Hemodynamic Alterations of Acute Pulmonary Thromboembolism

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Pulmonary thromboembolism as a complication of disease or surgical treatment has long been feared as a cause of death or prolonged morbidity. Although there have been extensive studies of the clinical, pathological, and hemodynamic features of this disease process, there still remain many gaps in our knowledge and the widest of these concerns the pathophysiology of pulmonary thromboembolism. An amazing variety of materials including lycopodium spores, glass beads, lead pellets, starch, penrose drains, barium sulfate, and many other foreign particles of varying sizes have been experimentally injected into the pulmonary arteries to simulate thromboembolism. With the notable exception of the studies performed in Europe, particularly in France, when fibrin or thrombotic material has been used, it has been injected into the venous system in a manner that has resulted in many minute emboli rather than the large embolus usually encountered in clinical medicine. When other techniques of experimental pulmonary embolism have been employed resulting in larger emboli, hemodynamic data of the pulmonary and systemic circulation have either not been obtained, recorded only in part, or the results of the study have revealed minimal or no significant hemodynamic alteration. In contrast to these investigations, the study of Moreau et al. was apparently complete, but their hemodynamic data are only briefly summarized. Further, the conclusions reached by these numerous studies to identify the hemodynamic consequences of pulmonary embolism have been varied and conflicting. Many have championed a mechanical obstruction theory, others have implicated a reflex, either neurogenic or neurohumoral, and still others have postulated a combined effect of these mechanisms. The sites of the vascular responses have also been a subject of controversy and designated as occurring in the main pulmonary arteries, the pulmonary arterioles, the pulmonary veins, or in pulmonary arteriovenous anastomoses. As a consequence, there remains considerable confusion in the elucidation of the acute hemodynamic alterations that occur as a result of pulmonary thromboembolism of a type that is comparable to the events in clinical medicine.

In an attempt to clarify these conflicting data and theories and to simulate more closely pulmonary thromboembolism in the human, this method of experimental pulmonary embolism was developed. More specifically, the purpose of this study is twofold: first, to localize the site of vascular obstruction that occurs in the pulmonary circulation secondary to thromboembolism and to determine whether it is of reflex or mechanical origin; and second, to examine the systemic hemodynamic alterations that also occur to determine if they can be specifically related to the pulmonary hemodynamic changes. Determination of reflex pathways that may be involved in these responses or evaluation of therapeutic measures in the treatment of pulmonary embolism are not a part of this study, but are undergoing separate evaluation in a related study.

Methods

The experimental data upon which the present report is based were derived from 84 embolic
episodes in 30 healthy mongrel dogs weighing from 12.7 to 35 Kg. The radiopaque clots employed were prepared in a manner suggested by the method of Allison et al.\textsuperscript{18} Blood drawn from the experimental animal the day prior to study was anticoagulated with disodium ethylenediaminetetraacetate. A paste obtained by decanting the liquid from a settled 50 per cent suspension of propyliodone\textsuperscript{*} was thoroughly mixed with the blood in the proportion of 0.3 Gm. paste to 4 ml. blood. Ten thousand NIH units of topical thrombin were dissolved in 5 ml. of molar calcium chloride. When the thrombin-calcium mixture was added to the blood (0.05 ml./ml.) in a water bath at 37 C, prompt clotting ensued. Injection of propyliodone in amounts up to 2 Gm. into the pulmonary arteries of the experimental animals was without effect on the pulmonary arterial pressure. Roentgenograms of the clots, obtained prior to each study (fig. 1), revealed homogeneous radiopaque fixation. Such clots were uniformly firm and well contracted; they closely resembled normal clots in consistency and friability. The clots were weighed immediately prior to use.

The dogs were anesthetized with morphine sulfate, 4.5 mg./Kg. subcutaneously, and intravenous pentobarbital sodium in a variable dosage sufficient to produce surgical anesthesia. At least three hours elapsed between initiation of anesthesia and beginning of the experiment to allow development of a steady state.\textsuperscript{38} To prevent pulmonary hypertension due to hypoxia,\textsuperscript{84,85} 100 per cent oxygen was administered continuously through a cuffed endotracheal tube, employing a closed system with soda lime carbon dioxide absorber and provision for recording respiratory rate and oxygen uptake.\textsuperscript{1} Respirations were unassisted. The dogs were positioned on their backs and not moved during the experiment.

