Influence of Dextran Infusion on the Pulmonary Hypertensive Effect of Concentrated Saline

By Raymond C. Read, M.D., Ph.D., F.R.C.S., James A. Vick, M.S., M.D., Ph.D., and Maurice W. Meyer, D.D.S., M.S., Ph.D.

BINET and Burstein reported in 1951 that the intravenous administration of concentrated saline produces pulmonary hypertension in the dog. The response was attributed to arteriospasm since it could be elicited in the isolated perfused lung. Eliakim and his associates aroused considerable interest in this phenomenon when they suggested in 1958 that its mechanism was pulmonary venoconstriction evoked by the rise in blood sodium-ion concentration. This interpretation was questioned by Semler, Shepherd, and Swan who reported that the site of obstruction was proximal to the capillary bed. However, Read and his colleagues obtained evidence for an associated pulmonary-venous-left-atrial pressure difference in all but a minority of experiments. Eliakim et al. now agree that pulmonary-venous obstruction is not uniformly demonstrable in the presence of salt-induced obstruction to blood flow through the lungs. A further objection to the sodium-ion receptor theory is the observation that 50 per cent glucose initiates changes in the pulmonary vasculature essentially the same as those seen with isosmotic sodium chloride. An alternative hypothesis was developed to explain the absence of pulmonary reactivity to concentrated salt solutions when erythrocytes were excluded from the perfusate. The role of the red cell became apparent when the typical pulmonary-hypertensive response was seen to be accompanied by cellular agglutination occurring throughout the microcirculation. Interference with the stability of the red-cell stream is now considered to be the cause of death in cardioangiography, while a similar reaction taking place in the systemic circulation is held responsible for ischemic arteriographic complications. These latter findings led to the suggestion that low-molecular-weight dextran, which has been reported to prevent the sludging of blood observed after trauma, might similarly decrease the toxicity of concentrated radiopaque agents. This idea received experimental support from Bernstein and Evans who were able to double the mean lethal dose of 90 per cent diatrizoate for the dog by the prior injection of dextran. The purpose of the present study was to determine whether the same technique would be effective against the pulmonary hypertensive action of concentrated saline. If prophylaxis could be demonstrated, then an attempt was to be made to establish its mechanism.

Methods

All experiments were performed on adult mongrel dogs weighing between 10 and 30 Kg. The animals were anesthetized with 30 mg./Kg. of pentobarbital sodium given by intravenous injection. They were ventilated with a positive-pressure respirator connected to a tracheal cannula. Intravascular pressures were measured by means of Statham transducers and recorded on a Sanborn Poly Viso. Heparin, 1 mg./Kg., was administered for anticoagulation. One ml./Kg. of 15 per cent NaCl was selected as the test dosage because, although it evokes marked transitory pulmonary-vascular changes, injections can be repeated at frequent intervals without death of the animal.
Open-Chest Preparation

The chest was opened through the left fifth interspace. Polyethylene catheters were inserted into the main pulmonary artery, the left atrium, the aorta through the femoral artery, and the inferior vena cava via the femoral vein. Test injections were made rapidly through a large catheter introduced into the contralateral femoral vein. The possible protective effect of 10 ml./Kg. of low- and high-molecular-weight dextran preparations, plasma, blood, or isotonic saline was investigated by prior infusion at a rate of up to 3 ml./Kg./min. The technique of administration was based on the earlier work of Bernstein and Evans. Some animals developed a shocklike reaction to homologous blood or plasma and were discarded from the study. The influence of phlebotomy on the response to test injections was studied before and after infusion. Finally, the role of left-atrial hypertension was investigated by producing this state with constriction of the ascending or descending aorta through the use of a screw clamp.

Isolated Lung Preparation

Lungs were isolated and perfused with the dog's own blood at constant flow by a technique which has been described previously. Pulmonary-venous return was drained by gravity, thus maintaining a constant left-atrial pressure. Autologous plasma, red cells, or saline dextran mixtures were added as indicated. Since the maximal pump flow compatible with approximately normal pulmonary pressures was only one-third to one-half the calculated resting cardiac output, and as test injections were given just proximal to the pulmonary artery, the dosage was here reduced to 0.5 ml./Kg. of 5, 10, or 15 per cent NaCl. The maximal pulmonary-arterial-pressure response was used as an index of the changes evoked.

