THROMBOEMBOLI AS A CAUSE OF COR PULMONALE*

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COR pulmonale is by definition heart disease of pulmonary origin. The ways in which the lung adversely affects the heart are twofold. The first is through the medium of pulmonary vascular obstruction that results in pulmonary hypertension which must be elaborated by the right ventricle. The second is largely through hypoxemia which adversely affects both ventricles. In general, however, the term acute cor pulmonale is reserved for the occurrence of acute pulmonary embolism, the main effect of which is to produce pulmonary hypertension although some degree of hypoxemia occurs. Various kinds of emboli produce acute cor pulmonale in man. These include such matter as air, fat, bone marrow, echinoccus cyst material, and amniotic fluid, and each adds some special feature to the disorder. However, the common embolus is a thrombus, and this discussion will deal with thromboembolism.

Pulmonary thromboembolism is currently the commonest lethal form of pulmonary disease at autopsy in adults in a general hospital population. It is the third most common nonlethal pulmonary disease, pneumonia and emphysema taking precedence. In 1960, it was the third commonest cause of death at the Peter Bent Brigham Hospital. It was the principal cause of death in 15 per cent of 225 consecutive patients at postmortem and was a contributing cause in another 19 per cent.[1] At times it was a blessing, as was pneumonia in former days, but usually it was tragic. This subject is extensive[2-4] and time does not permit of a detailed description of the many facets of this problem. Rather, I shall describe first the general circulatory disturbance that occurs as a result of thromboembolism; second, semiquantitative pathological fea

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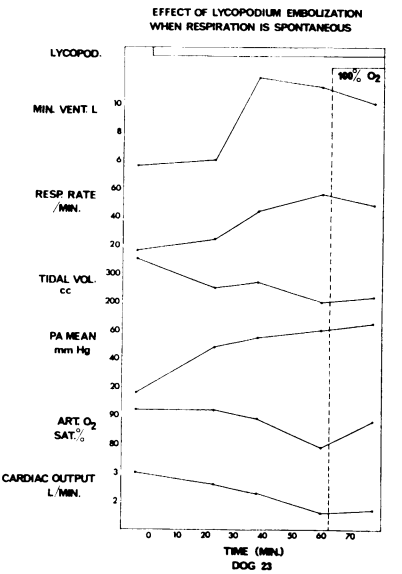

Fig. 1. Effect of pulmonary emboli (lycopodium spores) in dogs: see text.

tures; third, quantitative physiological features; and finally, some of the unsolved problems.

General Circulatory Disturbance

The over-all circulatory response to embolism is qualitatively the same in dogs as in man irrespective of the type of embolic material used. Figure 1 shows some of the responses that occur. These appear to be due entirely to obstruction to blood flow through the lung. The basic abnormalities are hypertension proximal to the obstruction and a reduction of blood flow. Thus there is a rise of pulmonary artery and right ventricular systolic pressures that, if sufficiently high, produce a rise of right ventricular diastolic, right atrial, and venous pressures, indicating right ventricular failure. Cardiac output falls. Not shown in this figure is that the systemic arterial pressure eventually falls to shock levels, that left atrial pressure remains normal until terminally, and that coronary blood flow is reduced.[5, 6] Hyperventilation, tachypnea, and reduced tidal volume regularly occur. Bronchoconstriction and reduction of compliance also occur.

In the otherwise normal human being, pulmonary thromboembolism

produces most of these same changes.[7] The clinical picture is well known and can be summarized as follows: 1) tachypnea, hyperventilation; 2) acute cor pulmonale: pulmonary hypertension, right ventricular failure; 3) circulatory collapse: hypotension, shock; 4) reduced coronary blood flow: coronary pain; and 5) left ventricular failure: pulmonary edema.

Tachypnea and hyperventilation occur regularly. Pulmonary hypertension, if severe, results in right ventricular failure with venous distension and hepatomegaly. If cardiac output is critically reduced, blood pressure falls, and syncope, collapse, or shock supervene. Substernal squeezing pain similar in every respect to that of an acute myocardial infarction is seen occasionally and occurs particularly in those with underlying heart disease, but it does not necessarily imply the existence of atherosclerotic narrowing of coronary vessels. Pulmonary edema, which cannot be produced in the otherwise normal experimental animal, is not seen in the spontaneous disease in otherwise normal man. However, it does occur frequently in patients with compromised cardiac function. Although its genesis has never been precisely explained, it is presumably due in part to a reduced coronary blood flow and in part to hypoxemia. It is associated with a rise of pulmonary capillary wedge pressure to pulmonary edema levels.[7] In any event, in patients with heart disease, the only manifestation of pulmonary embolism is frequently a subtle worsening of that patient's cardiac function, often presenting itself as pulmonary congestion rather than as cor pulmonale, there being nothing specific to indicate that pulmonary embolism has occurred.