Left lateral and posterior-anterior chest roentgenograms were obtained of each animal prior to and on completion of the experiment. A nine-inch image intensifier with provisions for cine-radiography was used and all radiographic factors were constant.

Electrocardiograms were taken at the beginning and end of each experiment. Standard lead I or II was monitored continuously throughout the procedure.

Systemic arterial pressure was monitored by cannulation of a femoral or carotid artery. Appropriately sized Cournand cardiac catheters were placed in the pulmonary artery and pulmonary arterial "wedge" position through the left jugular vein. To validate the pulmonary capillary pressures obtained in the initial phases of the study, pulmonary venous pressure was monitored in a series of experiments through a cardiac catheter positioned by retrograde passage through a femoral artery. At appropriate intervals during the experiment, the pulmonary venous catheter was withdrawn into the left atrium with continuous pressure recording. All pressures were monitored throughout the study and for periods up to 45 minutes after the last embolus in surviving dogs. Right atrial and right ventricular pressures were obtained at the beginning and end of the procedure. All pressures were measured with strain gauges,\textsuperscript{4} which were placed at the level of the midthoracic horizontal plane.

Cardiac output was determined from indicator-dilution curves utilizing indocyanine-green dye,\textsuperscript{86} and the standard method of derivation of pulmonary arteriolar resistance was used.\textsuperscript{87} The site of injection for successive curves was constant in a given experiment; in most cases the pulmonary artery, in a few the right ventricle or right atrium, was selected. Sampling for dye curves was from the right femoral artery.

\textsuperscript{*}Dionosil, Glaxo Laboratories, Ltd., Greenford, England.

\textsuperscript{1}Sanborn Metabulator.
Electrocardiogram, direct and electrical mean pressure tracings, and dye-dilution curves were recorded simultaneously with an eight-channel, variable speed photographic recorder with oscillographic monitor.  

At the beginning of the experiment, a baseline dye-dilution curve, direct and mean pressures from a systemic artery, the pulmonary artery, and pulmonary arterial "wedge" or pulmonary vein were recorded. The right jugular or, in some instances, the right femoral vein was cannulated with a large tapered glass syringe with exit bore of 2 mm. to 5 mm., depending on vein size. The weighed radiopaque clot was impacted at the opening of the syringe and sufficient normal saline solution added to act as an air seal. The clot was then injected by manual compression of a rubber bulb affixed to the syringe and passage of the embolus into the pulmonary arterial tree was monitored visually and cinefluoroscopically. Timing marks were recorded at the time of injection and at the time of impact of the embolus as seen fluoroscopically. An arbitrary number of emboli were used in each study at intervals of ten minutes to one hour and embolization proceeded usually until significant sustained pulmonary hypertension was evident. One to four embolic episodes were recorded in this fashion during each experiment. In some dogs, cineangiograms were performed by the rapid manual injection of 1.5 ml./Kg. of contrast material through an NIH cardiac catheter just prior to the first embolus and immediately following each embolus. In other cases, angio-

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*Electronics for Medicine, Inc., White Plains, New York.

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FIGURE 2
Left lateral chest film after the first embolism showing several large radiopaque emboli lodged in the pulmonary artery to the diaphragmatic lobe.

FIGURE 3
Gross appearance of radiopaque embolus impacted in a secondary branch of the pulmonary artery (arrow).

