Effects of Pulmonary Embolism on the Pulmonary Circulation With Special Reference to Arteriovenous Shunts in the Lung

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Pulmonary embolism using glass beads was investigated in anesthetized dogs. The instantaneous bradycardia and apnea immediately following the injection is a reflex mediated by the vagus. The subsequent respiratory stimulation is also reflex in nature mediated not only by the sensory vagus but also by the thoracic sympathetics and the aortic and carotid body chemoreceptors. The latter are activated by anoxemia which appears to be due to opening of arteriovenous communications in the embolized lungs. In the perfused lungs, the hypertension of embolization is the outcome of mechanical obstruction by the emboli plus reflex vasoconstriction which is partly mediated by the extrinsic pulmonary nerves.

Massive pulmonary embolism causes cardiac failure and death within a few minutes. On the other hand, embolization of only a small part of the pulmonary vasculature may have no discernible effects, either immediate or remote. The former is necessarily fatal regardless of treatment, whereas the latter apparently requires no treatment at all. Between these extremes, however, there appears to be a wide range within which the individual may survive for several hours or even days. Sixty per cent of the eventually fatal cases fall into this category and appropriate treatment might lead to survival of some of these patients.

The following experiments were undertaken for the purpose of elucidating the pathologic physiology of severe but not immediately fatal pulmonary embolism, in the hope that more effective therapy might be developed.

Methods

Experiments were conducted on dogs varying in weight from 7 to 20 Kg. The sole anesthetics were morphine (2 mg./Kg.) and chloralose (70-100 mg./Kg.). Mepesulfate* (50 mg./Kg.) was the only anticoagulant used. The trachea was cannulated routinely. Pressures in one carotid artery and, in some experiments, in the left atrium were measured by a saline or mercury manometer after insertion of appropriate glass cannulae and catheters. Respiration was recorded by means of a pneumograph and a spirometer whenever possible. Blood samples were obtained through a polyethylene catheter in one femoral artery and were analyzed for contents of oxygen and carbon dioxide, for total hemoglobin, and for oxygen saturation. Gas mixtures were administered through a bag attached to the inlet side of a double tracheal valve, or to the inlet side of a Starling "Ideal" pump (Palmer). Pulmonary arterial pressure was measured by means of the Lilly capacitance manometer through a catheter, or by a saline manometer after insertion of a glass cannula into a pulmonary lobar artery. The chest was opened, when necessary, by an incision through the left fourth intercostal space. In several experiments, the lower lobe of the left lung was perfused by means of a Dale-Schuster pump at a constant volume flow with blood from the right atrium of a donor dog. The venous outflow from the lung lobe was collected in a reservoir from whence it was returned to the donor.

Glass beads were used exclusively for embolization in the experiments reported here, because they fulfilled the following desirable requirements: (1) the beads are readily available in uniform and known sizes; (2) they have smooth surfaces not inducing mechanical or chemical irritation of the tissues and (3) they are retrievable from the blood at any instant in order to determine their passage, if at all, through the lungs. The major objection to their use is their specific gravity, which is greater than blood. As shown later in the paper, this was not of great consequence in deriving observations of respiration, sys-
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Tecmic blood pressure, pulmonary vascular resistance, and blood gas contents. The glass beads* used ranged in size from 60 to 420 micra. Unless otherwise denoted, they were injected into the right ventricle via a large bore polyvinyl tube (4 mm. inside diameter, 6 mm. outside diameter) that was inserted through the right external jugular vein. The injections were made by placing the emboli in a thistle tube filled with 0.9 per cent saline and the beads were then washed in with 10 cc. of saline from a syringe attached to a rubber stopper fitted over the open end of the thistle tube. This facilitated a rapid and uniform injection of 0.5 to 10 gms. of beads, which was always preceded by a control injection of physiologic saline solution.

RESULTS

The Over-all Response to Acute Pulmonary Embolization:

The injection of 5 to 8 Gm. of glass beads, administered in one or more divided doses, caused the death of ten anesthetized dogs within two hours. The terminal signs were predominantly failure of respiration and a fall in carotid blood pressure and were the expected consequences of a massive obstruction in the pulmonary circulation. The early changes, however, were found to include some points of unexpected interest. These included apnea, bradycardia and hypotension, immediately following the injection of glass beads, followed quickly by hyperpnea and partial or complete recovery of pulse rate and blood pressure. The immediate effects being analogous to those produced by the Bezold-Jarisch reflex, a role of the vagus was suspected.

