Effect of Hypertonic Saline on the Pulmonary and Systemic Pressures

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The intravenous injection of 20 per cent saline in anesthetized closed chest dogs causes a rise in pulmonary venous, pulmonary arterial, right ventricular and peripheral venous pressures. Left atrial pressure does not change or falls, and systemic arterial pressure decreases very markedly. These changes are shown to result from spasm at the pulmonary vein—left atrial junction. Stimulation of chemoreceptors in this region is assumed to be the cause of the spasm.

It has been shown that the intravenous injection of a 20 per cent saline solution in dogs causes a decrease of systemic blood pressure and a marked brief rise of pulmonary arterial pressure. This effect was obtained when the injection was made into the isolated lung in situ, perfused with a constant quantity of blood. The rise of pulmonary arterial pressure was attributed to spasm of the pulmonary arterioles.

The present study was carried out in order to clarify the mechanism of the effect of hypertonic saline solution on the pulmonary vascular tree in the closed chest dog.

Methods

Twenty-five mongrel dogs weighing between 14 and 24 Kg. were used. Anesthesia was induced by sodium thiopental, 0.03 Gm./Kg. intraperitoneally and was maintained, as needed by 0.08 to 0.16 Gm. of sodium pentobarbital intravenously. Heparin, 0.03 to 0.05 Gm., was given intravenously at the beginning of the experiment to prevent clotting in the catheters. Right heart catheterization was performed via the right jugular vein. Left atrial pressure was measured in 2 dogs directly by introducing a needle through a bronchoscope and puncturing the anteromedial surface of the right main bronchus to enter the left atrium. Right heart catheterization was performed via the right jugular vein. Left atrial pressure was measured in 2 dogs directly by introducing a needle through a bronchoscope and puncturing the anteromedial surface of the right main bronchus to enter the left atrium. The location of the needle in these 2 cases was indicated by the low pressure, the presence of arterial blood and by recording a typical atrial pressure pulse tracing. In 6 dogs the left atrial and the pulmonary venous pressures were measured simultaneously after left thoracotomy had been performed. Catheters were introduced into the left atrium through the atrial appendage and forwardly into the middle of the left atrium, and into one of the main left pulmonary veins, the tip lying about 3 cm. away from the heart as verified by palpation. A free flow was obtained from all catheters during the experiment. The location of the catheters was verified again at the conclusion of each experiment. In these open chest experiments, artificial positive pressure breathing was maintained. Catheters were also introduced into the abdominal aorta and the inferior vena cava. Blood pressures were measured by two electromanometers (Sanborn) and two strain gauge transducers (Statham), and recorded on a four-channel direct writer. Respiration was recorded by means of a rubber chest pneumograph.

A 20 per cent saline solution was injected in a dose of 1 ml./Kg. The total volume of fluid was administered within 10 sec. The sites of injection were femoral vein or inferior vena cava, pulmonary artery, common carotid artery, and aorta.

A total of 85 injections were given: 62 into the femoral vein or the inferior vena cava, 9 into the pulmonary artery, 10 into the descending aorta, and 4 into the common carotid artery. Several types of experiments were performed after injection into the peripheral veins or the pulmonary artery. Pressure was simultaneously measured in the pulmonary artery, the aorta and the inferior vena cava 25 times; pulmonary artery and aorta 16 times; pulmonary artery, aorta and left atrium 14 times; pulmonary artery, right ventricle and aorta 6 times; pulmonary artery, pulmonary vein, left atrium and aorta 7 times; and pulmonary artery, pulmonary wedge pressure and aorta 3 times. In all experiments in which the injection was made into the descending aorta or the common carotid artery, pulmonary arterial, aortic and peripheral venous pressure was...
FIG. 1. Twenty per cent saline (1 ml./Kg.) intravenously. Closed chest experiment. Time of injection in figures 1-4 is marked at bottom of record. Time in seconds. Note the marked rise in pulmonary arterial pressure, the decrease in aortic pressure, the rise in peripheral venous pressure and the apnea, followed by hyperpnea. These immediate changes are followed by a second wave of similar changes.

measured. Respiration was recorded in almost all experiments, and electrocardiograms in 10 experiments.

Control experiments with the same quantities of normal saline and a 50 per cent solution of glucose were performed.

RESULTS

Injection of hypertonic saline solution into the femoral vein or the inferior vena cava (fig. 1) was followed within 4 to 8 sec. by a long period of apnea usually succeeded by slight hyperpnea. In all experiments the aortic pressure fell very markedly, sometimes reaching 5 to 10 mm. Hg. This effect lasted about 20 sec. A second fall of aortic pressure, usually less pronounced, was frequently observed approximately 10 sec. later. The aortic pressure returned to normal within 60 to 90 sec. Sometimes, when the first wave of pressure fall persisted, it fused with the second wave.