Pathological Features

Pathological aspects of a semiquantitative nature have been studied in collaboration with Dr. George Smith, whose work this section largely represents.[1] Most emboli originate from thrombi in leg veins. The thrombus tends to proliferate and finally breaks off. If it is a fresh soft thrombus, it is usually fragmented into a myriad of particles of varied size as it is churned in its passage through the right ventricle.[8] The more mature and retracted the clot is, the more resistant it is, of course, to fragmentation by the right ventricle.

A blood clot may be so fragmented that it lodges as a shower of tiny particles in the lungs. At other times, it passes relatively unchanged and

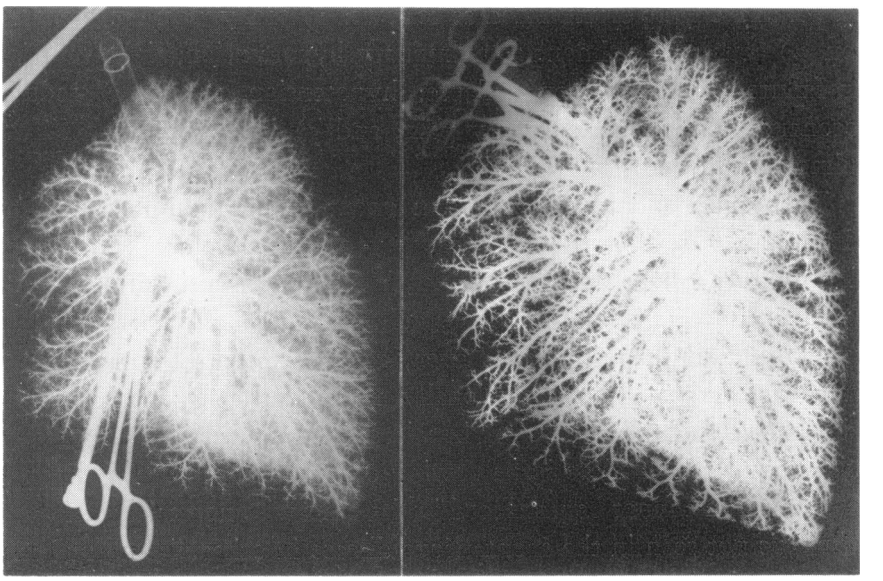

Fig. 2. Postmortem arteriograms of two normal human lungs. Note the long lobar, first- and second-order branches extending almost to the pleural surface and the short third-order and lobular arteries. The atrial arteries can be seen in the original film.

blocks the main pulmonary artery or its main branches. Figure 2 shows postmortem arteriograms of two normal lungs. Note the size and length of the main branch and of its first two subdivisions, the lobar and first order arteries. These vessels, the elastic arteries, taper down to about 1 mm. in internal diameter and accompany the main stem branches, lobar, and first-order bronchi. The muscular arteries taper from about 1 mm. to 0.1 mm. in internal diameter, and they correspond to the second- and third-order, lobular, and atrial arteries; they accompany the second and third order bronchi, terminal bronchioles, respiratory bronchioles, and alveolar ducts. The arterioles vary from 0.1 to 0.03 mm. in internal diameter and have muscle in their walls for only about half their length. Capillaries arise from the unmuscled portion of the arteriole.

Figure 3 is an arteriogram of a patient who died of embolism. Note how defoliated the vasculature appears.

It is occasionally stated that a single small embolus can produce death. In each of the 35 patients dying of embolism there was extensive