FIGURE 4
Left lateral chest films obtained before and after repeated thromboembolism showing impaction of the radiopaque emboli in the distal branches of the pulmonary arteries of the apical, cardiac, and particularly the diaphragmatic lobe. Note dilatation of the heart, primarily right ventricle, and pulmonary artery in the postembolic film.
PULMONARY EMBOLISM

FIRST PULMONARY EMBOLISM

PRESSURES - BEFORE AND AFTER EMBOLISM

mean systemic
mean pul. artery
mean pul. vein
mean pul. "wedge"

FIGURE 5

Graphic representation of the maximum acute hemodynamic response to an initial thromboembolism in 30 dogs showing mean systemic arterial, pulmonary arterial, and pulmonary venous or "wedge" pressures before and after (shaded symbols) the embolic episode. Note the progressive increase in the ratio of the gram weight of clot embolus to the kilogram weight of the dog, plotted along the abscissa. Death of the animal is indicated by a cross. See text for comment.

Results

The large radiopaque clots were partially fragmented on injection into a peripheral vein and further fragmentation was observed during the turbulence of cardiac passage. Nevertheless, the size of the resulting emboli was large in relation to the pulmonary arteries. They were found to obstruct large pulmonary arteries both on roentgenographic (fig. 2) and postmortem study (fig. 3). The time of transit from a major peripheral vein to pulmonary artery as visualized fluoroscopically was only a few seconds. Occasionally, large fragments of the embolus were seen to be retained in the right-heart chambers through four or five cardiac systoles. There was no statistically significant predilection for either lung as far as the site of lodgment was concerned, although the diaphragmatic lobes were more commonly involved (figs. 2 and 4). An interesting phenomenon observed was the manner in which the emboli were progressively impacted into the distal pulmonary vasculature, resulting in a virtual thrombotic cast of the pulmonary arterial tree after repeated embolic episodes (fig. 4).

A summation of the intravascular pressure changes resulting from this method of pulmonary embolism is charted in figures 5 and 6. Figure 5 records the hemodynamic data of the first embolism and reveals a consistent alteration in pulmonary hemodynamics. Excepting a single case in which a very small embolus was used, significant pulmonary hypertension was uniformly produced. Otherwise, the size of the embolus did not seem to influence the magnitude of the pressure response. Pulmonary wedge or "capillary" pressures and pulmonary venous pressures showed only minor variation from the baseline, frequently being unchanged or showing a slight fall but always remaining within normal limits. No significant gradient between the pulmonary venous and pulmonary "capil
MULTIPLE PULMONARY EMBOLISM

MEAN PRESSURES — BEFORE AND AFTER EMBOLISM

Graphic representation of the maximum acute hemodynamic response in each dog resulting from the last of a series of multiple pulmonary emboli. The hemodynamic data are grouped according to the maximum number of emboli for each animal. The format is otherwise as in figure 5.

Characteristically, the rise in pulmonary artery pressure was noted promptly (figs. 7, 8, 9) on impact of the embolus in a large pulmonary artery and progressed to its maximum increase over the next three to six seconds; a similar timed response was noted in the systemic hemodynamic alterations. The duration of the pulmonary hypertension was transient, often lasting less than ten minutes and falling to baseline levels or remaining only slightly elevated for more prolonged periods up to 30 minutes (figs. 10, 11, 12).

Similar data obtained after repeated pulmonary embolism are shown in figure 6 and differ from the results of the first embolism primarily in regard to the magnitude of the systemic arterial pressure changes. The baseline pulmonary artery pressure was usually but variably elevated due to the prior embolic episodes. On subsequent embolism, a marked though transient rise in pulmonary artery pressure was uniformly produced as with initial embolism. The magnitude of the response could not be related to the size of the embolus or the number of prior embolic episodes. Also, the actual pressure rises for each embolic episode in this group did not seem to be any greater than the pulmonary arterial pressure rise produced in the first embolism group. However, the height of the mean pressure was greater than in the first embolism group because of higher pre-embolic baseline pressures. A systemic hypotensive response was the usual alteration expected and was consistently more pronounced than on initial embolism.

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Often severe systemic hypotension resulted in death, but in a few instances the hypotension was shown to be reversible (fig. 9). Occasionally, a mild rise in systemic arterial pressure was produced, but this was less frequent than in the single embolism group. Although neither the size of the single embolus nor the frequency of embolic episodes could be related to the severe hypotensive episodes, total weight of the multiple clot emboli seemed to be an important factor, particularly when above 0.39 Gm. of clot per Kg. of dog weight (fig. 6) had been given.