Marked changes were observed in the lesser circulation. Pulmonary venous (fig. 2) and wedge pressures showed a marked rise, followed one beat later by an increase of pulmonary arterial pressure (fig. 3) and a fall in left atrial pressure (fig. 2). The left atrial pressure, however, sometimes showed no change (fig. 3). The right ventricular and the peripheral venous pressures (fig. 1) showed changes similar to those in the pulmonary artery. The rise of pulmonary arterial pressure and the fall in left atrial pressure preceded the fall in aortic pressure. The change of pressures in the lesser circulation and in the peripheral veins usually lasted less than 20 sec. and was frequently succeeded by a second wave of similar changes, simultaneous with the second bout of aortic pressure fall. The electrocardiogram showed bradycardia and other marked changes which will be described separately.

Following vagotomy, the injection of hypertonic saline solution no longer caused apnea, and resulted in either no change or a slight increase or decrease in the respiratory rate. Bradycardia was also abolished. However, vagotomy did not affect the changes in blood pressure following hypertonic saline (fig. 4).

Atropine and phentolamine (Regitine) also had no effect on the pressure changes caused by hypertonic saline solution. However, in
PULMONARY VENOUS CONSTRICTION

Fig. 2 Top. Twenty per cent saline intravenously. Open chest experiment. Time in seconds. Note the very marked rise in pulmonary venous and pulmonary arterial pressures, and the fall in left atrial and aortic pressures. Bradycardia follows the injection. The dog died after this injection.

Fig. 3 Bottom. Twenty per cent saline intravenously. Open chest experiment. Paper speed 25 mm/sec. The rise in pulmonary venous pressure precedes the rise in pulmonary arterial pressure by one beat. Left atrial pressure shows no change. Marked bradycardia follows the injection.

3 experiments, the administration of hexamethonium appeared to accentuate the response to the hypertonic saline solution.

Injection of hypertonic saline into the pulmonary artery resulted in changes in respiration and pressures similar to those seen after an intravenous injection, but the response occurred only after a latent period of 2 sec. Repeated injections of hypertonic saline into either the peripheral veins or the pulmonary artery of the same dog usually caused a lesser response (tachyphylaxis).

Control experiments with injection of a 50 per cent glucose solution or isotonic saline into the peripheral veins or the pulmonary artery had no effect on respiration and on the pressures at the various points of the circulation.

The injection of hypertonic saline into the descending aorta caused, within 5 sec. respiratory arrest which lasted several seconds. During the period of apnea there was a marked rise of peripheral venous pressure and a slight rise of aortic and pulmonary arterial pressures. All changes in blood pressures disappeared with resumption of respiration. Similar changes in respiration and blood pressures were caused by the injection of a 50 per cent glucose solution into the descending aorta while equal quantities of isotonic saline were completely without effect.

The injection of 20 per cent saline into the common carotid artery caused apnea, bradycardia, a fall in aortic pressure, a slight rise of pulmonary arterial pressure and no appreciable change in peripheral venous pressure.
DISCUSSION

The results presented demonstrate that the rapid intravenous injection of a 20 per cent saline solution causes a very marked rise in pressure in the pulmonary veins, the pulmonary artery, the right heart and the peripheral veins. Left atrial pressure either does not change or decreases, and aortic pressure falls to very low levels. Apnea and bradycardia appear as well. The pressure gradient between the pulmonary veins and the left atrium suggests very strongly that the cause of this profound change in pressures is spasm at the pulmonary vein-left atrial junction. Spasm at this site leads to trapping of blood in the lungs and diminished inflow to the left heart, thus causing a rise of pressure in the lesser circulation and a fall of pressure in the systemic circulation. We have no evidence for additional factors leading to systemic arterial hypotension, though such factors may exist.

The presence of a sphincter at the venoatrial junction has been known to anatomists for many years, and a "throttle valve" action has been ascribed to it. Its activity in man has been demonstrated by angiocardiography. Spasm of the large pulmonary veins in vitro has been produced by acetylcholine, epinephrine and histamine. A venoconstrictive effect of carbon dioxide in the isolated perfused lung of the cat and of the dog has been also demonstrated.

As mentioned, pulmonary venous spasm leads to pulmonary vascular congestion and possibly to pulmonary edema. Some data obtained in animals with pulmonary edema suggest an increase in pulmonary arterial pressure which might be due to vasoconstriction. It is evident from the very marked effect of the hypertonic saline solution that pulmonary venous spasm may play an important role in the development of pulmonary edema. Lung biopsy taken at the heights of the pulmonary arterial pressure rise following the injection of hypertonic saline solution shows extreme congestion of the pulmonary capillaries (fig. 5).

