Pressor Effect of Hypertonic Saline on Pulmonary Circulation

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It has been suggested that the pressor effect of hypertonic solutions of sodium chloride on the pulmonary circulation results from spasm of the pulmonary veins at their junction with the left atrium. These studies demonstrate that the increased resistance in the pulmonary vessels develops upstream to this site and that it may result primarily from mechanical blockage of vessels by clumped erythrocytes rather than from vasoconstriction.

The finding of a pronounced, brief increase in pulmonary-artery pressure after the intravenous injection of a 20 per cent solution of sodium chloride in the dog led Binet and Burstein\(^1,2\) to suggest that this was caused by constriction of the pulmonary vessels proximal to the capillary bed. Later, Eliakim and associates\(^3\) attributed the pulmonary hypertension caused by the hypertonic saline to spasm of the pulmonary veins at their junction with the left atrium as a result of stimulation of chemoreceptors at this site. As this concept raises the issue of specific cells in this region that are sensitive to high concentrations of sodium ion,\(^4\) we have repeated the experiments.\(^5\) Our observations suggest that the increased resistance caused by hypertonic saline occurs in vessels upstream to the site postulated by Eliakim and co-workers. This increased resistance is not necessarily due to vasoconstriction but could, as suggested by Read and associates,\(^6\) be caused by reversible agglutination of erythrocytes.

METHODS

Fourteen mongrel dogs weighing 15 to 20 Kg. were anesthetized by the intravenous injection of pentobarbital sodium in a dose of 25 mg./Kg. body weight. Cardiac catheters (no. 6 F., with an external diameter of 2.0 mm.) were introduced into the jugular vein. Under fluoroscopic control, one catheter was positioned in the pulmonary artery and the other was advanced until its tip impacted in a small pulmonary artery (the pulmonary-artery wedge). Through a small suprasternal incision, a hollow steel tube containing a metal obturator with a rounded tip was directed by fluoroscopy to pass caudally and posteriorly to the right pulmonary artery. Cardiac pulsations transmitted via the obturator indicated that its tip lay against a cardiac chamber. The obturator then was removed and was replaced with a needle 1.83 mm. in internal diameter and 23 cm. in length that punctured the left atrium.\(^7\) The position of the tip of this needle in the left atrium was verified by withdrawing arterial blood and recording a typical atrial pressure pulse. Through the lumen of this needle a no. 4 F. cardiac catheter 1.32 mm. in external diameter was introduced and, with fluoroscopy, manipulated into a pulmonary vein until its tip lay 1 to 2 cm. peripheral to the cardio-pulmonary border. This catheter was used to record pressure in the pulmonary vein. Left atrial pressure was recorded via the residual lumen between the shaft of the no. 4 catheter and the wall of the needle, the tip of which lay in the left atrium. Figure 1 is a roentgenogram of the thorax, showing the catheters and the needle in position. Another catheter was advanced into the femoral artery to record systemic blood pressure, and a tube with an internal diameter of 2.0 mm. was positioned in the right atrium via the femoral vein for rapid injection of the solutions. Pressures were recorded from each of the catheters by means of strain-gage manometers (Statham P23D). The zero reference point was the level representing one half of the anteroposterior depth of the thorax.

The solutions injected were hypertonic sodium chloride (usually 20 per cent), dextrose (20 and 50 per cent) and urea (20 and 50 per cent). These usually were injected in amounts of 1 ml./Kg. of body weight and were given rapidly within a period of 4 to 10 sec. into the right atrium or pulmonary artery. At the completion of the studies, each animal was examined at necropsy to verify...
the position of the catheters and to examine the trachea and lungs for evidence of edema and congestion.

RESULTS

The changes in vascular pressures that are characteristic of a sudden injection of a 20 per cent solution of sodium chloride into the right atrium are shown in figure 2, for which the various catheters were in the positions illustrated in figure 1. Immediately after the injection, a period of apnea occurred, accompanied by a precipitous decrease in femoral-artery pressure from a level of about 200 mm. Hg systolic and 135 mm. Hg diastolic to a value of 25 mm., and an equally rapid increase in pulmonary-artery pressure from about 15 to 20 mm. systolic and 5 mm. diastolic to about 100 mm. systolic and 50 mm. diastolic. When the increase in pulmonary-artery pressure was at its maximum, the pressures in the pulmonary-artery wedge, pulmonary vein and left atrium had scarcely changed. Severe cardiac irregularities developed, which apparently consisted of multiple ventricular premature beats. The pulmonary-artery pressure returned to the preinjection level within 20 sec., while the femoral-artery pressure had only reached 100/50 after approximately 85 sec. The irregularities in the electrocardiogram continued throughout this period. Despite these dramatic changes, the pressures had returned to the preinjection level in a few minutes.

