Mechanical vs. Reflex Effects of Diffuse Pulmonary Embolism in Anesthetized Dogs

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The effects of repeated pulmonary embolisms with glass spheres on systemic and right intracavitary pressures and on arterial oxygen saturation of anesthetized dogs are described. The results of studies of intact dogs and of the isolated perfused left lower lobe indicate that the hemodynamic effects were due to mechanical obstruction to the flow of blood through the lungs eventually followed by right heart failure. Evidence for reflex effects on the blood vessels or heart was lacking. The systemic arterial unsaturation which eventually developed after repeated embolisms was completely overcome by the inspiration of oxygen and was attributed to a reduction of the diffusing capacity of the lung.

Although most investigators agree that large pulmonary emboli produce death by mechanical obstruction to the flow of blood through the lungs, controversy exists as to the importance of nervous reflexes in producing the hemodynamic response to small pulmonary emboli. Since 1920, it has been well known that the intravenous injection of starch granules in cats, rabbits, dogs and goats will cause an increased systemic venous pressure, decreased systemic arterial pressure and death. Some investigators have felt that reflex vasoconstriction must have developed, since only small amounts of starch caused death. Information is lacking as to the number of vessels actually obstructed by the starch, as well as to the number of vessels of a given size that are normally patent in the lung. Thus, 1 Gm. of starch, the minimal lethal dose in rabbits, might well contain enough small particles to occlude all the blood vessels in the lung which are normally patent. DeTakats, Beck, and Fenn found that the minimum lethal dose of starch in rabbits was not increased by atropine. Parin found that elevation of the pressure in the vascular bed of a lobe of the lung in cats caused a reflex decrease in systemic pressure, but Schweitzer was unable to confirm this.

This study concerns primarily the effects of repeated embolism of dog lungs with small glass spheres on the pressures in the pulmonary artery, right ventricle, and right atrium, and the effects on vascular resistance of repeated embolisms of the isolated, perfused left lower lobe of the lung before and after denervation. Consideration is also given to the mechanism of the production of cyanosis which occurs during experimental pulmonary embolism, and the effect of oxygen breathing on it.

Methods

All experiments were performed on dogs anesthetized by the intravenous injection of sodium pentothal (25 mg./Kg.) followed by sodium barbital (200 mg./Kg.). Intact dogs were studied during spontaneous respiration from an oxygen filled spirometer, whence oxygen consumption and respiratory indexes were calculated, or during positive pressure respiration with room air from a constant volume pump. Mean pressure in the femoral artery was measured on a mercury manometer, and arterial blood was analyzed spectrophotometrically for oxygen saturation. Mean pressures in the right ventricle and atrium and in the pulmonary artery were measured on a saline manometer by means of a plastic catheter inserted into the right heart or pulmonary artery. Mixed venous blood was withdrawn from this catheter for measurement of oxygen saturation. Pulmonary embolism was produced by the intravenous injection of known aliquots of 60 micra glass beads. The particles were either added to a saline

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infusion which ran into the brachial vein, the foreleg being suspended from an infusion stand so that the beads flowed directly to the axilla, or they were introduced into the pulmonary artery or right atrium or ventricle via the plastic catheter from a funnel which contained a small amount of saline.

Open chest dogs were prepared as described previously. The left lower lobe of the lung was perfused from the abdominal aorta through a rotameter, and the mean pressure in the artery leading to the left lower lobe was measured on a saline manometer. The rate of flow was kept constant by means of a screw clamp on the tubing leading to the rotameter. Embolism was produced by stopping the inflow and allowing the mixture of beads and saline to run from a funnel through a Y tube into the pulmonary artery to the left lower lobe. In some experiments the mean pressure in the right pulmonary artery was also measured during embolization of the left lower lobe. In all experiments the blood was rendered incoagulable by the intravenous injection of heparin.

