Site of Action of Hypertonic Saline in the Pulmonary Circulation

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The intravenous injection of 20 per cent saline to open-chest dogs has been shown to cause a marked though transient rise of pulmonary arterial pressure, attributed to spasm of the pulmonary arterioles.1,2 Subsequently we demonstrated that the intravenous administration of hypertonic saline causes, in addition, a marked rise of pulmonary venous pressure and a fall or no change of left atrial pressure.3 This finding led us to the assumption that hypertonic saline causes spasm of the large pulmonary veins close to their junction with the left atrium.3

Read and his associates performed experiments similar to ours and found, in two-thirds of the cases, a reaction identical with that described by us.4,5 However, in the remaining cases the rise of pulmonary arterial pressure was not accompanied by a similar rise of the pulmonary venous pressure. Semler et al.,6 working with closed-chest dogs, found a rise of pulmonary arterial pressure after the injection of hypertonic saline but could not confirm the effect on the pulmonary venous pressure.

Since our first report3 we have observed that the pulmonary arterial pressure rise that follows the injection of hypertonic saline was not invariably accompanied by a rise of pulmonary venous pressure; thus a reaction similar to that noted by Semler et al.6 and sometimes by Read et al.4,5 was recorded. The cause of this variability was not clear until it was found that the type of reaction of the pulmonary venous pressure usually depended on whether the pressure was measured in the superior or the inferior pulmonary vein.

A series of experiments was, therefore, performed in which simultaneous pressure measurements were made in the pulmonary artery, the pulmonary veins of the upper and lower left lung lobes, and the aorta. The present report will describe the results of these experiments.

Methods

Nineteen dogs weighing between 14 and 22 Kg. were used. Anesthesia was induced by sodium thiopeptone, 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 used as anticoagulant at the beginning of the experiment. The catheter in the pulmonary artery was introduced via the jugular vein. Midsternal thoracotomy was performed, and artificial respiration was maintained by intermittent positive pressure. Catheters were introduced through the atrial appendage into the pulmonary veins of the upper (or middle) and the lower lobe of the left lung. A 6F catheter was introduced in the superior vein, and a 7F catheter into the inferior vein. The tips of the catheters lay at the lung border or, at most, 5 mm. within the lung tissue. The location of the catheters was verified during and at the end of each experiment. Systemic arterial pressure was measured through a catheter introduced into the femoral artery. Blood pressure were measured by two electromanometers (Sanborn) and two strain-gauge transducers (Statham), and recorded on a four-channel direct writer.

Twenty per cent saline solution was rapidly injected into the femoral vein in a dose of 1 ml./Kg. A total of 48 injections were given to the 19 dogs. The pressure in the pulmonary artery and the aorta was measured in all cases; simultaneous measurements in the left superior and inferior veins were performed 28 times; left inferior vein and left atrium, 15 times; left superior vein and left atrium, 2 times; left middle and inferior veins, 3 times.

Biopsies of both the upper and lower lung lobes were taken simultaneously in seven dogs at the moment of the most marked hemodynamic changes in the pulmonary circulation. Swab holders were used for this purpose, in order to secure an instantaneous clamping and isolation of the lung.
tissue. After fixation in formalin, paraffin sections were stained with hematoxylin and eosin. Anatomical and histological examinations of the pulmonary veins at their junction with the left atrium were made in seven dogs.

Results

The pressure changes in the pulmonary artery, the left atrium, and the femoral artery were similar in all cases, and did not differ from those previously described. Four to eight seconds after intravenous injection of hypertonic saline, the mean pressure in the pulmonary artery rose markedly to values that usually exceeded 40 mm. Hg. This hypertensive phase was reversible, usually within 20 seconds. The pressure in the left atrium fell or did not change, while the systemic arterial pressure decreased markedly, sometimes to 5 to 10 mm. Hg. The rise in pulmonary arterial pressure preceded the fall in left atrial and systemic arterial pressures by one to two seconds.

