Hypertonic Mannitol in the Therapy of the Acute Respiratory Distress Syndrome

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Increased pulmonary artery pressure, an increase in pulmonary vascular resistance and an increase in physiologic dead space are consistent findings in patients with post-traumatic respiratory distress. Since mannitol has been shown to decrease renal vascular resistance following trauma, the effect of a bolus injection of 100 ml of 25% solution of this drug on pulmonary hemodynamics and physiologic dead space was investigated in 11 patients who had suffered multiple trauma. Five minutes after the injection, pulmonary vascular resistance fell ($p < .01$), cardiac index increased ($p < .001$) and physiologic dead space decreased ($p < .05$). In contrast, the administration of 40 mg of furosemide produced no significant change in any of these parameters. Mannitol rapidly equilibrates in the extracellular space and exerts an osmotic effect across cell membranes. We postulate that the beneficial response to mannitol on the pulmonary vascular resistance and the improved perfusion of ventilated regions of the lung is due to a reduction in cell swelling and is not explainable by its diuretic effect. Improvement in the distribution of perfusion of pulmonary blood flow by mannitol may be a useful aid in the treatment of the post-traumatic form of the respiratory distress syndrome.

THE POST-TRAUMATIC form of the acute respiratory distress syndrome is characterized by a fall in arterial P_{O_2} due in large part to an increase in the intrapulmonary shunt.[13] The shunt is a consequence of continued perfusion of regions of the lung which are not exposed to inspired gas. Absence of ventilation to large numbers of alveolar units has been demonstrated by a fall in the functional residual capacity (FRC). Furthermore, improvement in intrapulmonary shunt occurs when the FRC returns towards normal.[18] Major emphasis in the therapy of the acute respiratory distress syndrome has thus far been concentrated on methods of ventilatory support which provide maximal expansion of alveolar volume. On the other hand, recent reports have indicated that the increased airway pressure, often required to achieve a normal FRC, may result in a substantial decrease in cardiac output[8,19] and may produce a redistribution of pulmonary blood flow away from well ventilated to poorly ventilated regions of the lung.[20]

An additional manifestation of the acute respiratory distress syndrome, namely an increase in pulmonary artery pressure and pulmonary vascular resistance has been known for several decades but there have been few attempts to treat this aspect of the disorder. Increased vascular resistance may result from narrowing or occlusion of portions of the pulmonary vascular bed. When regions of the lung with vascular occlusion continue to be ventilated, they become dead space. Since patients with respiratory distress syndrome have a limited number of ventilated alveoli, the additional loss of gas exchange surface resulting from failure to perfuse the remaining open alveoli will lead to an increase in intrapulmonary shunt. Alternatively, an increase in the quantity of pulmonary blood flow directed through well ventilated regions of the lung will partially correct the deleterious effects of the intrapulmonary shunt (Fig. 1).

The present study was undertaken to assess the effects of hypertonic mannitol infusion in patients with post-traumatic respiratory distress. The use of this agent was suggested by previous observations on its effects on vascular resistance in the kidney,[9] the brain,[1] and the myocardium.[21] Additional pulmonary blood flow directed through well ventilated regions of the lung that were previously part of the physiologic dead space, may improve arterial P_{O_2} and oxygen delivery. We therefore wish to present a new therapeutic approach to the management of the acute respiratory distress syndrome based on reduction of the dead space component of this syndrome.