The mechanism by which hypertonic saline causes pulmonary venous spasm is still not clear. It has been shown that raising the pressure in the pulmonary artery, by perfusion or by ligating the pulmonary veins, will cause a fall in systemic pressure and bradycardia. Sensory fibers in the venous side of the pulmonary vascular tree have been suggested as receptors of this reflex reaction. However, this reflex is abolished by vagotomy. There is no doubt that the rise of pulmonary arterial pressure and the other phenomena caused by the injection of hypertonic saline solution are not due to the mechanical effect of the injection. Any mechanical effect of
PULMONARY VENOUS CONSTRICION

such a small volume of fluid administered into the peripheral veins would most likely be dissipated before reaching the pulmonary circulation. Furthermore, experiments with similar quantities of normal saline solution had no effect. Similarly, injections into the pulmonary artery gave rise to no effect which could be ascribed to mechanical causes since such a mechanical effect would have been abolished by vagotomy. The rapid infusion of large quantities of normal saline, isotonic glucose, whole blood or dextran solutions in man have been shown to raise the pulmonary arterial and capillary pressures. This rise, however, appears slowly, lasts longer, and is accompanied by no change in systemic pressure, respiration and pulse rate. An increase of blood volume has been considered the cause of this phenomenon. It may be argued that the hypertonic saline elevates the pressure in the pulmonary vascular bed by increasing pulmonary blood volume by virtue of its hypertonicity. However, this mechanism of action is improbable because it does not explain either the drastic fall of systemic pressure or the apnea. Furthermore, control experiments with injections of a hypertonic glucose solution had no effect whatsoever.

The syndrome of apnea, bradycardia and a fall of systemic blood pressure has been experimentally produced by the injection of veratrine derivatives, nicotine, adenosine triphosphate, heterologous serum, various amides and 5-hydroxytryptamine. The last substance has been shown to cause a rise of pulmonary arterial pressure as well. The reflex action caused by these substances has been shown to originate in the left ventricle and in the lungs. The effect of all these substances is abolished by vagotomy, in contrast with the changes produced by hypertonic saline. In our experiments vagotomy abolished only the apnea and the bradycardia, but did not affect the change in pressures. This fact indicates that the effect of hypertonic saline on the respiration and the heart rate is dependent on a mechanism different from that of the effect on the pressures. A nonvagal reflex mechanism may be responsible for the latter effect. Nonvagal reflexes leading to systemic vasodilatation have been described by Moe and Gruhzit. The receptor area for this reflex is probably in the thoracic aorta, and thoracic sympathectomy abolishes the reflex. However, the change in pressures produced by hypertonic saline solution is not affected by hexamethonium and phentolamine. This speaks against a mechanism similar to that of the reflex described by Moe and Gruhzit.

The most probable explanation of the mechanism of the profound changes caused by hypertonic saline solution is that the spasm of the pulmonary vein-left atrial junction is a direct result of the high concentration of NaCl. Cells sensitive to a high concentration of either Na+ and/or Cl− may be present in this area, and their response to this stimulus may be spasm. Our current experiments show that equivalent hypertonic solutions of sodium iodide, sodium fluoride, sodium thiocyanate, sodium sulfate and lithium chloride have a similar effect on the pulmonary circulation.

The effect of hypertonic saline solution injected into the descending aorta is mediated through a different mechanism, the nature of which is unknown. It is probably dependent on the hypertonicity of the solution, since hypertonic glucose solution produces similar results. No further attempt was made to clarify this mechanism since injection of both hypertonic saline and glucose solutions into the descending aorta served as control experiments in this study.

SUMMARY

The effect of intravenous injections of 20 per cent saline on the pulmonary and systemic pressures was examined in 25 anesthetized dogs. Marked rise of pulmonary venous, pulmonary arterial, right ventricular, and peripheral venous pressures followed the injection. Left atrial pressure did not change or decreased and aortic pressure dropped to very low levels. Apnea and bradycardia were also observed.
The changes in pressure and respiration were not affected by the administration of atropine or phentolamine. Hexamethonium apparently accentuated the pressure response. Vagotomy abolished the respiratory response and the bradycardia, but did not alter the response of pressures.

It is assumed that the change in pressures, following the intravenous injection of hypertonic saline, is caused by spasm at the pulmonary vein-left atrial junction, as a result of stimulation of chemoreceptors at this site, sensitive to high concentrations of Na\(^+\) and/or Cl\(^-\).

**REFERENCES**

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