Vascular Effects of Hypertonic Solutions

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I. EFFECT OF HYPERTONIC SOLUTIONS ON SYSTEMIC AND CORONARY VASCULAR RESISTANCE.

During the course of an investigation into the relationship between peripheral resistance and acidosis, a consistent hypotensive response to the administration of concentrated alkaline solutions was encountered. Further study revealed that this effect was present regardless of any pH change, and that similar results occurred when either hypertonic glucose or saline was injected. The purpose of the present paper is to report these observations in detail and discuss their significance in relation to previous work.

Methods

Adult mongrel dogs weighing between 7 and 12 Kg. were lightly anesthetized with thiopental sodium, supplemented with enough succinylcholine to prevent spontaneous respiration. Total body perfusion was carried out by previously described technics. Arterial inflow and venous pressure were held constant and at near normal values under these conditions. Ventricular fibrillation was induced electrically to obviate any residual cardiac output. Bronchial flow, returning to the left heart, was drained through the left atrium. Blood flow through the myocardium was measured by the collection of coronary venous return along a cannula inserted into the pulmonary artery. Aortic and venous cannulas were monitored by means of polyethylene catheters connected to Statham transducer manometers. All recordings were made on a Sanborn Poly-Viso.

Five to 15 ml./Kg. of isotonic or molar solutions of NaHCO₃, NaOH, NaCl, or Na lactate were injected at rates of 3 to 60 ml./min. into the inflow of the arterial pump. Similar amounts of 50 per cent glucose, 50 per cent urea in isotonic saline and distilled water were also used. Alterations in vasomotor tone were induced by either decapitation and pithing, immersing the extraorporeal circuit in ice water, or ganglionic blockade with hexamethonium salt (5 mg./Kg.).

Results

Control Studies

Distilled water (2 X), 5 per cent glucose (2 X), 0.9 per cent saline (3 X), and isotonic NaOH (1 X) were administered to a total of 8 animals during perfusion. The amount of solution and the rate of injection were similar to the subsequent test studies. A slight fall in blood pressure occurred in all but 1 instance (fig. 1). The average change was 10 per cent from a mean of 122 mm. Hg with a maximum alteration of 20 mm. Hg. Coronary flow increased in 6 cases and decreased in 2 dogs with a range of +32 per cent to —21 per cent (fig. 2).

Studies with Hypertonic Solutions

Hypertonic solutions were injected 20 times in 16 experiments. Blood flow rates ranged from 42 to 114 ml./min./Kg. Blood pressure averaged 103 mm. Hg and in all but 1 instance fell as a result of the administration of the concentrated agents. This alteration in systemic resistance at constant flow was accompanied by a similar fall in coronary vascular resistance (mean change of 37 and 40 per cent, respectively). The typical pattern and time relationships are seen in figure 1. The percentage change in total peripheral resistance appeared to be a function of the rate of solute injection (fig. 2). It can be seen that at low rates of injection there was little if any change in resistance. As the rate of administration increased, resistance fell off rapidly until a plateau was reached at a level of 2 mOsm./
Arterial and venous pressure recordings in a dog perfused under ganglionic blockade with hexamethonium. Above, effect of 1 ml./Kg. of molar NaCl solution. Center, result following the rapid administration of a similar amount of 50 per cent glucose. Below, blood pressure response to the injection of a comparable volume of distilled water. Patterns obtained are similar to those observed before any alteration in vasomotor tone.

min./Kg. which is equivalent to an excess in the plasma of approximately 25 mOsm./L.

Effect of Alterations in Vasomotor Tone

Destruction of the central nervous system in 3 dogs, ganglionic blockade in 4 animals, and deep cooling to 5 C. in 3 other experiments failed to interfere with the usual hypotensive response to hypertonic solutions (fig. 1). Similarly, large doses (10 mg./Kg.) of the antihistaminics, diphenhydramine and promethazine hydrochloride did not affect the reaction of concentrated solutions when tested in 2 other perfusion studies.

Discussion

The results demonstrate that, in the dog, the intra-arterial administration of concentrated solutions produces a fall in arteriovenous pressure difference at constant flow. The experiments with distilled water and isotonic media indicate that this effect cannot be attributed to changes in viscosity from hemodilution. Thus, it appears that under these conditions the injection of hypertonic agents, regardless of chemical identity, results in either dilatation of existing vascular beds or the opening up of new channels.

