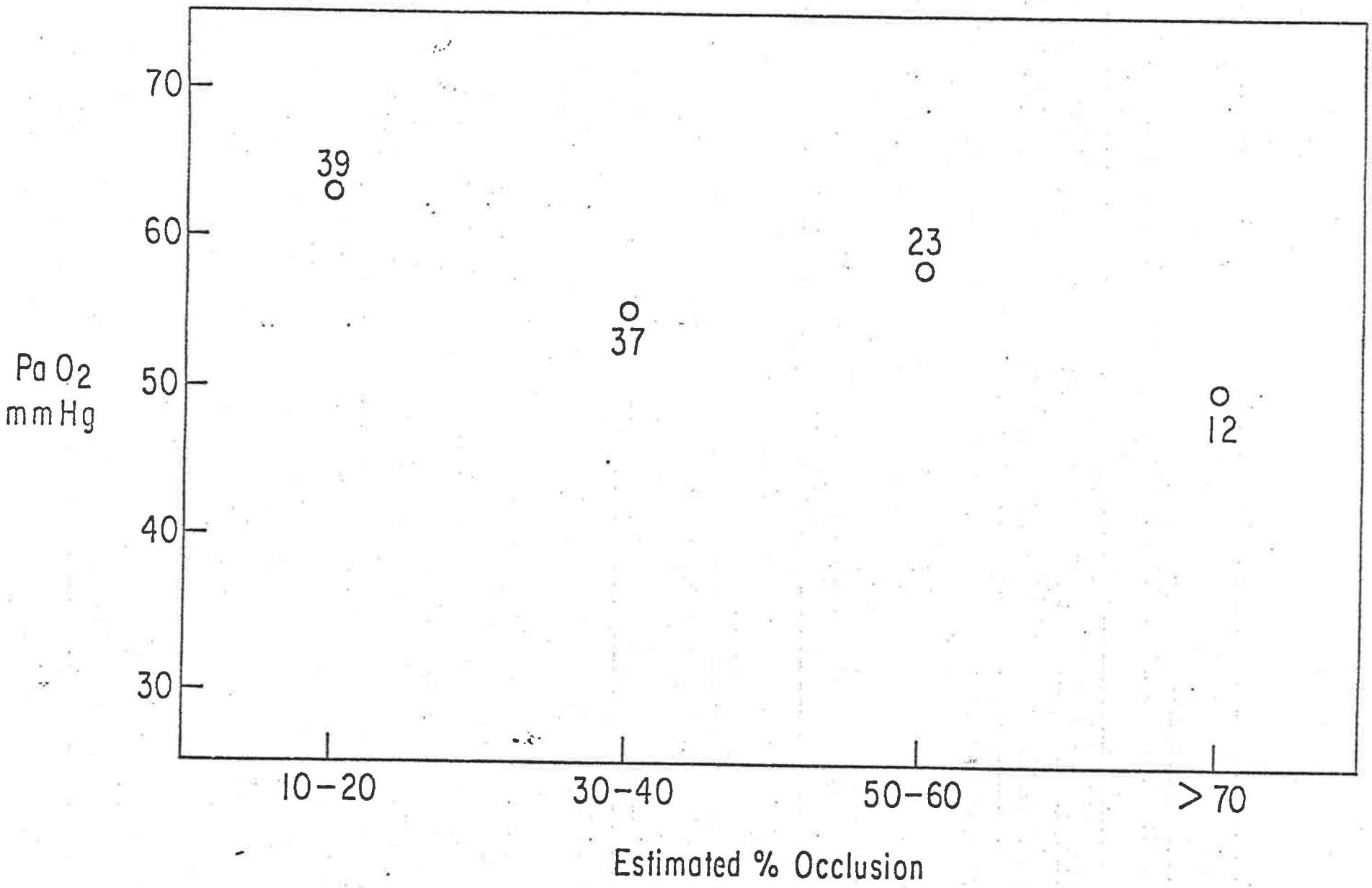
Laboratory studies including haematocrit, leukocyte count, leukocyte differential count, and lactic dehydrogenase and serum bilirubin demonstrated no consistent change following pulmonary embolism. The electrocardiogram was normal in 735 patients and in only 104 patients was it suggestive of pulmonary embolus. A chest radiograph was normal in only 291 patients, but in the majority of patients only non-specific abnormalities were observed such as parenchymal infiltrates, atelectasis, and pleural effusion. In 79 patients the proximal pulmonary artery appeared prominent and in 51 patients hypovascular lung regions were observed.