RESULTS

Hemodynamic Effects

Injections into Right Heart or Pulmonary Artery. Experiments were performed on 42 closed-chest dogs either spontaneously breathing oxygen or under positive pressure respiration with room air or oxygen. The injection of a .25 to .5 gm. aliquot of 60-micra glass beads into the right atrium resulted immediately in a 0 to 15 mm. Hg fall in systemic arterial pressure which was generally transient. Figure 1 shows the results of a typical experiment. After repeated injections (1 to 4 Gm. total), the femoral artery pressure fell precipitously. In 19 dogs the pressure rapidly returned to normal 1 to 5 minutes after the last injection. Nine dogs died. Adrenalin was administered intravenously to 19 dogs in which the systemic pressure did not rise spontaneously. In 5 of these dogs the femoral pressure rose promptly to normal, and the other 5 died. In 4 dogs insufficient beads were injected to cause a fall of systemic pressure.

Intracardiac as well as femoral pressures were measured in 30 dogs. Each .25 Gm. aliquot of beads caused a variable rise (1–25 cm. saline, average: 5.7 cm.) of the pressure in the pulmonary artery, which slowly returned towards normal. Similar trends were observed in the mean pressures in the right ventricle and right atrium, (fig. 1) although the magnitude of the change of pressure in the right atrium was less. In 4 dogs the injection of 25 to 50 mg. of hexamethonium into the right atrium caused no immediate fall of the pressure in the pulmonary artery. The response to the subsequent injection of beads was identical to that seen before the administration of hexamethonium.

After repeated injections of beads, a maximum pressure was reached in the right heart, whereupon further injections caused either no change of the pressure in the right ventricle or pulmonary artery, or an abrupt drop, which occurred a few seconds to two minutes after the decline in femoral pressure. The pressure in the atrium fell slightly or remained elevated during the period of hypotension. During this interval, the oxygen consumption decreased appreciably in 9 of 10 dogs, some times to imperceptible levels. Recovery of systemic pressure was associated with a rise of the pressure in the pulmonary artery or right ventricle, fall of pressure in the atrium and increase in oxygen consumption.

Injections into the Circulation of One Lobe. In order to control the rate of blood flow to the embolized area and to study the effect of resection of the bronchus on the response to embolization of a lobe, experiments were performed on 9 open chest dogs in which the left lower lobe of the lung was perfused at a constant rate from the aorta. Thirteen injections of .25 Gm. ali-
quote of glass beads into the artery to the left lower lobe resulted in a rise of left pulmonary artery pressure (1 to 36 cm. saline, average: 10 cm.) followed by a slow fall. On 10 occasions simultaneous measurements were obtained of the pressure in the right pulmonary artery. Repeated embolization of the left lower lobe never caused a significant change of the pressure in the right pulmonary artery. Eight injections of the same weight of beads into the artery to the left lower lobe of dogs in whom the left mainstem bronchus had been divided resulted in an even greater increase of pressure (4 to 22 cm. saline, average: 10 cm.). Four of these dogs were studied before and after resection of the bronchus. Figure 2 shows the results of one of these experiments. Clamping the bronchus caused no acute change of the pressure in the pulmonary artery. Subsequent injections of beads caused an even greater pressure rise. In three dogs with intact bronchi, eight postembolic injections of 25 to 50 mg. of hexamethonium into the left pulmonary artery caused no change of the pressure in the pulmonary artery for a given blood flow, and the response to subsequent bead embolisms was identical to that seen before administration.

The fall of pressure in the artery to the left lower lobe which occurred after the immediate postembolic rise of pressure might have resulted from the passage of beads through the lung capillaries. Therefore, six experiments were performed in which accurately weighed 1 Gm. aliquots of large (420 micra) glass beads were injected into the left lower lobe. At the end of the experiments, the lungs were digested and the beads were recovered and weighed. Inflow to the left lower lobe was maintained constant. In each experiment, the beads caused a rise of pressure in the artery to the left lower lobe (13 to 34 cm. saline, average: 21 cm. saline) followed by a slow fall (6 to 36 cm. saline, average: 16 cm. saline in 13 to 60 minutes). Digestion of the left lower lobe at the conclusion of the experiments resulted in the recovery of from 86 to 98 per cent of the injected beads (average: 93 per cent).