Cardiac rate was not significantly changed (figs. 7, 8, 9) immediately after pulmonary embolism. Premature ventricular beats were occasionally recorded on passage of the embolus through the right ventricle, but the cardiac catheters may have been the responsible stimulus. Only when severe systemic hypotension or pulmonary edema occurred was an appreciable change noted, and this was frequently the development of sinus tachycardia or bradycardia, followed by atrioventricular (A-V) block, an idioventricular rhythm, ventricular standstill, and often ventricular fibrillation as a terminal event.

In over half of the experiments, cardiac output determinations were made immediately following embolism (fig. 8). Except in those experiments in which severe systemic hypotension occurred, there was little change from the baseline determinations. Although increased or unchanged cardiac outputs were recorded, the usual response (figs. 10, 11, 12) was a slight decrease in cardiac output following the initial embolism and only minimal variation in subsequent nonfatal embolic episodes. However, calculated pulmonary arteriolar resistance rose in every instance.

Spirometric studies of respiration revealed only minimal changes as a result of the initial embolus, usually a mild tachypnea (fig. 13). If pulmonary edema developed, this became much more pronounced. A deep inspiration followed by a brief but variable period of apnea commonly accompanied the more severe systemic hypotensive episodes (figs. 9, 13) and seemed to be related to the systemic response more than to the extent of pulmonary hypertension produced. When measured, there was little change from the baseline in arterial oxygen saturation after embolism (fig. 10) and the initial minimal decreases from normal that were recorded could be explained as slight hypoventilation probably due to the anesthesia.

As compared with baseline studies, the angiocardiograms (fig. 14) obtained immediately after an embolic episode uniformly revealed definite dilatation of the pulmonary arterial tree from the main to the tertiary branches. These studies confirmed the experience of Lockhead et al. 38

Three patterns of response to repeated pulmonary embolism were identified during this study. The first was one of the development of a progressively severe pulmonary hypertension with survival of the animal (fig. 10). The second was characterized by the development of pulmonary edema (fig. 11) and the third, the development of severe systemic hypertension.
FIGURE 8
Hemodynamic data illustrating the results of an embolus weighing 3.7 Gm. which was the last of four clot emboli weighing a total of 7.2 Gm. Note that pulmonary venous (PV) and carotid arterial (CA) pressures are normal and uninfluenced by the embolism. However, the pulmonary arterial pressure (PA), already elevated due to previous emboli, shows an abrupt rise on impact of the embolus in the main pulmonary artery as monitored fluoroscopically. Cardiac rate remains unchanged, though the respiratory rate shows a slight decrease as indicated by the respiratory fluctuations of the PV pressure tracing. Note the time interval of determination of cardiac output after embolism, that was the usual standard in these experiments. In this particular experiment, cardiac output was calculated at 3.0 L./min., representing a decrease of 0.6 L./min. from the baseline. Pulmonary arteriolar resistance increased from a baseline of 250 to 1,333 dynes sec. cm⁻².

Seventeen dogs died (figs. 5 and 6) in the postembolic period, most after repeated embolisms. Nine died as a result of severe systemic hypotension and eight of pulmonary edema occurring ten minutes to several days after embolism. Most showed the terminal development of A-V dissociation and finally ventricular standstill or fibrillation. The occurrence of pulmonary edema has been documented by others,⁵¹,²⁴,²⁶ and this mechanism of death is being subjected to further investigation.

Postmortem studies were carried out in all deceased dogs, including histopathological examination in the majority. These studies revealed various-sized emboli which lodged in the major branches of the pulmonary artery. Further fragmentation of the embolus with minute peripheral embolism distal to the site of major obstruction was also shown to have occurred (fig. 15). Histological studies of multiple lung sections failed to reveal evidence of diffuse minute emboli in areas other than those involved by grossly visible emboli. Hemorrhagic pulmonary infarctions were produced in all of the animals that died. Diffuse pulmonary edema in varying degrees was an accompanying finding in eight of the cases.