These findings are in agreement with studies by Bellet et al., performed in the perfused hindlimb of the dog using molar sodium lactate. These workers also reported coronary vasodilatation with the same agent. Haddy and collaborators have encountered a similar phenomenon in the forelimb of the dog. They described dilatation of small vessels following an increase in \((\text{Na}^+), (\text{K}^+), (\text{Mg}^{++}), \text{or} (\text{H}^+)\) concentration of 8 to 12 mEq./L in the brachial artery. This threshold is similar to that observed in the present work, but the latter investigators with Friedman have attributed the response to a specific ionic stimulus rather than an osmolar mechanism. Recently, renal vasodilatation has been shown to occur from hypertonic solutions.

At the present time, radio-opaque organic iodides constitute the main group of concen-
Effect on the circulation of the intravenous administration of 1 ml./Kg. of 50 per cent urea in saline. Response illustrates the typical delayed hypotension with tachycardia and increased pulse pressure. Immediate reaction is hypertension with bradycardia. Note the absence of preliminary pulmonary hypertension. Later shallow rise in venous pressure and pulmonary artery pressure may be a result of adrenergic release. Time in seconds (1 mm. = 1 second).

Perfused solutions given parenterally. Peripheral vasodilatation has been suspected to be the cause of the feeling of warmth which frequently follows their intra-arterial administration in angiography. Advantage has been taken of this phenomenon in the treatment of peripheral vascular disease. The decline in peripheral resistance, observed in the experimental animal with these commercial preparations, persists after destruction of the central nervous system and again includes the coronary circulation. The beneficial effect of concentrated solutions on myocardial blood flow helps to explain their value in cardiac resuscitation, despite previous reports of toxicity. The local mechanism responsible for the dilatory action remains obscure.

II. RELATIONSHIP BETWEEN THE PULMONARY AND SYSTEMIC EFFECTS OF CONCENTRATED SOLUTIONS

This study was initiated to determine the role of vasodilatation in the complex vasomotor response to the intravenous adminis-

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Acute cor pulmonale produced by the rapid intravenous injection of 1 ml./Kg. of 20 per cent NaCl. Time in seconds (1 second = 1 mm. on abscissa).

Figure 5

Acute cor pulmonale produced by the rapid intravenous injection of 1 ml./Kg. of 20 per cent NaCl. Time in seconds (1 second = 1 mm. on abscissa).

Figure 6

Initial stage of another diphasic response seen after the administration of 1 ml./Kg. of 50 per cent glucose. Pulmonary venous hypertension is demonstrated with a marked left atrial difference. Early reduction in systemic pulse pressure with accompanying bradycardia and subsequent recovery is also seen.

Acute cor pulmonale produced by the rapid intravenous injection of 1 ml./Kg. of 20 per cent NaCl. Time in seconds (1 second = 1 mm. on abscissa).

Acute cor pulmonale produced by the rapid intravenous injection of 1 ml./Kg. of 20 per cent NaCl. Time in seconds (1 second = 1 mm. on abscissa).

Systemic Hypotension without Preceding Pulmonary Hypertension

This type of response was seen after all of the urea and 5 per cent NaCl injections, and with most of the 50 per cent glucose studies. Characteristically (fig. 3), an immediate systemic hypertension with bradycardia missed beats, and a rise in left atrial pressure was followed by a more prolonged hypotension with tachycardia and an increased pulse pressure. The late fall in blood pressure was associated with a shallow rise and fall in pulmonary artery and venous pressure. The dicrotic notch disappeared from the aortic pulse tracing at this time.

Systemic Hypotension with Early Pulmonary Hypertension

This pattern (fig. 4) was seen after injection of 8 to 20 per cent NaCl, and as an unusual occurrence (9/30) in the glucose studies. The later phase of systemic hypotension was similar to that described previously. The initial stage, however, was different in that the early systemic hypertension was here replaced almost completely by a fall in blood pressure associated with pulmonary hypertension, and a decline in both left atrial pressure and peripheral pulse pressure. The increase in pulmonary artery pressure was transitory; its resolution was accompanied by an overshoot in left atrial pressure, with a partial recovery in systemic blood pressure, fading later into the prolonged late hypotensive phase.

In its more severe form, as seen in the majority of the 20 per cent NaCl studies, the
The picture was that of acute cor pulmonale (fig. 5). Immediately after injection, the blood pressure fell precipitously to levels of about 20 mm. Hg. Pulmonary artery pressure increased markedly while venous pressure rose steadily with vigorous pulsations. Left atrial pressure fell below normal. Electrocardiography showed that the irregularity in the blood pressure decay curve was more a result of intermittent cardiac injection than the occasionally observed bradycardia and heart block. In 6 instances, systemic blood pressure did not recover and the animal eventually died, although the heart continued to beat for some time. In the dogs who survived, intravascular pressures reverted toward normal after 20 to 90 seconds; the later hypotensive phase again resembled that previously described.