Microscopic Studies

The circulation in the intact lung was observed microscopically with an Ultropak before, during, and after test injections. Vascular diameters were measured with a calibrated ocular micrometer. The preparation and technique used for observing these vessels were modified from those of Vogel, who has performed high-speed cinematography on the microcirculation in the lungs of cats. To avoid vibration, diffusion respiration with oxygen was instituted 30 to 60 seconds before and after test injections. Control studies had demonstrated that this maneuver for such an interval did not alter either resting pulmonary pressures or the usual hemodynamic response to hypertonic saline.

Results

Effect of Low-Molecular-Weight Dextran

One ml./Kg. of 15 per cent NaCl was rapidly injected into the venous system of 10 dogs before and after 10 to 15 ml./Kg. of 15 per cent low-molecular-weight dextran in saline had been infused over a period of 3 to 30 minutes. The maximal pulmonary-arterial-pressure response to the test injections decreased from a mean rise of 29 mm. Hg in the controls to 7.5 mm. Hg after treatment with dextran. The degree of protection tended to increase in proportion to the rate of infusion. The incidence and severity of immediate bradycardia, cardiac arrhythmia, hypotension, and narrowed pulse pressure were also less (fig. 1). However, the usual delayed fall in blood pressure remained unaffected or was actually increased. It was possible to correlate the degree of protection provided by dextran with the increment in left-atrial pressure which resulted from its infusion (fig. 2).

A second series of 10 dogs was subjected to the same type of experiment, except that infusions of 6 per cent standard clinical dextran in saline, plasma, isotonic saline, or blood were substituted for those of low-molecular-weight dextran. Practically identical results were obtained (figs. 3 and 4). Hypervolemia resulting from these infusions produced slight pulmonary hypertension, an elevated left-atrial pressure, and an increase in systemic blood pressure with widening of the pulse pressure. Little or no change in central venous pressure was noted.

In four studies, the pulmonary-hypertensive response of the isolated lung to the test injections was found to be unaltered when the perfusing blood was changed to a red-cell suspension of the same hematocrit made up in plasma containing 10 per cent by volume of low-molecular-weight dextran (fig. 5).

Effect of Bleeding

Five animals were bled from a contralateral vein at the same rate as they were being infu-
Figure 1
Pressure tracings taken from an open-chest dog in which 1 ml/Kg. of 15 per cent NaCl was rapidly injected into the femoral vein before (above) and after (below) treatment with low-molecular-weight dextran. The upper record demonstrates the typical response to concentrated saline. The lower tracing shows amelioration of the pulmonary-hypertensive effect with an associated reduction in the usual immediate systemic hypotension, bradycardia, and cardiac arrhythmia. Note that the later hypotensive phase remained unaffected.

Fused. Left-atrial pressure was thus held essentially constant. Significant protection was no longer provided by the various solutions (fig. 6). However, return of the shed blood to the circulation was associated with a rise in left-atrial pressure and a diminished response to concentrated saline. Vice versa, whenever a state of relative immunity to the pulmonary-vascular effects of 15 per cent NaCl had been conferred by infusion, the dog's original susceptibility could be restored by bleeding until the left-atrial pressure returned to normal (fig. 7). It was found to be possible, by graduated transfusion and hemorrhage, to pass an animal repeatedly through such a cycle, the only limitation being the eventual development of pulmonary edema. Successive re-establishment of a normal left-atrial pressure required the removal of more blood from the circulation than was introduced. Left-atrial pressure fell below normal if phlebotomy was purposely excessive, then, provided the blood pressure had not fallen to shock levels, a heightened response to test injections was seen.

Effect of Left-Atrial Hypertension

In a final series of six dogs, the pulmonary-arterial-pressure response to concentrated saline was studied before and after the induction of left-atrial hypertension by aortic constriction. A relationship which was essentially similar to that described after hypervolemia could be established between the magnitude of response and left-atrial pressure (fig. 8).