Discussion
Although much remains to be desired in the experimental simulation of human pulmonary thromboembolism, the method described in this experimental study has at least permitted measurement of certain hemodynamic consequences of embolism of large clots as well as documentation of the temporal relationships of these alterations to the course of the embolus.
PULMONARY EMBOLISM

Compromises were necessary to maintain a closed-chest animal under basal conditions and the effects of anesthesia had to be accepted. The effects of hypoxia on the pulmonary vascular bed, particularly as regards the production of pulmonary hypertension, presumably due to vasoconstriction, have been well documented. For this reason, 100 per cent oxygen was used for respiration with periodic monitoring of systemic arterial oxygen saturation to insure that hypoxia was not a feature of concern. The salutary effect of 100 per cent oxygen in minimizing the hemodynamic changes of pulmonary embolism is known. Nevertheless, the overwhelming problem under these circumstances was to ensure that hypoxia was not a significant factor in causing the pulmonary hypertensive response to embolism.

Clots formed in vitro cannot be considered exactly the same as those formed in vivo, but then in vitro clots do resemble the propagating tail of the thrombus which is the part most apt to become embolic. The clots in this study were altered only slightly by the admixture of the radiopaque material. This method of clot formation was necessary to quantitate accurately the size of the embolus and to allow cinefluoroscopic visualization.

Although fragmentation occurred during embolism, the embolized clots were large and obstruction of major branches of the pulmonary artery occurred as well as of the smaller vessels distal to the primary site of lodgment of the embolus. A similar type of phenomenon with fragmentation of the embolus is a well known finding in postmortem studies of the human who has suffered pulmonary thromboembolism.

An identification of the specific characteristics of the pathophysiology of pulmonary thromboembolism is a major challenge and the controversy as to the site of the pulmonary vascular alteration and the cause, whether reflex vasospasm or mechanical blockage, still exists. Many still favor mechanical blockage as the explanation for the hemodynamic changes of pulmonary embolism.

From the data accumulated in this study, the site of the increased resistance in the pulmonary vascular bed may be localized to the small pulmonary arteries or arterioles, and the increased resistance may be attributed predominantly to vasospasm unless massive or repeated embolism has occurred. The site of the vascular obstruction may be determined without difficulty. The pulmonary "capillary" and pulmonary venous pressures remain normal and are not significantly altered by the embolism (figs. 5 and 6). Since increased pulmonary artery pressures are recorded only proximal to the pulmonary "capillary" and since dilatation of the large and medium-sized pulmonary arteries is shown to occur after embolism, the obstruction must be localized between these two sites; namely, in small pulmonary arteries and arterioles.

This, however, does not clarify the more complex problem of determining the cause of this increased vascular resistance; that is, whether it results from vasospasm or simple mechanical blockage. There are four reasons why vasospasm may be considered the important factor, at least during the initial thromboembolic episode. First and most important, the data in this study (fig. 5) demonstrate that marked pulmonary and systemic arterial hemodynamic alterations could not be correlated with the weight of the pulmonary embolus in the initial embolic episode. It has been shown by repeated experiments as well as clinical studies that for significant pulmonary hypertension to be produced by mechanical blockage at least 50 to 80 per cent of the pulmonary vascular bed must be obstructed. Therefore, the demonstration of severe hemodynamic alterations resulting from small pulmonary emboli that could not produce generalized mechanical obstruction would exclude this as a factor. Second, the failure to demonstrate by histological study embolized clot in the small arteries or arterioles in other than sites distal to grossly obstructed pulmonary arteries is evidence against diffuse small embolism. Undoubtedly, some embolism distant from the site of major...
A continuous recording, with time breaks as indicated, showing the severe hemodynamic alterations following a third pulmonary embolism of a 5.1-Gm. clot (total of 14.8 Gm.). The temporal relationship of the embolus impact in the main pulmonary artery to the pulmonary and systemic pressure changes, and the development of apnea and bradycardia is indicated. The pulmonary arterial pressure (PA) shows the typical abrupt rise, but the monitoring catheter is dislodged into the right ventricle (RV). The most significant alteration is the severe systemic hypotension initiated simultaneously with the PA pressure change and persisting five minutes before recovery. Note particularly the time relationship of the development of apnea and bradycardia. As reflected by the respiratory variations in the mean pulmonary "capillary" (PC).
PULMONARY EMBOLISM