Systemic Effects of Elevating the Pressure in the Left Pulmonary Artery. In order to determine the presence or absence of reflex effects of the elevated pressure in the pulmonary artery on the systemic pressure, the following experiments were performed. A balloon tied on the end of a cardiac catheter was placed in the left pulmonary artery of open chest dogs either through the jugular vein or through a small incision in the right ventricle. This balloon was distended with water so as to occlude the pulmonary artery. The pulmonary veins to the obstructed area were ligated. The mean pressure in the occluded segment was measured through a polyethylene cannula inserted into the left pulmonary artery via the artery to the left upper lobe. The nerve supply to the occluded segment of the vascular bed was not interrupted. Repeated elevation and lowering of the pressure (20 to 40 cm. saline) by injection and withdrawal of blood through the pressure cannula resulted in no change of the systemic pressure in four dogs.

Effects on Oxygen Saturation

In 31 experiments on dogs breathing room air under constant, positive pressure respiration, the oxygen saturation fell considerably after repeated embolisms, the average maximum fall being 35 per cent below the control level. The saturation reached the lowest level
when the blood pressure reached the peak of the rise after the precipitous fall, although occasionally the saturation started to fall as the blood pressure fell, or during the period of hypotension. The first few injections of beads rarely caused a change of the oxygen saturation. During the period of recovery, as the pressure in the pulmonary artery slowly fell towards normal, the saturation also returned towards normal. However, repeated observations of the oxygen saturation in 31 experiments on 23 dogs breathing oxygen revealed no significant fall. Two dogs, each of which had thrice at two week intervals shown a marked fall in saturation during room air breathing, were subsequently given emboli during oxygen breathing and neither developed a drop in saturation.

Seven experiments were performed on the effects of repeated embolisms when the inspired mixture was alternated from room air to oxygen. Figure 3 shows a typical example. Sufficient beads were injected each time to cause a fall of systemic pressure and, after the pressure had returned to control level, the inspired mixture was changed and more beads were injected. Although the saturation fell 20 to 55 per cent (average: 39 per cent) after embolism produced during room air breathing, there was no fall of the saturation after embolism produced during the inspiration of oxygen. Changing the inspired gas mixture without further embolisms resulted in immediate changes of saturation of from 8 to 58 per cent on 18 occasions (average: 31 per cent). As shown in table 1, the venous oxygen saturation was actually lower during the inspiration of oxygen than it had been during room air breathing in two of the three dogs studied. In four of these dogs pulmonary edema developed near the end of the experiment, and, in these animals the saturation fell 10 to 15 per cent during oxygen breathing.

**DISCUSSION**

These experiments illustrate the sequence of events which follows diffuse embolism of the pulmonary vascular bed. Each injection of beads caused an increase of the pressure in the pulmonary artery, which slowly returned towards normal. Similar changes of the pressure in the pulmonary artery were seen in the isolated, perfused left lower lobe and were not influenced by denervation of the lobe. Hexamethonium did not immediately affect the pressure in the pulmonary artery nor the magnitude of the pressure response to beads either in the intact animal or in the isolated, perfused lobe. These results suggest that the pressure rise after embolism in anesthetized dogs was due to obstruction of the pulmonary vascular bed and
that reflex spasm of the blood vessels did not contribute to the observed changes in pressure.

The subsequent fall of pressure in the artery to the left lower lobe which followed the post-embolic rise of pressure occurred in the perfused lobe when inflow was kept constant. It would thus appear to have resulted either from the opening of new blood vessels after occlusion of the existing vascular channels or from the forcing of beads through the blood vessels. Since similar changes were seen after embolism produced with large (420 micra) glass beads following which most of the injected beads were recovered from the digested lung, and since the pulmonary vascular resistance has been shown to be an inverse function of intravascular pressure, the former explanation appears to be more likely. The fact that the pressure fell slowly might be construed as an argument against the opening of new blood vessels, but a similar development is seen after the blood flow is abruptly increased to the perfused left lower lobe.

Repeated injections of beads eventually resulted in massive obstruction to the pulmonary circulation and right heart failure. This was characterized by a rapid drop of the pressure in the pulmonary and femoral arteries and right ventricle and sustained elevation of the pressure in the right auricle. These changes were similar to those which follow mechanical obstruction to the flow of blood through the lungs and only occurred after repeated injection of beads, each .25 Gm. aliquot containing approximately 800,000 beads. Reflex effects of pulmonary hypertension on the systemic pressure could not be demonstrated. The development of right heart failure may be explained on a mechanical basis, and evidence for a reflex component is lacking.