The pressure changes in the pulmonary veins depended on the location of the catheters in the veins and on the choice of pulmonary vein for pressure measurements. When the tip of the catheter was located distally to the lung border, the pressure change in both the superior and inferior veins was similar to that in the left atrium. However, when the tip of the catheter was at the lung border or several millimeters within the lung tissue, the pressure changes depended largely on whether the superior or the inferior vein was used. In the superior vein, a rise in pressure was most frequent (23 of 33 estimations); a fall in pressure was recorded only seven times and a double (rise and fall) response in three cases. In the inferior vein, the usual response was a fall or no change in pressure (39 of 46 estimations). However, a rise in pressure in this vein was recorded in the remaining seven experiments.
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Figure 3
Twenty per cent saline intravenously. Paper speed, 1 mm/sec. The hypertensive response in the inferior pulmonary vein is progressively reversed. Note also the appearance of a marked pressure gradient between the pulmonary artery and the pulmonary veins.

The results are illustrated in figures 1 to 4. Figure 1 demonstrates a typical experiment. It may be seen that, after the injection, pulmonary arterial hypertension was accompanied by a marked rise in the venous pressure of the left superior pulmonary vein, while the pressure in the inferior vein fell.

Figures 2, 3, and 4 demonstrate the dynamics of the mechanism responsible for the pressure change in the inferior pulmonary vein. In the record shown on the left side of figure 2, a reaction similar to that shown in figure 1 was recorded. However, when a stronger stimulus was used (3.5 M NaSCN instead of NaCl), the pressure rose in both veins.

Figure 3 demonstrates several noteworthy features. The first injection of hypertonic saline caused a rise of pressure in both veins (left tracing). However, on repeated injections, the response of the inferior vein diminished (middle tracing), and was finally reversed (right tracing). It should be stressed that the catheters remained in the same position during the whole experiment. Therefore, it must be assumed that the mechanism responsible for the pressor effect in the lower vein had been exhausted.

It can further be seen from figure 3 (left tracing) that, although the pulmonary venous pressure rose after the injection, a marked pressure gradient appeared between the pulmonary artery (maximal pressure about 45 mm. Hg) and the pulmonary veins (maximal pressure, 14 mm. Hg).

Figure 4 demonstrates a double response of pressure in the superior pulmonary vein. In this experiment, an initial rise in pressure was immediately followed by a fall, similar to that in the inferior vein.

Histological Studies of Biopsy Specimens from the Lungs
Biopsy specimens from both the upper and the lower left-lung lobes were taken simultaneously when the hemodynamic changes
were most pronounced. Marked congestion in the pulmonary arteries was observed in all instances in both lung lobes. However, congestion in the septal capillaries was more frequent in the specimen from the upper lobe (six out of seven) than in the lower (two out of seven biopsies). This is well illustrated by figure 5. Figure 5 (upper) shows severe congestion in both the capillaries and the larger arterial branches of a dog in which both the pulmonary arterial and venous pressure rose after the injection. The specimen from the lower lobe, taken at the same time, shows arterial congestion but normal capillaries (fig. 5 lower); the venous pressure in this lobe had fallen at the moment when the biopsy was taken.

In the upper lobe, the capillaries had sometimes burst and the alveoli had filled up with extravasates. The larger arterial branches were sometimes full of homogenous eosinophilic material. In the capillaries, the red blood cells were usually well separated from each other, even when severe congestion was present.

**Anatomical Studies of the Pulmonary-Vein–Left-Atrial Junction**

Dissection of the pulmonary-vein–left-atrial junction showed uniform findings in all dogs.
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Figure 7
Schematic presentation of the muscle fibers around the pulmonary veins. (Left) Posterior view of left atrium shows a circular arrangement of thick muscle fibers. (Right) Planimetric view showing the difference between upper and lower pulmonary veins.