Hypertonic mannitol has at least two specific actions

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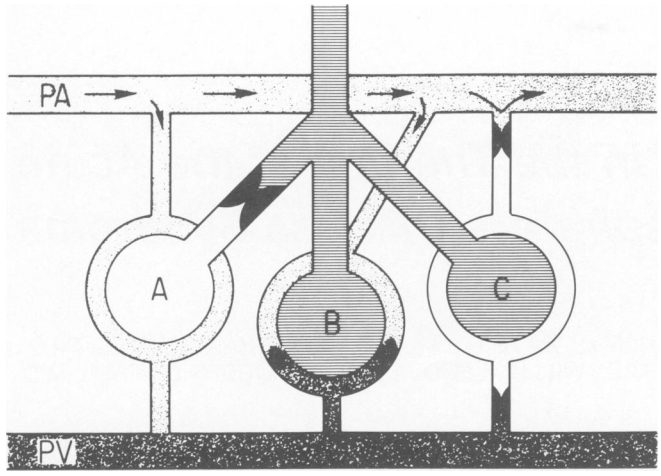

FIG. 1. Schematic diagrame of possible combinations of distribution of ventilation and perfusion. The middle alveolar capillary unit receives equal quantities of ventilation and perfusion. (B) The left unit receives no ventilation, (A) while the right receives no perfusion. (C) Consequently, the left and right units do not participate in gas exchange.

in the body. First, it is a diuretic and second, it has been shown to reduce cellular swelling.[16] Therefore, we compared the effects of mannitol with that of another potent diuretic, furosemide.

Methods

Eleven patients were admitted to the Albany Trauma Center following initial resuscitation and operative treatment of their injuries. (Table 1) A radial artery cannula and a pulmonary artery balloon-tipped flow directed catheter were inserted. Intravascular pressures were measured by strain gauge transducers and recorded on a polygraph. Cardiac output was determined by injecting indocyanin dye into the pulmonary artery and calculating the resultant dilution curve with an on-line digital computer. Pulmonary vascular resistance was calculated off-line from the cardiac output and the difference between pulmonary artery and pulmonary capillary wedge pressures. Arterial and mixed venous blood gases were measured on an Instrumentation Laboratories blood gas analyzer and were corrected for temperature and pH. Intrapulmonary shunt was computed from the Berggrens formula. Hemoglobin concentration and serum sodium levels were measured by standard techniques.

All patients were maintained on a volume cycled ventilator so that total ventilation remained constant throughout the study. Alveolar ventilation was computed from the equation:

$$\dot{V}CO_2 = \dot{V}_A \times FA_{CO_2}$$

where $\dot{V}CO_2$ is production per minute, $\dot{V}_A$ is alveolar ventilation and FA_{CO_2} is the fractional concentration of CO_2 in perfused alveoli. $\dot{V}CO_2$ was calculated from the Fick equation by multiplying the difference in CO_2 content between the pulmonary artery and systemic artery by the cardiac output. CO_2 contents were calculated from the measured PCO_2, pH and hemoglobin concentration using the Singer and Hastings nomogram. FA_{CO2} was calculated by dividing the arterial PCO_2 by the barometric pressure minus the partial pressure of water vapor. The dead space ventilation ($\dot{V}_D$) was obtained by subtracting $\dot{V}_A$ from the total ventilation delivered by the ventilator. The absolute value of dead space was obtained by dividing $\dot{V}_D$ by the respiratory rate. There are certain possible errors in this calculation. An intrapulmonary shunt will increase the arterial PCO_2 since the shunted venous blood has a higher PCO_2 than alveolar gas. The absolute value of the shunt did not change during the course of the study, therefore, this correction was negligible and was ignored. Furthermore, compression of gas by the ventilator may increase total expired dead space ventilation. Since total ventilation was maintained at a constant