Embolization after vagotomy was performed in five other dogs. The immediate apnea, bradycardia and hypotension described above were completely lacking. The subsequent gradual and persistent fall in carotid blood pressure and increase in respiratory depth (but rarely increase in rate) occurred as in the animals with the vagi intact. Thus the immediate Bezold-like response appears actually to be a vagus reflex, but the subsequent hyperpnea and the eventually fatal hypotension are not. Vagotomy did not alter significantly the time of survival after embolization.

Acute bilateral sympathectomies were performed on two dogs. To insure completeness of the denervation, the entire chain of thoracic ganglia (T1 to T6) was removed bilaterally in toto. The chest was then closed and the animal embolized. In these animals, the marked increase in respiratory depth which usually develops after embolization in vagotomized animals was replaced by a primary increase in respiratory rate and consequently in respiratory minute volume. Thus it appears that the sympathetics play an important but not exclusive role as the sensory arm for the respiratory stimulation.

Blood Gas Changes:

In an attempt to determine the role, if any, of the respiratory center and chemoreceptors on the increase in respiratory minute volume seen after embolization, studies on blood gases were performed. In 12 dogs a simultaneous fall in arterial carbon dioxide and oxygen content was regularly found after embolization. The hypocapnia was attributable to the concomitant hyperpnea and may be regarded as unimportant except as an indication that alveolar gas exchange was still adequate at least as far as carbon dioxide is concerned. The anoxemia however was suspected as a cause of the hyperpnea. Subsequent denervation of the carotid and aortic chemoreflex zones in six dogs significantly reduced, but did not eliminate, the respiratory stimulation after embolism. The latter therefore is only partly the result of anoxemia.

The anoxenia was considered as a potential cause of death and a reasonable direction for therapeutic intervention. We therefore investigated it further with the following results:

1. The average fall in arterial oxygen content after embolization in 12 dogs amounted to 3 volumes per cent. The fall was often practically maximal within five minutes after the embolization; this seems too soon for a change in the permeability of the alveolar membrane to develop, and the concomitant fall in arterial carbon dioxide content argues in the same direction.

2. Forced ventilation with air did not appreciably alleviate the anoxemia; this

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* Beads were obtained from B. F. Drakenfeld & Co., Inc. and Arthur S. Lapine & Co.
suggests that bronchoconstriction was not a prominent factor.

(3) Administration of 100 per cent oxygen, either by spontaneous breathing or artificial respiration, led to prompt and complete removal of the anoxemia; this relief, however, could not be maintained for more than about thirty minutes, after which anoxemia again developed and the animals died in spite of continuous administration of oxygen.

These findings led us to suspect that changes in the alveolar capillary circulation might be involved. The experiments next to be described were undertaken in hopes of elucidating these changes.

The Pulmonary Circulation Following Embolization:

Following the injection of glass beads there was an immediate, sharp rise in pulmonary arterial pressure which was seen in ten dogs (fig. 1). The degree of increase varied with the amount injected; pressures as high as 60 cm. of water (45 mm. Hg) could be obtained with 8 Gm. of 125 micra beads. Failure of the left ventricle was not the cause of this rise in pulmonary arterial pressure since pressure in the left atrium did not rise significantly except just before failure of the entire circulation. Changes in pulmonary blood flow were not measured, but the perfusion experiments discussed below show definitely that changes in vascular resistance of the lung are, in part at least, a cause of the pulmonary hypertension. It is interesting to note that the pulmonary arterial pressure did not remain at the level reached immediately after embolization but became unstable, either further increasing or decreasing. The secondary changes might be reflections either of changes in pulmonary blood flow or pulmonary vascular resistance. To settle this point we decided to utilize perfusion experiments.

Reflex and Nonreflex in Vascular Resistance of the Perfused Lung: The artery of the left lower lobe was perfused (with mixed venous blood from a donor feeding a Dale-Schuster pump) at a constant rate so that any changes in pressure in the lobar artery could be interpreted as changes in vascular resistance in that lobe. To obviate an extrinsically denervated preparation, the cannulations were made such that there was no direct manipulation and cannulation of the arterial branch to the perfused lobe.