Arterial blood gas determinations were available in 625 patients with pulmonary embolism. The Pa O_2 averaged 58.1 ± 15.3 mmHg and Pa CO_2 averaged 33.4 ± 10.3 mmHg and the pH averaged 7.45 ± 0.12 in these patients. More than 90% of patients with pulmonary embolism had a Pa O_2 less than 80 mmHg. Observation of arterial oxygen desaturation provides a useful screening test in patients suspected of pulmonary embolism. The respiratory alkalosis associated with pulmonary embolism reflects the hyperventilation common with the disorder. Pa O_2 determinations were available in a group of 110 patients in whom the magnitude of the pulmonary embolus could be assessed by pulmonary angiography. The relationship between the severity of embolus and the severity of hypoxaemia is shown in Figure 3.

Specific diagnostic procedures

Radionuclide lung scanning provides a useful approach for initial evaluation of patients with pulmonary embolism. In the present study, a normal lung scan was considered sufficient evidence that significant embolism had not occurred and patients

Fig. 3. The relationship between estimated percentage occlusion of the pulmonary vasculature in pulmonary embolism and PaO_2.



with no perfusion defects on lung scan were eliminated from the study. Therefore, 658 of the 1,000 patients included in this study had lung scans which proved compatible with pulmonary embolism in all but 10 patients who were retained in the study because of other evidence of pulmonary embolism. Five had a pulmonary arteriogram considered suggestive of pulmonary embolism, and three patients with a negative lung scan had small peripheral pulmonary emboli demonstrated at the time of post-mortem examination. The other two patients with an initial negative lung scan had an episode of pulmonary embolism possibly subsequent to the scan and the diagnosis was confirmed by post-mortem examination. In one of these patients, the initial scan was technically inadequate. The second patient was not treated and sustained a massive pulmonary embolus five days later resulting in death. Lung scan data obtained in the present study are not useful in determining the incidence of false negative studies. In 424 patients, the lung scan was compatible with pulmonary embolism but not diagnostic because of other potential causes of perfusion defects apparent by history or on chest radiograph. In 224 patients, a positive scan in association with a normal chest radiograph provided sufficient evidence for diagnosis of pulmonary embolism. A positive scan and a negative arteriogram occurred in 26 patients. However, 15 of these patients had known heart failure or chronic lung disease. In most of the other 11 patients a 48 hour or greater interval was interposed between the lung scan and the pulmonary arteriogram.

Pulmonary arteriography was performed in 277 patients and provided a definitive anatomic description of pulmonary embolism in 223 patients. In 22 patients, a regional delay in contrast material transit was considered compatible with but not diagnostic of pulmonary embolism. The pulmonary arteriogram showed no

abnormality in 32 patients. The 26 patients with a positive lung scan but a negative arteriogram were retained in the study and frequently appeared to have sustained very small peripheral emboli. The remaining 6 patients with a negative arteriogram were retained in the group because the diagnosis of pulmonary embolism was confirmed histologically by lung biopsy or by post-mortem examination. In each of these patients, small peripheral pulmonary emboli were observed which did not appear to contribute to death.