In two-thirds of the cases, pulmonary venous pressure rose concurrently with that in the pulmonary artery, in contrast to the reduced pressures existing in the left atrium (fig. 6). In the remainder, pulmonary venous pressure followed that in the left atrium.

Discussion

The present studies extend the original observations of Binet and Stoicesco, in demonstrating that the intravenous administration of hypertonic solutions of nonelectrolytes, as well as electrolytes, produces systemic hypotension. When the osmolar concentration of the injected material is kept below 2, the fall in blood pressure is delayed and accompanied by pulse pressure and pulse-wave changes consistent with a reduction in peripheral resistance. This resemblance to our earlier experience with the intra-arterial route is in agreement with the work of Muirhead et al., who have previously presented plethysmographic evidence for a peripheral vasodilatory action independent of the central nervous system. Recalculation of their data gives a threshold for intravenous administration of 4 mOsm./Kg./min. This figure is about double that we observed for arterial administration. The difference may be attributed, in part, to the ability of the intact preparation to moderate hypotension by changes in cardiac output and adrenergic release, as suggested by the tachycardia and simultaneous increase in pulmonary and venous pressures observed during the hypotension.

The question of chemical damage to the myocardium contributing to the changes in blood pressure remains unanswered. The rapidly occurring sinus bradycardia and intracardiac block support this contention. However, the constant finding of an initial hypertensive phase, presumably hypervolemic in nature from osmotic withdrawal of fluid into the circulation, renders this possibility unlikely. Further argument against this point can be derived from recent electromagnetic flow studies indicating that right-heart output is not reduced by hypertonic agents.

If the concentration of the injected saline is increased above 2 osm./L., systemic hypotension becomes aggravated by obstruction to blood flow through the lungs. The typical delayed fall in pressure is now preceded by an initial hypotensive phase. The increase in pulmonary vascular resistance may become so severe that the animal develops the picture of acute cor pulmonale, with death from right heart failure before the peripheral vascular dilatation can take effect.

Eliakim and others concluded that the pulmonary vascular effects of strong salt solutions are mediated through pulmonary venous spasm brought about by an increase in sodium ion concentration. Semler, Shepherd, and Swan cast doubt on this hypothesis by reporting that the change in resistance occurs proximal to the capillary bed. The present studies indicate that the site of obstruction is variable and may be at either or both the venous and arterial levels. The finding that glucose, despite previous denials, can produce a similar pulmonary vascular block negates the theory of specific ionic activity. However, the problem is complicated by the fact that concentrated urea solutions do not interfere with blood flow through the lungs. This paradox is the subject of later work.
III. INFLUENCE OF PERFUSATE CHARACTERISTICS ON THE PULMONARY HYPERTENSIVE EFFECT OF CONCENTRATED SOLUTIONS.†

The exact mechanism responsible for the pulmonary vascular effects of hypertonic solutions remains questionable, despite previous work. It seemed possible that the response was related to serotonin release, or some other change in the cellular fraction of the blood. It was decided, therefore, to reinvestigate this phenomenon in the isolated lung where the influence of perfusate characteristics could be more easily determined.

Methods
Dog lungs were isolated and perfused at constant flow. The chest was opened under artificial respiration by splitting the sternum longitudinally. The azygos vein and venae cavae were ligated after heparinization, and the heart, lungs, and aorta were removed without interrupting ventilation. A plastic cannula, which had been filled to its tip with perfusion fluid, was inserted through the outflow tract of the right ventricle and tied into the main pulmonary artery. Care was taken to keep air out of the pulmonary circulation. The pericardium, both ventricles, and the right atrium were bisected, and the left atrium drained at near zero pressure. The lung was suspended in a perforated plastic plate, and venous drainage was collected in a plastic funnel and recirculated with a Sigma-motor pump. Perfusion was begun, after an interruption of less than 2 minutes, at a rate consistent with normal pulmonary pressures monitored through a needle-tip catheter. Oxygenation was maintained by ventilating the lung throughout the experiments. Per fusates consisted of either whole blood, red cell suspensions, plasma, serum, or dextran-Ringer's solution. If blood was not to be used initially, the lung was first flushed with large volumes of saline and dextran. Thoroughness of the rinsing was gauged by the whiteness of the lung surface and the clarity of the solution emerging from the venous drainage. Test injections of concentrated solutions were made proximal to the arterial pump.

Results
Sixteen lungs were perfused at flow rates of between 25 and 115 ml./min./Kg. body weight.