In five perfused preparations the injection of 1 Gm. of the smaller beads (60 to 200 micra) caused an initial rise in perfusion pressure, followed by a further gradual increase (fig. 2).
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Fig. 3. Reflex effects on pulmonary perfusion pressure of left lower lobe (top tracing), elicited by glass embolization of the other lobes supplied by animal's own heart. Pulmonary arterial hypertension is observed in the lobes receiving the beads (middle tracing) and in the perfused lobe which did not receive the beads. Embolization was performed before and after denervation. See text for details of perfusion.

On the other hand, a comparable injection of a similar or greater weight of the larger beads (250 to 420 micra) produced only the initial rise, the delayed further increase being totally absent. This difference in response appears to be a manifestation of two forces, (1) mechanical obstruction, which produces the abrupt initial rise and (2) delayed constriction of pulmonary blood vessels, elicited only when the beads are less than 250 micra in size. This constriction was not eliminated by thoracic vagotomy and thoracic sympathectomy, hence is interpreted as a local phenomenon elicited only by the presence of the smaller beads in vessels of 200 micra in diameter or less.

Intravenous injection of beads into the recipient dog carried them to the lobes (right side) supplied by the animal's own heart. This induced a rise in pressure in the artery of the lobe (left side) perfused at a constant volume flow, although the beads never reached the latter. This effect was significantly lessened when the lungs were denervated (as above) although a reduced effect sometimes persisted (fig. 3). The vagus and sympathetic trunks therefore appear to be the important but not the sole pathways for these effects induced between lobes. The rise in pressure in the perfused lobe can be attributed to reflex pulmonary vasoconstriction of that lobe, since the aortic pressure remained constant and therefore the bronchial circulation of this lobe presumably was unchanged.

Pulmonary Arteriovenous Communications: In order to investigate the possible role of arteriovenous passages in the lungs in the production of the anoxemia which follows pulmonary embolization, twelve perfused lungs, prepared as above, were used to test the passage of beads through the lungs by passing the pulmonary venous blood outflow through a sieve. Blood readily passed through the openings of the sieve unaltered. In two other experiments, the donor dog and perfusion of the lobar artery were omitted; the artery of left lower lobe was supplied by the animal's own heart, but the corresponding vein was cannulated to sieve the outflowing blood. Only one pump was used to return this outflow back to the animal's own right atrium.

Following the injection of beads, varying from 60 to 420 micra, into the pulmonary artery of the lobes supplied in either manner (by pump or by animal's own heart) the beads could be recovered from the venous blood leaving the injected lobe. The beads collected in the sieves were examined and counted under a dissecting microscope, with the following results: (1) Communications between the pulmonary artery and vein exist and are at least 420 micra in size. (2) Increasing the perfusion pressure of the pulmonary artery increases the number of beads which pass through these communications. (3) Ventilation of the lungs with 100 per cent oxygen decreases the number of beads recovered while 10 per cent oxygen increases the number.

If the number of beads reflect the nature of these arteriovenous communications, one can conclude that, in the perfused lung, the shunts open when pulmonary pressure is increased or when the alveolar oxygen tension is decreased. This opening of pulmonary channels can be correlated with the other effects described above in the intact animal. There is a consistent correlation between pulmonary arterial pressure and arterial oxygen saturation.
The immediate sharp rise in pulmonary arterial pressure upon glass embolization is followed by a gradual decline, which is associated with a further decrease in oxygen saturation of pulmonary venous (femoral arterial) blood.

**Discussion**

The changes in pulmonary arterial pressure following the injection of glass beads were difficult to analyze directly in the intact animal with closed chest, because of the absence of a suitable technic for measurement of pulmonary flow from minute to minute. It has been emphasized that indirect measurements of vascular resistance of the lungs based on pressure and flow are often complicated by passive changes in resistance induced by alterations in pulmonary blood flow. Since the primary concern of this investigation was to obtain unequivocal evidence as to the behavior of the lung vessels, the perfusion technique was utilized on the lung that still maintained its normal innervation and bronchial blood supply. This procedure has revealed at least three components in the response to pulmonary embolization: (1) primary mechanical obstruction of the vessels which produces the immediate rise in pulmonary arterial pressure; (2) secondary local vasoconstriction, as shown by the further rise in pressure only when glass beads less than 250 micra in diameter are used and (3) vasoconstriction extending to the other lobes. This interlobar vasoconstriction is partly, but not entirely, mediated by the vagus nerve trunks, which have been shown to carry vasomotor fibers to the lungs. The vasoconstriction (interlobar and intralobar) remaining after acute denervation may be a form of axon reflexes or ganglionic reflexes utilizing the nerve cells reported to be plentiful in the mediastinum. The site and innervation of the receptors are at present quite unknown.