Time chart showing the pressure changes in the pulmonary and systemic circulations in response to three separate pulmonary embolic episodes. Note the relative transient periods of pulmonary hypertension following each embolism with a gradual but stepwise increase of relative sustained pulmonary hypertension as embolism proceeded. Note right atrial pressures obtained at the beginning and end of the experiment were normal. The variations in cardiac output were determined in the immediate postembolic period (fig. 8) as were the arterial oxygen determinations. (See text for comment.) This dog survived these multiple pulmonary emboli with no apparent subsequent ill effect.

The embolic clot did occur, but not of a magnitude to cause a diffuse obstructive phenomenon that would account for the pulmonary hypertension on the basis of obstruction alone. The prompt response (figs. 7, 8, 9) of the pulmonary and systemic hemodynamic alterations produced when the embolus strikes the main or large pulmonary arteries is a third factor favoring a vasomotor reaction so long as mechanical obstruction of these large arteries can be excluded. A prompt increase in the pulmonary artery pressure was recorded in the tertiary branches at the time of initial impact of the embolus. This is distal to the...
Figure 12

Time chart illustrating an experiment of multiple pulmonary embolism and showing the hemodynamic alterations in the systemic and pulmonary circulation prior to and including the development of severe systemic hypotension after the fourth embolus. There is no significant gradient between or change in the pulmonary venous or "capillary" pressures. The right atrial pressure is unchanged. Note the mild, transient systemic hypotension produced by the initial emboli and the tendency to develop a hypertensive overshoot, considered to be due to a reflex increase in systemic arterial resistance. The cause of death was ventricular fibrillation.

site of possible mechanical obstruction of the proximal main or large pulmonary arteries and therefore excludes this factor. Finally, a fourth finding favoring a vasomotor reaction is the transient nature of the pulmonary hypertension after embolism (figs. 10, 11, 12) without a corresponding decrease in cardiac output. The magnitude of this transient pressure response was similar in almost all embolic episodes (figs. 5 and 6) regardless of the weight of the embolus, the number of embolic episodes, or the pre-embolic pulmonary arterial pressure. Mechanical obstruction would be expected to give a more linear relationship dependent upon the size and number of emboli. In fact, this latter type of pressure response was also demonstrated in these experiments by the sustained stepwise rise of pressure that occurred after repeated emboli (figs. 10, 11, 12). It is obvious that mechanical obstruction resulting from embolism could not be removed over the brief period that the transient type of pulmonary hypertension persisted. Calculation of "pulmonary arteriolar resistance" is a useful semiquantitative expression of overall hindrance to flow in the pulmonary arterial circuit. This value shows a sharp rise soon after embolus impact with

Figure 13

Series of typical spirograms, each encompassing a four-minute period, beginning on release of a clot embolus in the jugular vein. All these pulmonary emboli resulted in pronounced hemodynamic changes. (1) Initial pulmonary embolism with a clot weighing 2.49 Gm. showing no appreciable effect on respiration. (2) A series obtained in a second animal during each of three embolic episodes: (a) Initial embolism of a 2.34-Gm. clot showing development of a mild tachypnea with brief periods of apnea; (b) The second embolism (2.3-Gm. clot) resulting in moderate tachypnea but for only a brief period; (c) A moderate tachypnea was evident prior to the third embolism of a 2.1-Gm. clot which produced a short period of apnea.
a slow fall toward control values subsequently. The opening of pulmonary vascular channels normally closed except for periods of increased pulmonary blood flow and pressure, the opening of arteriovenous communications, or a decrease in arteriolar vasomotor tone are the primary considerations in speculating on the cause for the decrease in pulmonary vascular resistance.