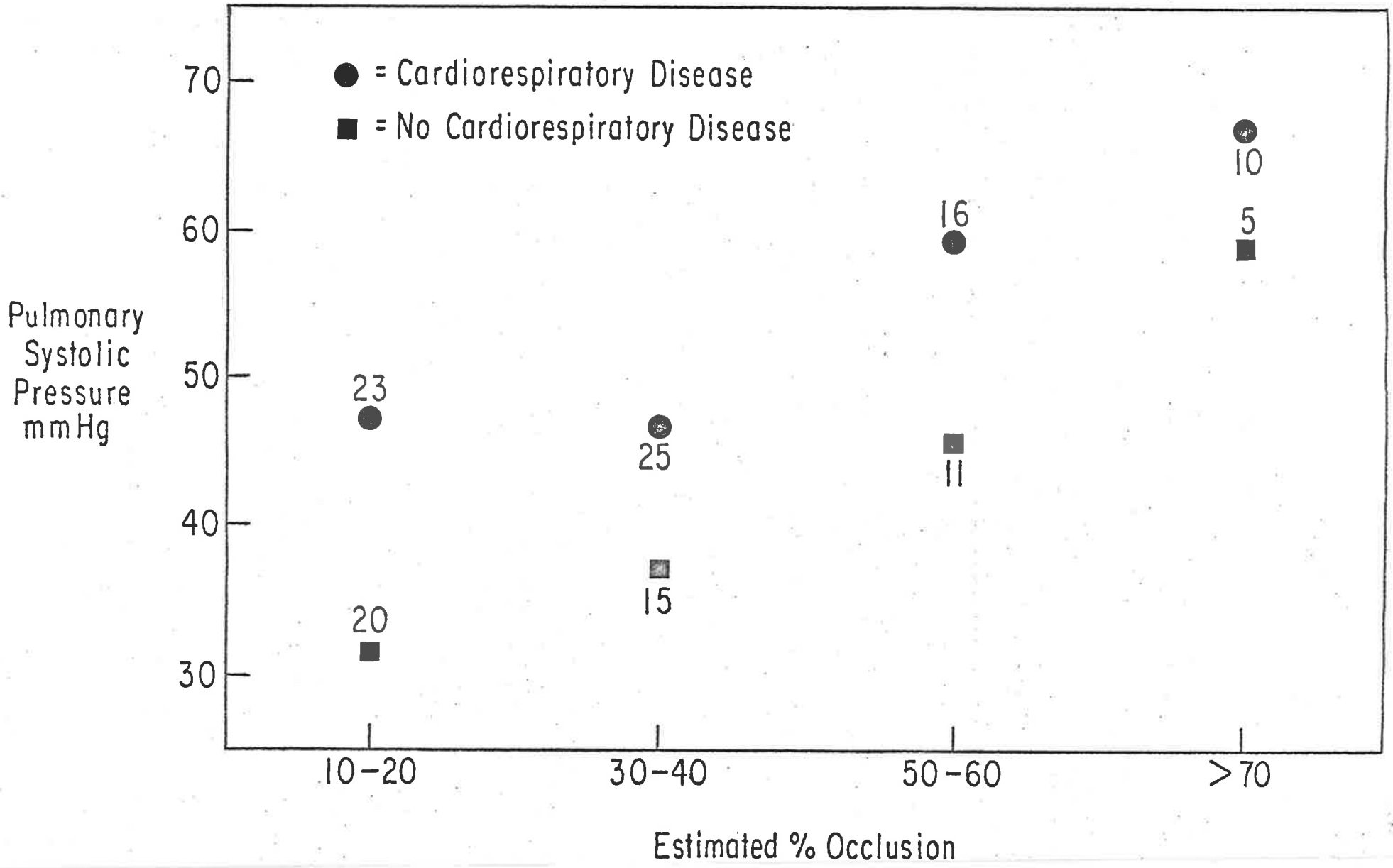
The interrelationship of three quantifiable variables was examined for prognostic significance. Haemodynamic measurements and arterial oxygen determinations were available in 110 of the 223 patients with definite angiographic evidence of pulmonary embolism. The relationship of the magnitude of embolic occlusion estimated on pulmonary arteriogram was compared to the pulmonary artery systolic pressure and the degree of hypoxaemia. In 77 patients without previous cardiorespiratory disease, the average pulmonary artery systolic pressure (PASP) was 38 mmHg and the mean arterial blood oxygen partial pressure ($Pa\,O_2$) was 62 mmHg. In 93 patients with a history of chronic cardiorespiratory disease prior to embolism, the PASP averaged 54 mmHg and the mean $Pa\,O_2$ was 57 mmHg.

In both groups of patients, the magnitude of pulmonary arterial hypertension and the severity of hypoxaemia increased with the magnitude of pulmonary arterial occlusion (Fig. 4).

Treatment

Of the 1,000 patients in the study, 192 were not recognised to have pulmonary embolism until the time of post-mortem examination. Fortyeight patients with minimal pulmonary embolism were

Fig. 4. The influence of cardio-respiratory disease on pulmonary systolic pressure in patients with pulmonary embolism.



not treated because the embolus was considered insignificant or because of specific contra-indications to anticoagulation. Anticoagulation was used in 729 patients and represented the major form of treatment. Most patients started with heparin anticoagulation and were later converted to coumadin for subsequent treatment. Major complications from anticoagulation occurred in 52 patients and minor complications were observed in 42 patients. In only 2 patients did complications appear responsible for death.