The presence of these powerful intrapulmonary reflexes is unmistakable in the perfused lungs in which proper precautions have been taken to avoid denervation (see Results). Attempts in the past to demonstrate them in the intact animal have produced conflicting results. This was due to the difficulty in interpreting the pressure changes in the lungs if the emboli are localized in one lobe by means of an intravascular catheter. The placing of a ligature about a pulmonary artery (as is so often done) probably interrupts the vasomotor nerve fibers which are believed to course in the adventitia of the vessel, thus abolishing any possible reflex.

Surprisingly enough, the early anoxemia seen following embolism has been almost entirely ignored by others. In the experiments reported here, the anoxemia was unmistakable and was partly responsible for the stimulation of respiratory depth. Intrathoracic sensory receptors supplied by the vagi and the sympathetics were also partly responsible for the respiratory stimulation seen after embolization. No attempts were made to determine the exact location of these receptors in the lungs.

It has been established that shunting of blood occurs from artery to vein in certain special circulatory beds, e.g., in the kidney and in the peripheral circulation. Only in recent years has the question of channels short-circuiting the pulmonary alveolar bed been raised. Clinically, pulmonary shunts bypassing the capillaries have been suspected from the passage of certain parasites and cancer cells through the lung. Also the not uncommon finding of telangiectases and the spontaneous development of arteriovenous fistulae within the lung suggests exaggerations of normally existing shunts.

The demonstration of arteriovenous communications in the perfused lung confirms the radiographic and post mortem anatomical studies of others. However recent work on rat and rabbit lungs has failed to support these studies. These shunts appeared to be quite labile in our experiments because the passage of glass beads was observed to change in the lung perfused at various pressures and ventilated with different gas mixtures. The shunts open while pulmonary arterial pressure is increased and close while the lung is ventilated with high oxygen. It would be desirable to devise methods applicable to the intact animal for measurements of these shunts that are distinct from the alveolar capillaries. Such
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methods would test the theory suggested by perfusion, namely, embolism causes an immediate anoxemia by opening the pre-existing arteriovenous communications and the early relief of anoxemia by high oxygen is brought about by their closure.

The central position (fig. 4) occupied by pulmonary A-V shunts during clinical embolism is purely speculative. The importance of opening and closing of these communications at specific times in pulmonary crises to decongest the lung, although theoretical at the present, certainly indicates the need for future investigative work in this field concerning the extent of their functioning in health and disease.

SUMMARY AND CONCLUSIONS

Pulmonary embolism using glass beads was investigated in anesthetized dogs. The following observations were prominent:

Death by respiratory and circulatory failure occurred within two hours following the use of 5 to 8 Gm. of beads (125 micra).

The sensory vagus was responsible for the instantaneous bradycardia and apnea immediately following the injection of beads and for the subsequent stimulation of rate of respiration.

The thoracic sympathetic was responsible in part for the respiratory stimulation.

The stimulation of depth of breathing, seen after vagotomy, was due partly to the fall in oxygen saturation of arterial blood. This anoxemia occurred even when the lungs were artificially ventilated with air but was completely reversed by spontaneous or artificial ventilation with 100 per cent oxygen.

The pulmonary hypertension was analyzed in the perfused lung and the increased vascular resistance was found due not only to mechanical obstruction by the emboli but also to vasoconstriction, locally and in the whole lung bed. This intrapulmonary reflex (intrapulmonary and extrinsic nerves of the lungs).

The perfused lung shows arteriovenous communications that are at least 420 micra.
in diameter. The passage of large beads was facilitated by increasing pulmonary arterial perfusion pressure and hindered by ventilation with 100 per cent oxygen.

This marked lability of pulmonary shunts suggests that pulmonary embolism opens them, thus aggravating the concomitant anoxemia, but at the same time minimizing the rise in pulmonary artery pressure.

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