Mean pulmonary artery pressure ranged from 11 to 27 mm. Hg. The rapid injection of 1 ml./Kg. of 5 to 20 per cent NaCl or 50 per cent glucose resulted in a phasic change in pressure when blood was used as perfusate. The degree of response obtained was proportional to the osmotic pressure of the agent, used with a threshold of 1,500 to 1,700 mOsm./L. Repeated reactions led to pulmonary congestion and edema. Concentrated urea solutions did not evoke this phenomenon. The characteristic response to hypertonic solutions was eliminated by replacing blood in the perfusate with dextran (fig. 7), plasma, or serum, although the lungs would still react typically with serotonin. A response to concentrated sugar and salt solutions could be reestablished by adding red cells, but not other blood elements either to the perfusion fluid or the test injection. These latter mixtures were inactive when administered to a lung perfused with the hypertonic agent itself.

Discussion
The experiments show that concentrated solutions produce pulmonary hypertension, not only in the vagotomized animal, but also in the completely isolated organ perfused with

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†Presented in part at the Annual Meeting of the American Physiological Society, Atlantic City, April 1959.
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Circulation Research, Volume VIII, May 1960
blood, as first noted by Binet and Burstein.\textsuperscript{29} It is apparent that the materials do not act directly on the lungs, but require the presence of erythrocytes for their pulmonary vascular effects to become manifest. Further, the response does not arise from a simple interaction between hypertonic reagent and red cell. The characteristic phenomenon occurs only when the treated cells become exposed once more to a normal osmotic environment. Finally, the concentration of the exciting solution must be at least five times that of plasma. Soderstrom\textsuperscript{21} has shown that red cells handled in this way become damaged by a process of "paradoxical hypertonic hemolysis." This reaction, operating intravascularly, is apparently responsible for the pulmonary vascular effects of concentrated solutions. Urea solutions, known to be incapable of exerting an osmotic differential across the red cell membrane, would not be expected to affect red cells in this manner.

The increase in pulmonary vascular resistance brought about by concentrated saline and glucose is, in spite of recirculation, so transitory that it is unlikely to result from the release of vasoactive materials from the damaged erythrocytes.\textsuperscript{22} It appears more probable that osmotic damage to the formed elements interferes with the stability of the red-cell stream. The possibility of a viscous obstruction to blood flow was investigated more directly in a later study.

IV. INTRAVASCULAR RED-CELL AGGLUTINATION FROM MARKEDLY HYERTONIC SOLUTIONS\textsuperscript{34}

Previous work suggested that the pulmonary hypertensive effect of concentrated solutions depends upon changes in blood viscosity rather than alterations in vascular dimensions. The general applicability of this phenomenon was determined by examining microscopically the circulation through various tissues after the intra-arterial administration of markedly hypertonic solutions.

\textsuperscript{*}Presented in part at a meeting of the Society for Experimental Biology and Medicine, Mayo Clinic, Rochester, Minn., October 1958.

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HYPERTONIC SOLUTIONS

Effect; however, the more concentrated salt and sugar solutions produced an initial hypertensive phase (fig. 8). Frequently 20 per cent NaCl produced an irreversible obstruction to blood flow.

Microscopic Observations

A total of 17 experiments were performed: 7 on the mesentery, 3 on the pia mater, 3 in the leg, and 4 with the lung. A similar response to 2 to 3 ml. of concentrated saline and glucose was observed in all preparations. Characteristically, within 5 to 10 seconds of injection, the following microscopic changes occurred practically simultaneously: (1) blood flow through the arterioles slowed and finally stopped, as demonstrated by the fact that individual cellular elements could be distinguished; (2) clumps of red cells were seen in both arterioles and venules, temporarily plugging some of the smaller branches; (3) the blood became hyperchromatic; (4) the meta-arterioles and venules became lighter and filled with plasma with or without a small axial stream of red blood cells; (5) vasoconstriction was not observed; (6) re-establishment of blood flow occurred within 30 to 60 seconds and was accompanied by vasodilatation; and (7) after repeated injections reversibility was delayed and red-cell leakage occurred. Fifty per cent urea solutions produced only a mild fall in pressure was elicited. Time on abscissa is in seconds (1 second = 1/2 mm.). Second injection mark on the above should be at the first recovery peak.

Discussion

The results demonstrate another difference between the intravenous effects of concentrated salt and sugar solutions as opposed to urea. The red-cell clumping and stickiness observed throughout the lung after the use of the former agents explains the previous hemodynamic data which had suggested that changes in red-cell viscosity were responsible for the production of pulmonary hypertension. The occurrence of this phenomenon in the systemic circulation provides a pathologic basis for the reports in the literature of hypertension and gangrene following the intravenous injection of highly concentrated saline in both animals and man.