The failure to demonstrate systemic arterial oxygen desaturation in the immediate postembolic period (fig. 10) is evidence against the opening of a significant number of venoarterial shunts in the lung as an explanation. Also in this same regard, the opening of previously closed or resting precapillary arterioles as an explanation for the fall from the transient peak of pulmonary hypertension is not warranted. It may be postulated that in those experiments in which severe sustained pulmonary hypertension has been produced by repeated embolism, a critical closing pressure has been exceeded and there is maximal distention of the pulmonary arteriolar bed. The transient pulmonary hypertension that may then occur on a subsequent embolization and, in particular, the fall in that pressure would best be explained by vasomotor responses in these vessels rather than mechanical blockage with opening of accessory channels. Although the sustained pulmonary hypertension that results from repeated emboli may be attributed to mechanical blockage, reflex responses cannot be excluded. Either hormonal influences such as might be produced by serotonin release or a neurogenic reflex such as the feedback mechanism postulated by Whitteridge may be responsible.

The systemic pressure response to acute pulmonary embolism deserves more consideration than has been accorded to it in the past. The pulmonary hemodynamic alterations have dominated the attention of most investigators; and although systemic hypotension has been recognized as a feature that may accompany these pulmonary changes, this has usually been considered solely the result of decreased cardiac output incident to obstruction of blood flow in the pulmonary circuit. The results of our studies and others would question the assumption that only alterations in cardiac output could explain the systemic pressure changes. As with the pulmonary hemodynamic alterations of embolism, the prompt initiation of the systemic response, its transient nature, and the reversibility of the hypotension, even when severe, would favor a reflex mechanism as playing a role. Further, systemic arterial pressure response was unpredictable (figs. 5 and 6) and bore no direct relation to the degree of pulmonary hypertension produced or the size of the embolus. Occasionally, moderate systemic hypertensive responses (figs. 5, 6, 10, 11, 12) followed embolism as previously reported, and this is suggestive of either an increased cardiac output or increase in peripheral arterial resistance secondary to vasomotor changes. When
pronounced systemic hypotension occurred, it was often followed by death (figs. 5 and 6). This type of response became more frequent as the total weight of repeated thromboembolism increased, and in this regard mechanical obstruction to pulmonary blood flow was a contributing factor. Even when death did not result immediately, a severe hypotensive episode was a serious prognostic finding, often heralding pulmonary edema (fig. 11) and correlating well with subsequent demise after the next embolus. State and Salisbury demonstrated exaggerated systemic hypotension in their investigation by producing a definite increased mortality rate in those animals which had been rendered hypotensive prior to embolism. The magnitude of this systemic response thus seemed to be influenced by changes in the systemic arterial resistance and apparently the inability of the systemic arteriolar bed to respond to reduced cardiac output with an appropriate rise in resistance.

Although significant changes in cardiac output occurred, usually showing slight decreases in the immediate postembolic period and particularly after initial embolism (figs. 10, 11, 12), none of these changes were pronounced except when severe systemic hypotension occurred. Under these circumstances, the profound decrease in cardiac output may be explained as the result rather than the cause of hypotension. In the milder systemic hypotensive episode, changes in cardiac output could not be specifically incriminated as the sole cause of the hypotension, but undoubtedly a decreased cardiac output was a major factor.

The cause of a severe but potentially reversible systemic hypotension following pulmonary embolism therefore appears to be due to a combination of factors including a decrease in cardiac output and reflex changes that influence the systemic arteriolar resistance.

Stretch reflexes in the lung have been shown to cause systemic hypotension and may be activated by the pulmonary ventilatory and circulatory responses to embolism. A more likely reflex, particularly when severe systemic hypotension occurs, would be a proprioceptive reflex initiated in the right ventricle, similar to the Bezold-Jarisch chemoreflex producing associated apnea and bradycardia (fig. 9), or a baroreceptor-type reflex in the pulmonary artery, as might be suggested by the studies of some investigators. Although the site of stimulation of the presumed reflex cannot be definitely identified, it is not due to increase in pressure in the pulmonary veins or left atrium as has been suggested. Preliminary investigations initiated during this experimental study also show that this type of response does not seem to be influenced by atropinization of the animal. Another possible mechanism is the effect of serotonin, which has been shown to be released in abundance at the site of a thrombus or pulmonary infarction, resulting in systemic hypotension either as a direct response or secondary to release of additional substances such as histamine. The fallacy of drawing conclusions in regard to these hormonal responses, particularly in translating such animal studies to the human, has been demonstrated.