Twentyone patients underwent inferior vena cava interruption and the majority of these patients had ligation of the inferior vena cava. Death which occurred in 4 of these patients appeared to be caused by pulmonary embolism only in 3. A pulmonary embolectomy was performed in 11 patients and 6 patients died.

Analysis of deaths

A total of 380 deaths occurred in patients treated without surgery. In 77 of the patients (Group I) pulmonary embolism appeared to be the direct cause of death. Of the 77 patients with death caused by pulmonary embolism, 63 were not treated because of incorrect diagnosis and only 14 patients treated for pulmonary embolism died. Of the 63 patients dying without treatment for pulmonary embolism, 7 died suddenly and 1 had symptoms less than twenty-four hours before death. The remaining 55 patients were symptomatic for more than one day which would represent an adequate interval for diagnosis and treatment. Of the 14 patients who died with pulmonary embolism during anti-coagulation therapy, 5 patients had anticoagulation discontinued an average of five days before the terminal event. Of the remaining 9 patients only 1 died of pulmonary embolism in whom the adequacy of anticoagulation was fully documented.

In the 124 patients in Group II in whom pulmonary embolism may have played a role in death but could not be documented to be the sole cause of death, 95 patients were not treated. Of the 29 patients initially treated with anticoagulation, 9 had been stopped an average of 6 days before death. None of the remaining patients had full documentation of anticoagulation therapy. Furthermore, 13 of the 20 patients had clotting times indicating inadequate anticoagulation prior to death.

DISCUSSION

Whilst it has been well documented that the risk of pulmonary embolism increases with age (Nicolaides and Irving, 1975), and the majority of patients in this study were over the age of 50, pulmonary embolism in the young should not be overlooked. The youngest patient in this series was two days old at the time of massive embolus and death, and Jones and Sabiston (1966) have reported 146 cases of pulmonary embolism occurring in infants and young children.

Our study emphasises once again the importance of cardiac disease as an associated factor in the development of pulmonary embolism and others have recently commented on this as an important risk factor (Sigel et al., 1975; Coon, 1976). The other major predisposing factor was recent operation or trauma, and this again has been much commented on in recent times (Coon, 1976; Ludbrook and Jamieson, 1977).

In 1933, White emphasised the clinical manifestations of pulmonary embolism as including tachycardia, accentuation of the second pulmonary sound, dilation of the cervical veins and an enlarged and pulsating liver. In our study only tachycardia was a common finding in pulmonary embolism and dyspnoea was the only sign to be found more frequently than tachycardia. Often

taught as the classical diagnostic triad for pulmonary embolism, dyspnoea, pleuritic pain and haemoptysis was infrequently reported. Our findings are similar to those of a recent prospective study of pulmonary embolism (Urokinase Pulmonary Embolism Trial, 1973). There the classical triad was reported in only 28% of patients and dyspnoea was a very common finding occurring in 81% of patients. Tachypnoea occurred more frequently than dyspnoea being recorded in 88% of their patients. Given that 77% of our patients suffered dyspnoea it seems likely that tachypnoea went unrecorded in many of the patients in our series.

The other point worthy of note is the low incidence of clinically apparent leg vein thrombosis at the time of pulmonary embolism. Thus it was less than 25% in our series and only 30% in the UPET prospective study.

Elevated serum lactic dehydrogenase (LDH) and serum bilirubin in the presence of normal serum glutamic-oxalacetic transaminase (SGOT) has been reported as being useful in establishing the diagnosis of pulmonary embolism (Wacker and Snodgrass, 1960).

Another prospective study carried out in fifty patients with angiographically proven embolism reported elevation in LDH in 83% of the patients (Szucs et al., 1971). The mean value of the LDH in 672 of our patients however was only just above the upper limit of normal. It is probable that in the prospective study only patients with massive pulmonary emboli were chosen and overall the non-specificity of the test is such that its helpfulness in making a diagnosis is small. The mean bilirubin in our patients was normal in spite of small numbers of individual cases in whom it was raised.