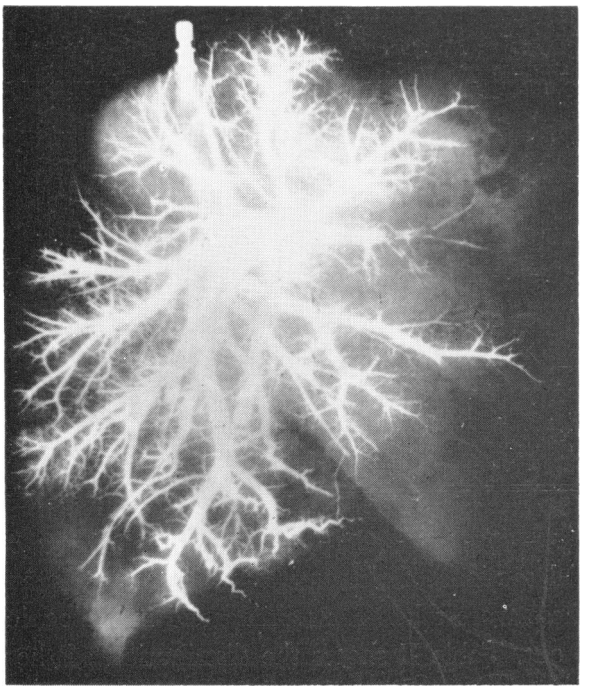

Fig. 3. Postmortem arteriogram of lung of patient who died of pulmonary thromboembolism. Note the multiple large areas not filled with Schlessinger mass and the relative absence of fine arborization of the vascular tree. Histologic studies confirmed embolic obstruction at all sites suspected in this arteriogram.

embolization. In no instance could death be attributed to a single small embolic occlusion.

Some measure of the amount of embolic material in the lungs of 20 patients dying a typical embolic death was derived from recording the volume of modified Schlessinger mass required to fill the pulmonary arterial tree. Because of its viscosity, this mass does not pass into arterioles. The results are shown in Table I.

The average arterial volume of embolized lungs was only about one-third normal. Although such a reduction is not synonymous with a reduction of cross-sectional area of the pulmonary vasculature, it suggests that the embolization was characteristically massive.

The distribution of embolic particles in the arteries of the lung was studied by first performing postmortem arteriograms as shown and these served as a guide map. Next, they were fixed in formalin. Arteriograms

TABLE I—ARTERIAL VOLUME OF HUMAN LUNGS POSTMORTEM

	No. Cases	*Normal ml./sq.m.*	*No. cases*	*Embolism ml./sq.m.*
Right lung	8	63 ± 3.1	10	21 ± 9.8
Left lung	12	56 ± 4.3	26	22 ± 11.6

TABLE II—LOCATION OF EMBOLI IN 34 HUMAN LUNGS

Arteries	*Size mm.*	*No. cases*	*Frequency*
Elastic	> 1.0	8	Few
Muscular	0.1-1.0	34	Common
Arterioles	0.03-0.1	13	Rare

of 1 cm. serial sections of the entire lung were made and finally thin sections of these were taken for staining and microscopic examinations were carried out. Table II shows the distribution of the emboli in the lungs of 34 patients so studied. It will be noted that emboli would have been detected in only 8 of the 34 cases by gross examination of the pulmonary vessels since gross dissection beyond the elastic arteries is impossible. On the other hand, the majority of the patients had one or more infarcts that might have been detected but, even so, the extent of embolization would not have been appreciated.

Although thromboembolic occlusion was extensive, less than 10 per cent of the thromboemboli were associated with infarction. There were only 53 infarcts in the lungs of the 34 patients, all of whom had multiple embolic occlusions. Reasons for the scarcity of infarcts are, in part, that many emboli only partially occluded the vessels and, in part, that bronchial collateral circulation maintained viability of the pulmonary parenchyma.

From these pathological studies it has been concluded 1) that fatal thromboembolism in man is massive and occludes large segments of the pulmonary vasculature; 2) that embolism without infarction is the rule rather than the exception; and 3) that thromboemboli characteristically occlude a multitude of small arteries, a few large arteries and, rarely, arterioles.