Microscopic Observations

Intravascular agglutination with transitory slowing and even cessation of blood flow was seen in the intact lung after administration of 15 per cent NaCl. This observation is in...
agreement with the response previously seen and reported using the isolated preparation.19
The diameter of the arterioles (35 to 70 μ) and venules (60 to 100 μ) increased by 17 to 25 per cent after infusion. Subsequent bleeding with restoration of the left-atrial pressure to normal reduced the vascular bore to its original dimensions. Red-cell agglutination could still be seen in the small vessels when hypertonic saline was injected in animals made hypervolemic by the various test injections; however, the duration of the phenomenon was less, perhaps because of vasodilatation.

Discussion
The results show clearly that low-molecular-weight dextran protects the dog against the pulmonary-hypertensive effect of concentrated saline. The prophylactic potentialities of this treatment are thus not restricted to the toxicity of radiopaque agents. An obvious explanation for these findings, consistent with the original hypothesis, is that dextran acts by preventing the development of red-cell agglutination subsequent to the intravascular administration of markedly hypertonic solutions.

Figure 3
Typical prophylactic effect of isotonic saline. The classical control response to concentrated saline was followed by a diminished reaction after the infusion of 10 ml./Kg. of 0.9 per cent NaCl. The induction of hypervolemia resulted in an elevated left-atrial pressure, increased systemic blood pressure, widened pulse pressure, and little or no change in central venous pressure.

Figure 4
This illustration is similar to figure 2, with the exception that the results of test injections made before and after blood, plasma, and saline infusions have been added to those previously obtained following dextran. These various solutions appear to provide a comparable degree of protection, while the inverse relationship between left-atrial pressure and subsequent pulmonary-arterial pressure response to 15 per cent NaCl is reaffirmed.

Unfortunately, there are objections to such a simple interpretation. In the first place, admixture of dextran with blood perfusing an isolated lung has no effect on the lung's reaction to concentrated saline. Secondly, the prior infusion of other dextran preparations, plasma, or even isotonic saline confers a similar immunity in the intact animal if, as with the use of low-molecular-weight dextran, the development of hypervolemia is not prevented by simultaneous phlebotomy. Finally, even when the typical pulmonary-hypertensive response to 15 per cent NaCl is inhibited by low-molecular-weight dextran, cellular aggregation can still be seen occurring throughout the microcirculation.

The evidence is obviously against the idea of a specific antiagglutinative action of dextran under these circumstances. It indicates
Figure 5
Pulmonary-arterial-pressure responses to the injection of 0.5 ml./Kg. of 15 per cent, 10 per cent, and 5 per cent NaCl in the isolated lung. (Above) perfused at constant flow with whole blood; (below) with a red-blood-cell-dextran-plasma mixture. Note that admixture with low-molecular-weight dextran had no effect on the usual hypertensive response to hypertonic saline.

Figure 6
Response of the dog to 1 ml./Kg. of 15 per cent NaCl injected intravenously before and after infusion of low-molecular-weight dextran with concurrent phlebotomy. Note the absence of protection under these circumstances. The blood-pressure tracings are practically superimposable despite the presence of circulating low-molecular-weight dextran.

instead that prophylaxis depends more upon the procedure of infusion itself than upon the nature of the solution used. Hemodilution cannot be a significant factor, because blood is equally efficacious. The single common denominator associated with protection appears to be the induction of hypervolemia. Oligemia leads to accentuation unless shock supervenes. The degree of protection obtained can be correlated with the increment in left-atrial pressure that results from the various infusions. That this relationship is of real significance can be demonstrated by its duplication when left-atrial hypertension is induced by a method which does not depend upon changes in blood volume.

Previous experience suggests only two ways by which left-atrial pressure could have such a marked influence upon the pulmonary-vascular response to concentrated saline. It must either determine the number and size of red-cell agglutinates produced by the intravascular administration of a standard dosage of 15 per cent NaCl, or it must, in some way, increase the tolerance of the lung to microembolism. It is possible that when left-atrial hypertension is induced by hypervolemia with increased venous return, the degree of agglutination precipitated by a given injection of concentrated saline might be reduced by a more rapid rate of dilution; but it is difficult to understand how the same reasoning could apply in the case of a rise in left-atrial pressure produced by heart failure with reduced cardiac output. The second alternative, therefore, seems to be more promising.