Recovery, either spontaneous or following the injection of adrenalin, was characterized by a rapid rise of the pressure in the pulmonary and femoral arteries and a fall of the arterial oxygen saturation. Inspiration of oxygen resulted in a return of the oxygen saturation to normal, and embolism produced during the inspiration of oxygen never was associated with a fall of the oxygen saturation unless pulmonary edema had developed. The oxygen unsaturation seen after embolism produced during room air breathing cannot be attributed to a form of venous admixture to arterialized blood, since a shunt of 50 per cent or greater would have been necessary to cause such a marked degree of unsaturation. Such a shunt would still have caused appreciable unsaturation during oxygen breathing unless the venous saturation were very high, and, in two of the three dogs studied, the venous saturation was actually lower during oxygen breathing than it had been during room air breathing.

The most likely explanation for the low saturation obtained in these experiments and for the marked effect of oxygen on the arterial oxygen saturation is that after repeated embolisms the mixed venous blood, greatly reduced in oxygen content after a period of right heart failure, flowed through a few, dilated capillaries at a rapid rate. This resulted in a greatly reduced diffusing capacity for oxygen so that even during room air breathing there was a marked difference between the oxygen tension in the alveoli and the blood leaving the alveoli. As new capillaries opened, the area available for gas exchange increased, the blood flowed through the capillaries at a slower rate, and the diffusing capacity increased. During the period of maximum decrease in diffusing capacity the inspiration of pure oxygen raised the alveolar pressure of oxygen to some 700 mm. Hg, and the theory of diffusion of gases requires that, under these circumstances, the blood leaving the alveoli had approximately the same oxygen tension as existed in the alveoli.

For example, figure 4 illustrates the effect of changing the alveolar oxygen tension from 100 to 700 mm. Hg on the oxygen tension in the alveolar capillary blood when the diffusing capacity was greatly reduced and the difference in oxygen tension between alveoli and mean capillary blood was 73 mm. Hg. The dotted line represents the results of the Bohr integration when room air was the inspiratory mixture, and the oxygen saturation rose slowly from 24 to 60 per cent as the blood flowed through the alveolar capillary. The straight line connecting the venous and arterial points is the mean rate of diffusion of oxygen from the alveoli into the capillary blood and the point M, where the cal-
Fig. 4. Schematic representation of the effect of changing the alveolar oxygen tension from 100 to 700 mm. Hg on the diffusion of oxygen across the alveolar membrane. During the inspiration of room air the venous oxygen tension rises slowly from about 20 mm. Hg to 39 mm. Hg (dotted line); whereas, during the inspiration of 100 per cent oxygen the venous oxygen tension rises rapidly to over 100 mm. Hg and, then, slowly to 700 mm. Hg (upper solid line).

The calculated slope of the dotted line is the same as that of the straight line, defines the mean capillary oxygen tension or saturation. When oxygen was the inspiratory mixture and the diffusing capacity was still at the same low value, oxygen diffused into the capillary blood extremely rapidly and the venous oxygen tension rose quickly from 20 to 700 mm. Hg, while the venous oxygen saturation rose from 24 to over 100 per cent. The mean slope, M, of this curve is somewhat greater than that of the room air curve because the oxygen intake has increased (assuming a constant blood flow), corresponding to an increase in the A-V difference of from 35 to 86 per cent. If the venous saturation were higher, the capillary blood would have become fully saturated even more rapidly. Stated differently, when a pressure head of 80 mm. Hg served to drive a given quantity of oxygen into the blood flowing through the alveolus in a given time interval, a pressure head of 680 mm. Hg served to drive eight and one half times as much oxygen into the blood during the same interval.

As the animals recovered, the pressure in the pulmonary artery fell toward normal coincident with a rise of the arterial oxygen saturation. These changes may be attributed to the opening of new blood vessels in the lung, resulting in a decrease in the pulmonary vascular resistance and an increase in the size of diffusion surface and, hence, of the oxygen diffusing capacity.