This finding was similar to that of Szucs et al., 1971 and Snodgrass et al., 1965. At the time they were entered into the study 50% of the UPET patients had a normal SGOT, LDH and bilirubin concentration. The triad of an elevated LDH and bilirubin and a normal SGOT occurred in only 4% of these patients (UPET, 1973). Overall the data suggests that abnormalities in these various biochemical parameters are not very helpful in establishing the diagnosis of pulmonary embolism.

The electrocardiogram is a safe, easy to perform, procedure which may be suggestive, but is not diagnostic of pulmonary embolus. The right heart strain which may be reflected in the ECG occurs only in patients with massive pulmonary embolus (Szucs, 1971). The ECG has been reported as showing abnormalities consistent with pulmonary embolus in 10-87% of patients (Littman, 1965; UPET, 1973). The incidence in our series was towards the lower end of this reported range.

A plain chest X-ray is also a safe, simple investigation and it often shows abnormalities but again is rarely diagnostic. Westermark's sign of hyperlucency in an area of oligaemia distal to the embolus is a reliable but infrequently occurring sign (Westermark, 1938). It was noted in only 5% of our patients compared with 15% in the UPET study but in both the incidence is far short of the 71% reported by Simon (1973). The more common radiographic abnormalities are lung parenchymal consolidation and atelectasis, elevation of diaphragm and pleural effusion and in these our findings were similar to the prospective UPET study.

Blood gas estimations provide a useful screening test for pulmonary embolism as more than 90% of our patients in whom blood gases were measured had a PaO_2 of less than 69 mmHg. The respiratory alkalosis associated with pulmonary embolism reflects the hyperventilation which occurs and has already been commented on

as being a reflex effect mediated by the vagus nerves (Widdicombe, 1972).

It is interesting that a direct relationship seems to exist between the severity of pulmonary embolism and the degree of hypoxaemia for the cause of the hypoxaemia remains unknown. As mentioned earlier in Section IV, ventilation-perfusion mismatch and opening of A-V shunts are often regarded as being responsible for the hypoxaemia (Sasahara et al., 1966; Sasahara, 1967) although at present it seems that the most likely cause is atelectasis leading to anatomical right to left shunting (Wilson et al., 1971). Little can be said about the lung scan data in this retrospective series, although, accepting that false positive lung scans do occur, we believe it made the diagnosis a more objective one than would have been the case had clinical data alone been used in making the diagnosis.

In patients in whom arteriography and haemodynamic measurements were made the magnitude of pulmonary hypertension tended to reflect the degree of pulmonary arterial occlusion. This is of interest because in the experimental animal the severity of pulmonary arterial occlusion by ligature or balloon occlusion is not linearly related to degree of pulmonary hypertension and it is only when occlusion occurs beyond 50% that a linear relationship is establishe (Davison, 1960; Ebert et al., 1967). However in man although this thesis is supported by some (Smith et al., 1964; Davison, 1960) more recent evidence supports the findings reported here (McIntyre and Sasahara, 1974; Hirsch et al., 1968). It should be noted however that in these series, and ours, angiograms have tended to be carried out only when a large embolism had occurred.

Pulmonary hypertension was much lower in patients who had

no prior cardio-respiratory disease and this finding was also reported by McIntyre and Sasahara (1974) who found that even with massive embolism pulmonary artery pressure did not rise above 40 mmHg unless patients had prior cardio-respiratory disease.

In terms of treatment it is difficult to draw conclusions from a heterogeneous retrospective study such as this. However one factor does emerge. Sixty-three of 77 patients who were regarded as dying directly of pulmonary embolism received no treatment because the correct diagnosis was not made. And, further, 55 of these patients lived for long enough after the presumptive embolic event for a diagnosis to be made and treatment to be instituted.

CONCLUSION

Pulmonary embolism is a serious disorder which often kills patients in the wards of our hospitals. Many patients who die from this condition do so within a few hours of embolism occurring. This study was undertaken in order to record the changes which occur in the first hours after embolism and to see if the early introduction of heparin or isoprenaline would modify these changes.

Although there has been a great deal published on this subject much of it has been in relation to micro-emboli with unphysiologica material. When large emboli have been studied then the usual method has been to use some form of autologous blood clot. In the one study in which thrombi were formed in flowing blood not enough thrombus was formed to cause a massive embolus.