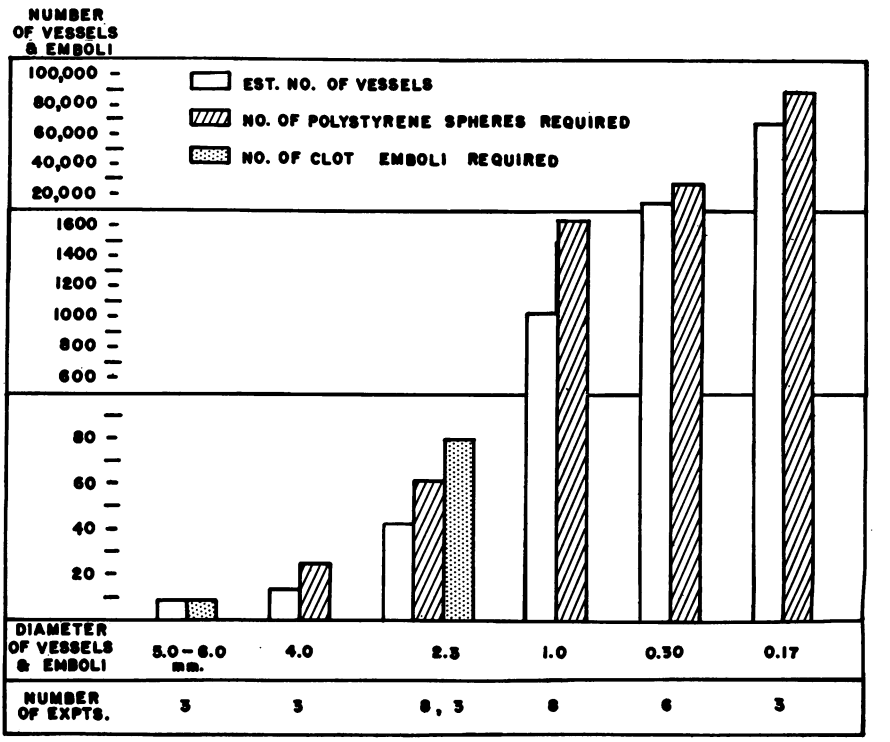

Fig. 4. Relation of number of arterial vessels of a given size to the number of emboli of that same size required to raise the pulmonary arterial pressure 5 to 10 mm.Hg. The ratio of number of vessels to number of emboli was approximately one over the whole arterial range.

Physiologic Aspects

The pathological physiology of the circulation in pulmonary embolism has been studied extensively for many years by many workers. The intact animal and the isolated perfused lung have served as experimental models, and embolic material has consisted of different types of particulate matter as well as fresh or old blood clot. The advantage of particulate matter is that it can be sieved to a given size and quantified, and that it can be made of radio-opaque material. Its disadvantage is that it is not blood.

It is well known that pneumonectomy does not produce pulmonary hypertension in man. In an attempt to assess pulmonary embolism quantitatively, polystyrene beads of different sizes have been injected intra-

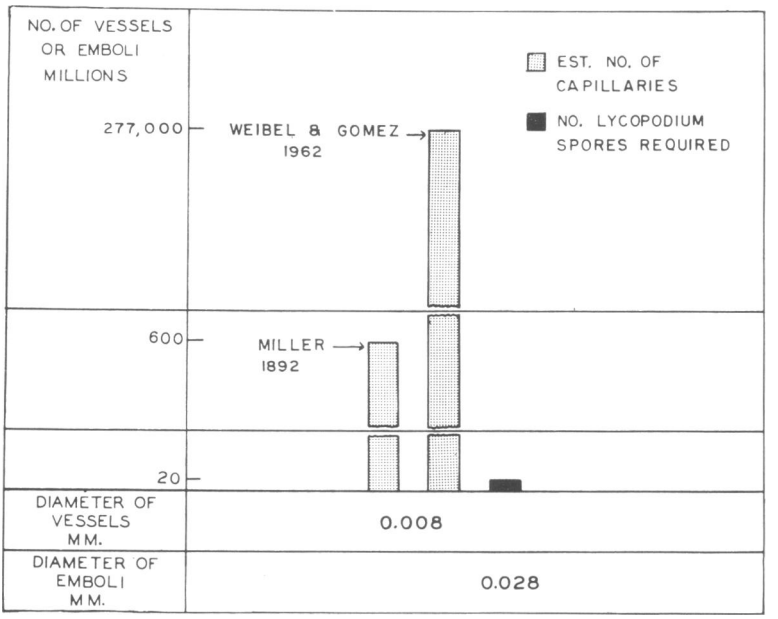

Fig. 5. Relation of number of capillaries to number of lycopodium spores required to raise the pulmonary arterial pressure 5 to 10 mm.Hg. The number of spores was only a small fraction of the number of capillaries as estimated by Miller (*J. Morph. 8*:165, 1893) and Weibel and Gomez (*Science 137*:577, 1962).