Reflexes previously considered to be initiated in the small vessels of the lung by multiple embolism and characterized by
tachypnea were apparently not an important factor in this study, since respiratory changes incident to embolism were not pronounced unless severe systemic hypotension or pulmonary edema developed. In this regard, a comprehensive review of the reflexes that may be initiated from the heart and lung vessels indicates the multiplicity of factors that must be considered in the identification of any specific reflex as the cause of the hemodynamic alterations of pulmonary thromboembolism. Reflex pathways through the vagus or the sympathetics may be implicated, while others believe that neither system is involved.

Although this study falls short in many respects of the ideal experimental simulation of human pulmonary thromboembolism, one cannot help but be aware that the hemodynamic, pathological, and clinical alterations produced in these experiments resemble closely the known alterations produced by this event in the human. Systemic hypotension of a transient nature is a characteristic feature in almost a third of clinical cases of pulmonary embolism and severe systemic hypotension often characterizes the fatal cases. In the majority, the results of pulmonary embolism reveal transient and often minimal evidence of pulmonary hypertension except after repeated embolic episodes when pulmonary hypertension may become sustained. However, the severity of the hemodynamic changes in the human, as in this study, has not always been related to the size of the pulmonary embolus. The importance of the response of the systemic circulation to pulmonary embolism and the relation of systemic hypotension rather than the degree of pulmonary hypertension to mortality re-emphasize the need for further evaluation of this systemic pressure response. Likewise, the mechanism of pulmonary edema secondary to pulmonary embolism as a cause of mortality in the experimental animal deserves further study, specifically, as it may be related to aggravation of congestive heart failure and death in the human.

Summary

A method is described of producing pulmonary embolism in the dog by the use of various-sized autologous clots made radiopaque. This method of experimental pulmonary embolism results in dilatation of the large- to small-sized pulmonary arteries and a consistent hemodynamic response in the pulmonary circulation, characterized by a marked rise in pulmonary arteriolar resistance with increased pulmonary arterial pressure but persistently normal pulmonary venous and 'capillary' pressures.

Data are presented to support the concept that the pulmonary hemodynamic changes that result from an initial pulmonary thromboembolism are primarily the result of vasoconstriction of the small pulmonary arteries or arterioles, presumably by a reflex mechanism. Mechanical blockage of the pulmonary vascular bed is considered to be of importance in causing hemodynamic alterations only after massive or repeated pulmonary embolism. The increase in pulmonary arteriolar resistance that results from the vasomotor response to pulmonary embolism is transient, whereas that due to mechanical blockage results in sustained pulmonary hypertension.

Systemic arterial pressure does not show a consistent response to pulmonary embolism and could not be related to the hemodynamic alterations that occurred in the pulmonary circulation. Severe systemic hypotension resulted unpredictably but was more frequent after repeated or extensive pulmonary embolism. The systemic hypotensive reaction to pulmonary embolism is only in part due to a decreased cardiac output. The more severe responses are best explained on the basis of a vasomotor reflex producing a decrease in systemic arterial resistance.

The two mechanisms of death in this experimental series were severe systemic hypotension with development of fatal ventricular arrhythmias and, almost as frequent, pulmonary edema that was characterized by severe pulmonary hypertension in the presence of a normal pulmonary venous pressure.
There are many similarities between the experimental findings of this study and the clinical event of human pulmonary thromboembolism. Attention is drawn to the need for further investigation of the mechanism of the systemic arterial pressure response that often causes death and appears to be independent of the magnitude of the pulmonary hemodynamic changes.

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References


PULMONARY EMBOLISM


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