We have used a preparation in the dog of grafting from the left common carotid to the left femoral artery to lead to thrombus which forms in flowing blood. The microscopic characteristics of thrombus formed in this way are similar to pulmonary emboli removed from patients.

We compared this graft induced thrombus with retracted autologous blood clot and found that they both led to an increase in the pulmonary artery blood pressure and pulmonary vascular resistance and decreased pulmonary blood flow and static and dynami lung compliance but the changes were always much greater with the graft induced thrombus. As well as being less marked the changes in the blood clot group tended to revert more rapidly to normal than changes in the thrombus group which were better sustained for the duration of the study.

Autopsy examination showed that there was little tendency for either embolus-type to fragment but the blood clot embolus was greatly reduced in size compared with the graft induced thrombus. The less marked changes in the blood clot group were probably a result of greater pliability allowing more blood to flow past

the embolus whilst the failure of blood clot to produce sustained changes was no doubt due to the marked reduction in size of the blood clot embolus compared to the graft induced thrombus.

A study was made of two drugs commonly used in the treatment of pulmonary embolism, namely heparin and isoprenaline in order to see if the early introduction of these agents would significantly modify the changes occurring in pulmonary embolism.

It was found that there was a greater reduction in size of graft induced thrombus in the heparin treated animals than in the control and isoprenaline treated groups and yet in spite of this there was little improvement in haemodynamic and respiratory disturbances in the heparin treated group compared with the other two groups.

The most noteworthy finding was the effect of isoprenaline on pulmonary blood flow and static and dynamic pulmonary compliance. Isoprenaline caused a reversal in the changes which had been induced in these parameters, returning them back towards pre-embolism levels.

In order to look at the distribution of ventilatory and perfusion changes a similar study to the foregoing was carried out using ventilation and perfusion lung scans with ^{133}Xenon as the radioactive marker. Whilst the greatest changes were seen in the perfusion to the embolised areas of lung, total alveolar ventilation fell after embolism with the greatest percentage fall occurring in the embolised areas also. Neither heparin nor isoprenaline had any obvious effect on either total or regional alveolar ventilation up to two hours after embolus. On the other hand whilst heparin had no significant effect on perfusion either, isoprenaline led to a reversal in the fall of pulmonary blood flow with the greatest increase in flow occurring in the unembolised areas of the lungs. In spite of the massive nature of the emboli and their lack of fragmentation at autopsy considerab

flow took place around the emboli.

It is concluded that thrombi formed in flowing blood have similar microscopic structure to human thrombi and that in this particular experimental design the graft induced thrombi caused severe haemodynamic and respiratory changes in embolised animals. Heparin given at an early stage is useful as it leads to a more rapid reduction in size of the emboli although in the two hours of study this did not reflect itself in improvement in haemodynamic or respiratory parameters. Isoprenaline reverses terminal airways bronchoconstriction but this does not improve alveolar ventilation as alveolar collapse is probably the cause of the fall in alveolar ventilation. Isoprenaline also leads to improvement in pulmonary blood flow and this is of obvious importance in maintaining a near normal cardiac output.

These studies give little support for reflex mechanisms contrib uting to pulmonary haemodynamics in massive pulmonary embolism and indicate that mechanical blockage is the most important factor. Reflex mechanisms and changes in CO_2 concentration may both play a part in changes in ventilation. However the study gives little support for serotonin release from platelets having much part to play in either ventilation or perfusion.

Whilst the size of the embolus emerges as the most important factor in determining the initial effects it is clear that both heparin and isoprenaline given as early as possible do induce changes which may be of benefit to the patient in the treatment of pulmonary embolism.

The clinical review of one thousand patients is noteworthy because an objective diagnosis of pulmonary embolism using perfusion lung scan, and/or pulmonary arteriogram and/or autopsy was carried

out in all patients. The findings are not original but tend to underscore recent prospective studies in which only small numbers of patients were reported. In particular, our study emphasises the importance of prior cardiac disease in the development of pulmonary embolism and, blood gases in charting the severity of pulmonary embolism. It also points to the many hours which usually elapse between an embolus occurring and diagnosis and treatment being undertaken.

Unexplained tachypnoea is the commonest sign of an otherwise silent pulmonary embolism and perhaps if this fact is more widely appreciated then earlier treatment with both heparin and isoprenalin may lead to a lower death rate from this condition.

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