venously into dogs weighing approximately 8 kg.[9] The size of the emboli were matched to the size of the different branches of the pulmonary artery and varied from lobar size to those of atrial arteries 0.17 mm. in diameter. Capillary embolism was produced with lycopodium spores, which are regularly 28 to 30 μ in diameter and occlude the capillary exit from arterioles.[10] Emboli were administered until the pulmonary arterial pressure rose 5 to 10 mm.Hg. It was postulated that if diffuse vasoconstriction occurred, the ratio of emboli to the number of vessels of a given size would be drastically reduced. As may be seen in Figure 4, the ratio was essentially unity for arterial occlusion. Note the small number of large emboli required to produce incipient hypertension in contrast to the many thousands of tiny emboli. Results were independent of the presence or absence of anesthesia. A 24-hour-old blood clot gave the same results. Evidence for widespread vasoconstriction did not appear to occur. On the other hand, the number of lycopodium spores required to produce pulmonary hypertension was

but a small fraction of the number of capillary orifices present (Figure 5). This, together with further evidence that time does not suffice to describe,[11] confirms the finding from the rather elegant studies of Price *et al.*[12] and of Bernthal *et al.*[13] that microembolism of arterioles does result in widespread vasoconstriction.

Comroe[14] suggested some years ago that a blood clot caught in the lung might liberate serotonin from platelets and thus produce widespread pulmonary vasoconstriction. This possibility has been critically examined by Sanders and his colleagues,[15] who found that the amount of serotonin in dog and human blood was too low to account for the pulmonary hypertension from embolism. Preliminary experiments in our laboratory are in complete agreement. On the other hand, Thomas and his co-workers[16] do have evidence suggesting that serotonin may play a role in the bronchoconstriction that occurs in experimental thromboembolism.

From the evidence cited, thromboemboli, as opposed to various other types of embolic material, characteristically obstruct arteries rather than arterioles and probably produce their effects by simple mechanical obstruction to the pulmonary circulation.

Some Unsolved Major Problems

Inherent difficulties in the study of pulmonary embolism both clinically and experimentally deserve emphasis.

The pulmonary vascular reserve is such that the cross-sectional area of the pulmonary vasculature must be reduced by more than half before any manifestations of embolism occur.[17] A massive embolus occluding the main trunk of the pulmonary artery is immediately fatal and little can be done. Fortunately this is rare. Embolization of only a small part of the pulmonary vasculature cannot be suspected by either patient or physician. Between these two extremes, there is a wide range of manifestations from mild to severe, and it is in this group that patients may or may not survive, depending on the recognition and institution of therapy.

Diagnosis or recognition of pulmonary embolism is extremely difficult because it only occasionally produces typical symptoms.[3,18] It may present as heart failure, pneumonitis, bronchitis, coronary occlusion, fever of unknown origin, or syncope. Furthermore, there is no simple diagnostic test. Pulmonary angiography and lung scanning[7,19] have re-