Figure 3 shows the results of another set of observations recorded at a slower paper speed to illustrate a variation in the response. The pulmonary-artery systolic pressure increased by 50 mm. Hg immediately after the injection of saline into the right atrium. The pulmonary venous and left atrial pressures were identical and behaved in a similar manner throughout. Initially, their mean pressure was 5 mm. Hg, and this increased for a few seconds by another 5 mm. when the pulmonary-artery pressure commenced to increase; however, when the latter had reached its peak, the pulmonary venous and left atrial pressures had decreased to a mean of about 2 mm. After about 20 sec., as the pulmonary-artery pressure decreased, both the pulmonary venous and left atrial pressures increased symmetrically to a level a few millimeters greater than the control value and then subsided to the control level. To obtain a better evaluation of the contour and time relationships of these changes in pressure, a second camera having a faster paper speed also was used to record simultaneously these pressure pulses and the pulmonary-artery wedge pressure. The pulmonary-artery pressure increased promptly as the injection was given (fig. 4), but the first changes in the contour and in the pressure in the left atrium and pulmonary vein developed later and were associated with the onset of cardiac irregularities.

A total of 46 observations after injection of hypertonic solutions of sodium chloride were made in 14 closed-chest dogs, and all consistently showed an immediate increase in pulmonary-artery pressure and a decrease in systemic arterial pressure. These effects
were not seen following injection of 20 and 50 per cent solutions of urea or of 20 and 50 per cent solutions of dextrose. The latter injections at times caused an increase in pulmonary-artery pressure that was delayed in onset, much smaller in magnitude and longer in duration; similar changes also could be produced by slower injection of the 20 per cent saline. With the more rapid injection of saline, this delayed increase sometimes succeeded the initial increase in pulmonary-artery pressure and followed closely the recovery in systemic pressure. Control injections of an isotonic solution of sodium chloride caused no significant change in the pulmonary-artery pressure. When the injection of 20 per cent saline took longer than 10 sec. or when the concentration was less than 20 per cent, little or no immediate change took place in the pulmonary-artery pressure. The pressures in the pulmonary-artery wedge, pulmonary vein and left atrium were recorded simultaneously with the pulmonary-artery pressure in 5 dogs (21 observations); in the remaining dogs, either the pulmonary-artery wedge or the pulmonary venous pressure was recorded with the left atrial and pulmonary-artery pressure. In all of these studies, with 2 exceptions, the injection of 20 per cent saline produced an immediate great increase in pressure between the pulmonary artery on the one hand, and the pulmonary-artery wedge, pulmonary vein and left atrium on the other. No increase in pressure occurred between the pulmonary vein and left atrium or the pulmonary-artery wedge and left atrium.

In 1 observation following injection of 20 per cent saline, a definite increase in the pulmonary-artery wedge pressure occurred for 4 heart beats at the same time that the pressure was maximal in the pulmonary artery and without any accompanying change in the pulmonary venous or left atrial pressure. Inspection of the individual wedge pressure pulses that had been recorded simultaneously at a fast camera speed showed that they were virtually identical in contour and time relationships to the pulmonary-artery pressure pulses. This transient increase in wedge pressure was thought to be caused by the greatly increased pulmonary-artery pressure distending the artery in which the tip of the catheter was wedged, with consequent transmission of pulmonary-artery pressure to the tip of this catheter.

In another observation, before the injection of hypertonic saline, the catheter was wedged in a small pulmonary vein, and the pressure resembled that of the pulmonary artery. The pulmonary-artery wedge and left atrial pressures were approximately zero. The pulmonary-vein wedge and pulmonary-artery wedge pressures showed the relationship described by Hellems. A pulmonary-vein wedge pressure also must have been recorded in one of the experiments of Eliakim and associates, as shown in their figure 2. In our experiment (fig. 5), when hypertonic saline was injected, the pulmonary-vein wedge pressure increased initially in step with the pulmonary-artery pressure and then slowly declined, with a loss of pulsation, the pressure approaching that of the left atrium and pulmonary-artery wedge. Meanwhile, the pulmonary-artery pressure showed a further and extreme increase in pressure for approximately 5 sec. Later, with the decrease in pulmonary-artery pressure, the pressure recorded by the catheter in the vein again could be recognized as that typical of a pulmonary-vein wedge. The left atrial and pulmonary-artery wedge pressures did not change except for one heart beat, when they reached 50 and 26 mm. Hg, respectively. This occurred shortly after the pressures in the pulmonary artery and the pulmonary-vein wedge had commenced to increase. This brief increase in left atrial pressure was clearly reflected in the other pulmonary pressures.

In attempting to explain the transient increase in pulmonary-vein wedge pressure, it should be noted that, when the pulmonary-artery pressure was at its peak, the pulmonary-vein wedge pressure had lost its pulsations and was slowly approaching the pressure of the left atrium. The presence of
Fig. 2 Top. Effect of an injection of 20 per cent saline (1 ml./Kg. body weight) in 4 sec. into the right atrium of a closed-chest dog.