A number of previous workers have commented upon the way that central blood volume rises and resistance to blood flow falls whenever left-atrial pressure is elevated. The pulmonary vasculature is distensible, its overall cross-sectional area increasing and decreasing in a mechanical fashion with changes in outflow pressure. This concept can be used to explain the present findings. It thus appears that the size and number of agglutinates produced under these conditions are such that significant vascular plugging no longer occurs if the pulmonary vasculature is distended. The microscopic data indicate an actual increase in capillary bore rather than simply an opening of new channels.

Circulation Research, Volume IX, November 1961
The observation that changes in left-atrial pressure affect only the early hypotensive phase is consistent with previous studies regarding the vasodilatory basis of delayed systemic hypotension evoked by hyperosmotic solutions. Similarly, earlier work indicating a relationship between the magnitude of the pulmonary-hypertensive response and the incidence of immediate bradycardia and arrhythmia (mediated by vagal reflexes) is confirmed.

Eliakim et al. believe a sphincter mechanism located at the left-atrial-pulmonary-venous juncture or, more specifically, in the region where the superior vein enters the main site at which concentrated saline acts on the pulmonary circulation. Unfortunately, certain observations remain unexplained by this interpretation. The reaction in the isolated lung no longer occurs in the absence of red cells. When a typical response is obtained using blood as perfusate, it remains unchanged after excision of the left-atrial-pulmonary-venous junctional area. Similarly, although tachyphylaxis in the intact animal has been explained by the onset of fatigue in the chemoreceptor mechanism, normal responsiveness can be easily restored if the increase in the animal's blood volume, resulting from withdrawal of fluid into the vascular space by repeated injections of markedly hyperosmotic materials, is eliminated by phlebotomy. The suggested relationship between tachyphylaxis and hypervolemia is strengthened by the fact that this phenomenon cannot be induced in the isolated preparation where left-atrial pressure is held constant by gravity drainage.

It remains to be explained why concentrated saline frequently evokes a left-atrial-pulmonary-venous pressure difference in the intact animal. At the present time, one can only speculate that interruption of blood flow at the arteriolar level with a continuing left-ventricular output causes collapse of the left atrium and eventually the need for an opening pressure. Left-atrial hypertension probably reduces the risk of this happening and thus,
perhaps in another way, protects the dog against the pulmonary-hypertensive effects of concentrated saline.

Summary

Low-molecular-weight dextran, which is known to prevent the sludging of blood cells seen in shock, has recently been reported to reduce the toxicity of concentrated radiopaque agents. Experiments have been performed to determine whether this latter effect applies to other hyperosmotic solutions. An attempt was made to delineate the mechanism involved. One ml./Kg. of 15 per cent NaCl was rapidly injected into dogs before and after infusion of 10 ml./Kg. of 15 per cent low-molecular-weight dextran. This treatment significantly reduced the usual pulmonary-hypertensive response. However, other dextran preparations, plasma, and blood were equally effective. Moreover, previous infusion of isotonic saline also conferred immunity when given at a rate sufficient to raise left-atrial pressure. Left-atrial hypertension produced independently of changes in blood volume evoked similar amelioration. If this latter change was prevented by concurrent bleeding, none of the infusions was beneficial. Vice versa, a fall in left-atrial pressure was associated with an accentuated reaction to 15 per cent NaCl. Microscopic examination of the intact lung during protection showed that red-cell agglutination still occurred from concentrated saline, but the small vessels were dilated. It is concluded that low-molecular-weight dextran and other infusions provide prophylaxis against the pulmonary-hypertensive effects of concentrated saline by reducing the susceptibility of the lung to microembolism through the development of left-atrial hypertension.

References


Circulation Research, Volume IX, November 1961
Influence of Dextran Infusion on the Pulmonary Hypertensive Effect of Concentrated Saline
RAYMOND C. READ, JAMES A. VICK and MAURICE E. MEYER

Circ Res. 1961;9:1240-1246
doi: 10.1161/01.RES.9.6.1240

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/9/6/1240

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/