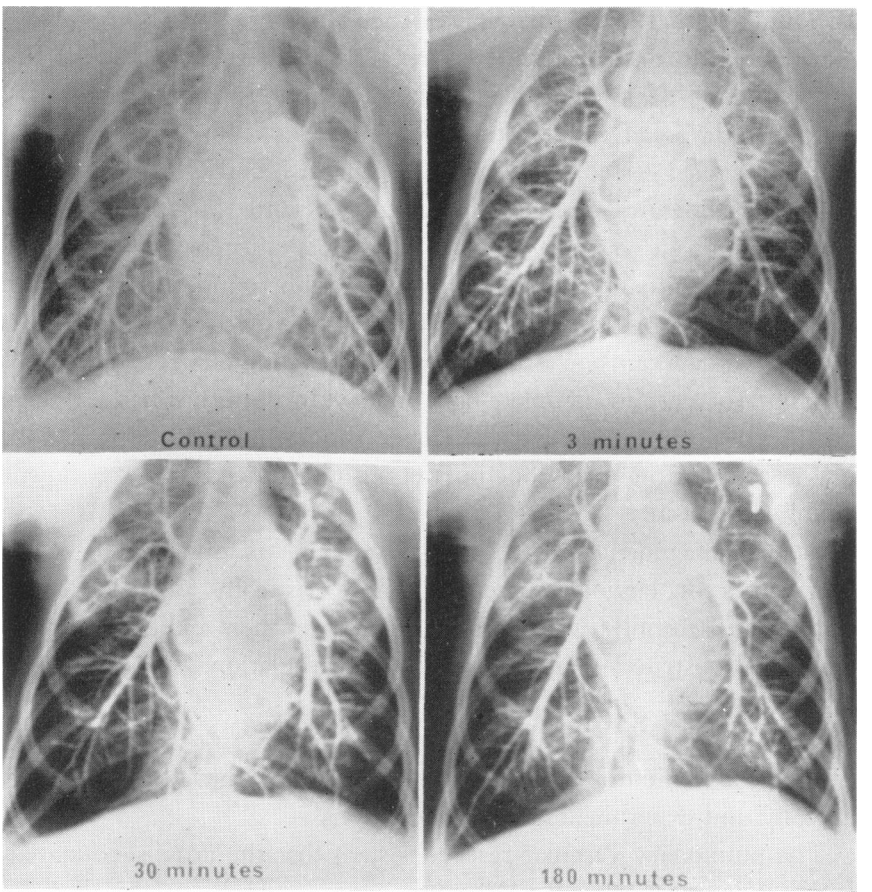

Fig. 6. Pulmonary angiogram of dog embolized with blood clot. Note oligemia of lower lobes and hyperemia of upper lobes after embolization; areas of cutoff and of partial occlusion in both lower lobes, progressive oligemia of right lower lobe, and apparent slippage of clot to the next bifurcation in the left lower lobe.

cently received considerable emphasis for diagnosis and offer promise of recognition of large emboli. However, the majority of emboli are small, and it remains to be seen if these techniques can be perfected to a point of recognizing anything more than the embolic occlusion of large vessels. The difficulties of recognition are such as to invalidate most statistical studies of the human disease and to make difficult the evaluation of efficacy of various therapeutic manoeuvres. Measures to enhance diagnosis of embolic events and, even more, of thrombotic tendencies are badly needed.

The fate of blood clot in the lung remains largely unknown. Circulating fibrinolysin lyses clots, but the speed with which this is accomplished must vary considerably from individual to individual. Propagation of thrombus after embolic lodgement may well occur in some individuals but this currently is poorly documented. We have observed it to occur histologically distal to bird shot used as embolus[20] but this does not by itself indicate that the same occurs following thromboemboli since bird shot is foreign material.

We have just begun to study this problem by taking serial pulmonary angiograms following the release of induced *in vivo* blood clot in dogs and correlating these pictures with postmortem arteriograms and histological examination.[20] An example is shown in Figure 6. This demonstrates 1) oligemia of both lower lobes and hyperemia of both uppers after embolization; 2) areas of cutoff and of partial occlusion with some circulation persisting as though the clot only partially occluded the vessel; 3) progressive oligemia of the right lower lobe, possibly due to extension of the clot or to vasoconstriction not reflected by physiologic measurements of pressure and flow since the area involved would be too small to produce general effects; and 4) reappearance of vessels in the left lower lobe apparently due to slippage of clot to the next bifurcation where the cross-sectional area of the pulmonary vasculature is larger and where, therefore, circulatory compromise is reduced. This, rather than vasoconstriction, may well account for the transient pulmonary hypertension that accompanies embolism.

It is quite apparent in human disease that repeated embolism may produce chronic cor pulmonale. Obviously the input of emboli has exceeded the lytic process or output. Little is known of the processes of thrombosis *in situ*, extension of the clot, lysis of clots, the effect of thrombolytic agents, or even what causes intravascular thrombosis in the first place. The status of the thrombotic process is not much farther along than where it was left by Virchow[21] over 100 years ago. Virchow offered the three basic explanations of stasis, trauma to vein walls, and hypercoagulability of blood. In the meantime, prevention by vein ligation and anticoagulants appear to be highly effective but to depend on recognition of an embolic event before being implemented. Surgical therapy, too, depends on diagnosis. The Trendelenburg operation has recently become rejuvenated through modern techniques of

placing the lung on by-pass and aspirating the clot from the pulmonary arterial system.[22] Indications for such surgical interventions are far from clear because of lack of knowledge of the prognosis without surgical therapy, of the fate of the emboli within the lung of that particular individual, or of the relative medical and surgical risks.

SUMMARY

Acute thromboembolism is common and is a serious disease. In our experience, embolism is massive when fatal. Small emboli cannot be suspected clinically. We have been unable to obtain evidence of widespread vasoconstriction from thromboembolism. However, this may well occur in other types of embolism that occlude arterioles, because evidence has been presented that arteriolar embolism does give rise to widespread pulmonary vasoconstriction. Therapy and prophylaxis are far ahead of diagnosis. It is the difficulty of recognition that prevents the institution of prophylaxis or of surgical removal of embolic material. However, even though a diagnosis is made, indications for surgical removal are far from clear because of lack of knowledge of the prognosis in any given individual.

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