Fig. 3 Middle. Effect of 20 per cent saline injected into the right atrium of an intact dog. Note the symmetric behavior of the pulmonary venous and left atrial pressures, and that these were at a minimum when the pulmonary-artery pressure was at its maximum. Solid lines at
oscillations with a frequency of about 12 c.p.s. in the recording of pressure in the pulmonary-vein wedge and the later return to its previous contour indicate that mechanical damping was not the cause of the slow decrease in pressure. At this time, therefore, the increase in pulmonary-artery pressure must have been caused by complete or almost complete obstruction to flow between the pulmonary artery and the catheter wedged in the pulmonary vein, and not by a constriction at the junction of the pulmonary vein and the left atrium.

The following observations suggest that the increase in pulmonary-artery pressure does not occur in the absence of erythrocytes. The isolated lungs of a dog were perfused at a constant flow with a solution of dextran; the injection of 20 per cent saline had no effect on the pulmonary-artery pressure under such circumstances, while an injection of 5-hydroxytryptamine increased the pressure, indicating that the vessels were reactive. The lungs then were perfused with blood at a constant flow, and the injection of 20 per cent saline caused a pronounced increase in pressure. In another study, a pulmonary lobe was perfused at a constant pressure with a solution of polyvinylpyrrolidone (fig. 6). The injection of 20 per cent saline caused no decrease but an increase in flow. When the perfusate was changed to whole blood, injection of 20 per cent saline now caused a decrease in flow. Following hemolysis of the erythrocytes by the use of saponin carbonate, a subsequent injection of 20 per cent saline failed to cause reduction in flow. This indicates that a decrease in blood flow does not occur unless intact blood cells are present.

**Discussion**

The striking increase in pulmonary-artery pressure produced by a 20 per cent solution of sodium chloride and accompanied by a transient period of apnea, decrease in systemic arterial pressure and cardiac irregularities is in complete accord with the earlier
observations of Binet and Burstein,¹ ² and Eliakim and co-workers.³ This immediate decrease in systemic pressure is consistent with a transient, near cessation in pulmonary blood flow. Little doubt exists that the increase in pulmonary-artery pressure is a consequence of increased difficulty in getting blood through the pulmonary vessels.

Our experiments on the isolated perfused lung are in agreement with the results of Read and associates.⁶ Thus, transient hemagglutination could explain the increase in pulmonary-artery pressure and the decrease in pulmonary blood flow occurring after the injection of hypertonic saline. The increased resistance to flow could result from mechanical obstruction alone or from a combination of obstruction and vasoconstriction. However, our experiments do not completely exclude the possibility that hypertonic saline might release a vasoactive substance from the blood, although the experiments using laked blood make this possibility unlikely.

In conclusion, then, we cannot find evidence to support the hypothesis that the injection of a 20 per cent solution of sodium chloride into the pulmonary arteries increases the resistance to flow through the pulmonary circulation by a specific action on the pulmonary vessels near their junction with the left atrium.⁷ The present observations are in keeping with the views of Read and his colleagues,⁶ who expressed the opinion that reversible hemagglutination is the primary cause.

**SUMMARY**

The injection of a 20 per cent solution of sodium chloride into the pulmonary artery or the right atrium of anesthetized closed-chest dogs was followed by a striking increase in pressure between the pulmonary artery on the one hand, and the pulmonary-artery wedge, pulmonary vein, and left atrium on the other. Since the flow of blood decreased, the increase in pulmonary-artery pressure was due to increased difficulty in getting blood through the pulmonary vessels. No increase occurred in pressure between the pulmonary vein and left atrium, or the pulmonary-artery wedge and left atrium. Therefore, the increased pulmonary vascular resistance could not be attributed to a specific constrictor action of the hypertonic saline on the pulmonary veins at their junction with the left atrium; it must have occurred in the vessels upstream to that site. Evidence is presented supporting the possibility that this increased resistance results primarily from blockage of vessels due to reversible agglutination of erythrocytes.

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**SUMMARIO IN INTERLINGUA**

La injection de un solution de 20 pro cento de chloruro de natrium in le arteria pulmonar o le atrio dextere de anesthetisate canes con thoraces intagte esseva sequite per marcate augmentos del tension inter (1) le arteria pulmonar e (2) le cuneco pulmono-arterial, le vena pulmonar, e le atrio sinistre. Viste que le fluxo de sanguine se reduceva, le augmento del tension pulmono-arterial esseva le effecto de un augmentate impedimento del fluxo de sanguine a transverso le vasos pulmonar. Nulle augmento del tension ocurreva inter le vena pulmonar e le atrio sinistre o inter le cuneco pulmono-arterial e le atrio sinistre. Ergo, le augmentate resistentia pulmono-vascular non poteva esser attribuite a un specific action constrictori del hypertonic solution salin super le venas pulmonar in le region de lor junction con le atrio sinistre. Illo debeva haber ocurritse in le vasos a un sito distanciate contra le currente. Es presentate observationes que supporta le these que iste augmentate resistentia resultava possibilemente super toto ab le blocage de vasos in consequentia del reversibile agglutination erythrocytic.

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