The stability of the red-cell stream is dependent upon a balance between the cohesive action of surface tension and the dispersive forces of electrostatic repulsion and kinetic factors. Fahraeus has inferred that the agglutinative effect of hydrophilic colloids is dependent upon changes in the first 2 considerations. The last parameter may be responsible for the sludging described by Kuisely under conditions of reduced blood flow. Apparently the only previous work regarding agglutination from concentrated salt solutions is that of Zahn, who in 1875 produced red-cell thrombi in the frog mesentery by the topical application of salt crystals.

It is well known that specific immune or even nonspecific hemolysins, when introduced intravascularly, first produce red-cell agglutination. Hemolytic crises may be accompanied by signs of regional circulatory obstruction. This initial clumping stage is understandable from the work of Abramson.
who demonstrated that damage to the red-cell membrane is associated with loss of electronegativity. These considerations suggest that agglutination from concentrated solutions is a manifestation of red-cell injury. The negative results with urea, the studies in the isolated lung, the in vitro work of Soderstrom and the reported potentiating effect of prior contact between the agent and blood indicate that 2 steps are necessary: first, erythrocytes must be exposed to a sufficient concentration of a solution whose rate of penetration is significantly slower than that of water; second, the hypertonic red cells need to be returned to a more normal osmotic environment.

These conclusions are in agreement with reports from the literature indicating that the cardiovascular effects of hypertonic solutions vary with the chemical characteristics of the substance investigated, as well as the rate, concentration, and site of administration. It is of interest that these findings of red-cell agglutination offer a rationale for the vasomotor complications and deaths which have been seen clinically following the use of concentrated organic iodide solutions in angiography.

**Summary**

During the course of an investigation into the treatment of metabolic acidosis arising from total body perfusion, it was noticed that the intra-arterial administration of concentrated alkalis resulted in a fall in arteriovenous pressure difference at constant flow. A similar decline in peripheral resistance could be produced by hypertonic sugar and salt solutions. This response was found to be independent of the central nervous system. The role of the vasodilatation in the complex vasomotor reaction to the rapid intravenous injection of hypertonic agents was then investigated in the intact and vagotomized dog. It was found that when concentrations of up to 1,500 mOsm./L were used, the predominant response was a delayed hypotension consistent with peripheral vasodilatation. This reaction was complicated by preliminary pulmonary hypertension when solutions containing more than 2,000 mOsm./L were administered.

Twenty per cent NaCl produced such a severe initial phase that the animals frequently died from acute cor pulmonale. The site of obstruction to blood flow through the lungs was variable. Fifty per cent glucose could incite pulmonary hypertension, but urea was anomalous in that it was never observed to produce pulmonary vascular effects. Studies in the isolated perfused lung indicated that, again with the exception of urea, all solutions with an osmolality equal or greater than 5 per cent NaCl evoked pulmonary hypertension. The increase in pulmonary vascular resistance was transient in spite of recirculation. No response could be elicited when red cells were absent from the perfusate even though, under these conditions, the lung was still sensitive to serotonin. Microscopic examination of the circulation through the brain, lung, mesentery and thigh of both cat and dog demonstrated that intravascular red-cell agglutination occurred after regional arterial injection of highly concentrated salt and sugar solutions. This alteration in the stability of the red-cell stream is considered to be responsible for the obstructive effects of hyperosmotic agents previously attributed to vasospasm.

**Summario in Interlingua**

In le curso de un investigation relative al tractamento de acidosis metabolique occasionate per perfusion del eorporo total, il esseva notate que le administration intra-arterial de alcalis concentrate resultava in un reduction del differentia inter le tensiones arterial e venose sub conditiones de fluxo constante. Un simile declino del resistencia peripherie poteva esser producita per solutiones hypertonic de sucro e de sal. Iste responsa se mostrava independent del sistema nervose central. Le rolo del vasodilatation in le complexe reaction vasomotori al rapide injection intravenose de agentes hyperosmotic esseva investigate subsequemente in intacte e in vagotomisate cane. Esseva trovate que quando concentrationes de usque a 1500 mOsm/L esseva usate, le predominante response esseva un retardate hypotension de character compatible con vasodilatation peripheric. Iste reaction esseva complicata per un preliminari hypertension pulmonar quando solutiones de un contento de plus que 3000 mOsm/L esseva administrate. NaCl in un concentration de 20 pro cento producera un phase initial si sever que le animales moriva frequentemente ab acute corde pulmonal. Le sito del obstruction in le fluxo de sanguine per le pulmones esseva
HYPERTONIC SOLUTIONS

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Circ Res. 1960;8:538-548
doi: 10.1161/01.RES.8.3.538
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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