**Summary**

The effects of diffuse pulmonary embolism have been studied in the anesthetized dog by introducing .25 to .5 Gm. aliquots of 60 micro glass beads into the brachial vein or right heart and observing the changes of the mean pressures in the femoral and pulmonary artery and right atrium and ventricle. Each injection of beads resulted in an increase of the pressure in the pulmonary artery and right ventricle and a small, transient decrease of systemic pressure. The pressure response in the pulmonary artery and right ventricle was unaffected by the administration of hexamethonium. After each injection of beads, all pressures gradually returned towards normal. Repeated embolisms resulted in right heart failure with fall of the pressures in the right ventricle, pulmonary and femoral arteries, a slight fall or sustained elevation of the pressure in the atrium, and fall in oxygen consumption. In half the dogs, recovery occurred spontaneously in 1 to 3 minutes and was associated with a rise of the pressure in the right ventricle, pulmonary and femoral arteries and a fall of the pressure in the right atrium. At this time, profound arterial oxygen unsaturation developed in animals breathing room air and was totally overcome by the inspiration of oxygen. The arterial unsaturation was apparently due to a reduction of the diffusing capacity of the lung because of the circulation of mixed venous blood through a small number of dilated lung capillaries.

Studies of the left lower lobe of the lung, perfused at a constant rate of flow, revealed pressure responses similar to those seen in the intact dog and the pressure changes were unaffected by denervation of the lobe or by injection of hexamethonium.

The hemodynamic effects of embolism with glass spheres in anesthetized dogs may be attrib-
uted to the mechanical obstruction of the pulmonary vascular bed followed by the slow opening of vascular channels in response to the high intravascular pressure. Evidence for reflex vasoconstriction of the pulmonary vascular bed is lacking and the eventual development of right heart failure and death can be explained on mechanical grounds alone.

**Summario in Interlingua**

Le effectos de diffuse embolismos pulmonar in canes anesthesiate esseva studiate per introducer aliquotes ab 0,25 a 0,5 g de perlas de vitro a diametros de 60 micros in le vena brachialis o le corde dextere pro observar le alterationes del pression median in le arterias femoral e pulmonar e in le atrio e ventriculo dextere. Omne injection de perlas resultava in un augmento del pression in le arteria pulmonar e le ventriculo dextere e in un parve e transiente reduction del pression systemic. Le responsa del pression in le arteria pulmonar e lc ventriculo dextere non esseva afficite per le administration de hexamethonium. Post le injection del perlas, omne pressiones retornava gradualmente verso nivellos normal. Repetite embolismos resultava in disfallimento dextero-cardiac con reduction del pressiones in le ventriculo dextere e le arterias pulmonar e femoral, un leve reduction o un persistente elevation del pression in le atrio, e un reduction del consumption de oxygeno. In un medietate del canes, le recuperation occurrevava spontaneamente intra 1 a 3 minutas, associate con un augmento del pression in le ventriculo dextere e le arterias pulmonar e femoral e un reduction del pression in le atrio dextere. A iste tempore, un profunde non-saturation oxygenic del arterias se disveloppava in le animals que respirava le aere del ambiente, sed iste non-saturation esseva completemente corrigite per le inspiration de oxygeno. Le non-saturation arterial esseva apparentemente causate per un reduction del capacitate diffusive del pulmones in consequentia del circulation de sanguine venose mixte a transverso un parve numero de dilate capillares pulmonar.

Studies del lobo infero-sinistre del pulmone, perfurante per un fluxo constante, revelava responsas de pression simile al responsas observe in canes intacte, e le alterationes del pression non esseva afficite per disnervation del lobo o per le injection de hexamethonium.

Le effectos hemodynamic de embolismo producite per perlas de vitro in canes anesthesiate pote esser asser attribuite al obstruction mechanic del arbre vascular pulmonar, sequite per le lente apertura de canales vascular como responsa al alte pressiones intravascular. Indicios de vasoconstriction refexe in le arbre pulmono-vascular non esseva trovate, e le subsequente disveloppamento del disfallimento dextero-cardiac e morte pote esser explicate unicamente per factors mechanic.

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