The myocardial fibers in this region were organized in fascicles that surrounded the apertures of the pulmonary veins, infiltrated into their walls for 5 to 20 mm., and sometimes reached the pulmonary border. The arrangement of the muscle fibers around the superior and inferior veins was quite different. While the muscular fascicles formed a strong and thick sphincter around the openings of the superior veins,* a similar arrangement was inconspicuous around the inferior veins (figs. 6 and 7). The upper part of the atrial wall was much thicker around the superior veins, and especially between the veins of the two sides; this region represented the center of decussation of the muscular fascicles that surrounded the vein apertures (fig. 7). On the other hand, the atrial wall around and between the inferior veins was thin, contained fewer muscle fibers, and appeared similar to the walls of the veins themselves. The sleeves of striated muscle that extended from the atrium into and around the venous walls generally projected further along the superior, than along the inferior, pulmonary veins. In the superior veins the muscle in the venous wall was much thicker and frequently extended as far as the lung border (fig. 8).

Discussion
Our observations suggest that hypertonic saline acts both on the pulmonary veins close to the left atrium and on the pulmonary arterioles. The rise of pulmonary venous pressure accompanied by a fall of left atrial pressure is the indication for the effect of hypertonic saline on the pulmonary veins. The fact that this reaction occurred much more frequently in the superior pulmonary vein requires explanation. The possibility that the catheter in the superior vein was wedged and in fact recorded the pressure of the pulmonary artery is not acceptable; the tip of the catheter lay close to the lung border where the vein is at least 4 mm. wide. It is possible that spasm of the pulmonary veins could bring the venous wall into close contact with the catheter, thus creating a situation in which the catheter would behave as if it were wedged. However, this would again imply spasm of the pulmonary veins caused by the hypertonic solution. Furthermore, the same considerations apply to the catheter that was located in the inferior veins where no pressure rise was usually recorded.

The description of differences in structure between the muscular fascicles around the superior and the inferior pulmonary veins conforms with the results of our hemodynamic studies. Spasm of the abundant and thick muscle fibers around the superior veins could

*The vein of the middle lung lobe joined the superior vein before its entrance into the left atrium.

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cause a rise in pressure in the pulmonary veins. On the other hand, the less prominent muscle fibers around the inferior veins would be activated only occasionally by hypertonic saline, and their activity might be easily exhausted (fig. 3). Stronger stimuli might contract this rudimentary sphincter even though hypertonic saline had failed to do so (fig. 2).

In spite of these considerations, there is a possibility that the contraction of the pulmonary veins is not due to spasm of the atrial striated-muscle sleeve but to spasm of the smooth venous muscle. However, if this were the case, it would be difficult to explain the different response of the superior and the inferior veins.

The difference in the pressure response to hypertonic saline in the superior and inferior pulmonary veins, as demonstrated in our experiments, may account for the variable results obtained by the different investigators. Neither Read et al. nor Semler et al. have specified in their reports the exact pulmonary vein in which the pressure was measured. However, figure 1 in Semler's report shows that the catheter was located in the inferior pulmonary vein. Semler and his associates used closed-chest dogs, and their technique would favor the introduction of the catheter into the inferior veins in which a pressure fall would more likely be recorded.

Our experiments indicate that hypertonic saline acts also at the pulmonary arteriolar level. This is indicated by the marked gradient created between the pulmonary artery and the inferior pulmonary vein, and sometimes between the pulmonary artery and the superior pulmonary vein (fig. 3). Furthermore, a double (rise and fall) response was sometimes recorded in the superior vein (fig. 4). This would indicate that the distal (venous) effect was operative at first, until the proximal (arteriolar) effect supervened; a block to blood flow at the latter level would then cause the fall of the pulmonary venous pressure.

Summary

The effect of intravenous injections of 20 per cent saline on the pulmonary circulation was examined in 19 dogs. A marked rise of pulmonary arterial pressure was recorded in all cases. The pressure changes in the pulmonary veins depended largely on the choice of the vein for pressure measurements. A hypertensive response was usually recorded in the superior vein, while in the inferior vein no change or a slight fall in pressure was the rule. Left atrial pressure either did not change or fell.

A difference in the anatomical structure of the muscle sphincter around the superior and inferior pulmonary veins is described. A potent sphincter surrounds the superior veins and infiltrates within their walls sometimes as far as the border of the lung. The sphincter around the inferior veins is rudimentary and inconspicuous.

Evidence is brought that hypertonic saline acts both on the pulmonary veins close to the left atrium and at the pulmonary arteriolar level.

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References


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