TABLE 1. *Patient's Clinical History*

Serial #	Age	Sex	Injuries
1	70	M	Ischemic gangrene of the bowel s/p resection of bowel
2	12	M	Trauma, penetrating injury of the abdomen, bowel injury, Fx. radius and ulna
3	69	M	Ruptured abdominal aortic aneurysm s/p resection and shock
4	38	F	Trauma, Fx. skull, Fx. zygoma, multiple rib Fx., Fx. pelvis, blunt abdominal trauma
5	61	M	Trauma, cerebral concussion, multiple rib Fx., Fx. clavical and lung contusion
6	28	M	Total gastrectomy, anastomotic leak and endotoxic shock
7	60	M	Trauma, Fx. (L) femur, ankle and wrist, Fx. skull, Fx. L1, L3 and lung contusion
8	16	M	Trauma, blunt abdominal trauma, intestinal injury, Fx. C2, C3 and (R) pneumothoax
9	52	F	Trauma, ruptured spleen, renal contusion, communited Fx. Pelvis
10	28	M	Trauma, Fx. (R) femur and patella, Fx. (L) ankle and clavicle, laceration of liver, fat embolism
11	25	M	Trauma, Fx. femur, Fx. zygoma, fat embolism and cerebral concussion

TABLE 2. *Effect of Mannitol and Furosemide on Calculated Cardiovascular and Pulmonary Physiological Changes, Hemoglobin and Serum Sodium in 11 Patients Entered in this Study*

	Mannitol			P Value*	Furosemide	
Time (min)	0 (Control)	5	60	0–5	0 (Control)	60
Cardiac Index (L/min/M²)	3.7	4.6	4.0	P < .001	3.7	3.6
SE	± 0.3	± 0.4	± 0.4		± 0.4	± 0.4
Pulmonary Vascular Resistance (Dyne-sec/cm⁵)	166	136	158	P < .01	143	145
SE	± 24	± 22	± 22		± 29	± 20
Pulmonary Artery Pressure minus Pulmonary Wedge Pressure (Torr)	13.8	13.6	14.2	NS†	10.8	11.5
SE	± 1.4	± 1.5	± 1.6		± 1.2	± 1.1
Physiological Dead Space (ml)	642	204	347	P < .05		
SE	± 135	± 129	± 252			
Physiological Shunt (%)	23.8	22.9	25.0	NS	18.6	22.2
SE	14.4	14.2	14.7		± 3.8	14.7
Arterial Oxygen Tension (Torr)	100	103	101	NS	110	102
SE	± 9	± 9	± 10		± 11	± 11
Hemoglobin (gm %)	10.8	10.1	10.6	P < .02		
SE	± 0.7	± 0.5	± 0.6			
Serum Sodium (mEq/L)	138	134	137	P < .02		
SE	± 2	± 3	± 2			

* P values are calculated from the results of Student's paired *t* test between control and 5 minutes. All differences between 0 and 60 minutes for both Mannitol and Furosemide were not significant.

† NS means P > .05.

level throughout the study, it was not necessary to provide corrections for compression of gas by the ventilator. This factor would become significant only if there was a change in lung volume.

Eleven patients received an intravenous infusion of hypertonic mannitol as a single bolus of 100 ml of a 25% solution. Five of these were also treated with a 20% solution for a period of one hour. Cardiac output, pulmonary capillary wedge pressures, arterial and mixed venous blood gases, hemoglobin and sodium concentrations were obtained just before the mannitol infusion at five minutes and at one hour. Furosemide was administered to 9 patients either one hour before or one hour after the mannitol infusion. The order of administration was determined on a random basis. All data were analyzed for significance using Student's paired *t* test.

Results

Mannitol produced an increase in cardiac index in all but one patient. This increase was associated with a rise in filling pressure of the heart as measured by the pulmonary capillary wedge pressure and a consistent fall in the hemoglobin concentration ($p < .02$) (Table 2). The increase in cardiac index was greatest at five minutes ($p < .001$) but was still significant at one hour ($p < .02$). Furosemide resulted in no significant change in hemodynamics.

Pulmonary vascular resistance fell from a control value of 167 ± 24 dyne-sec/cm⁵ to 136 ± 22 dyne-sec/cm⁵ ($p < .01$) (Fig. 2). All values returned to pretreatment levels by one hour. The change in pulmonary vascular resistance was due to an increased pulmonary blood flow with no significant change in the pulmonary artery-pulmonary wedge pressure gradient (Fig. 3). The increase in pulmonary blood flow was associated with a fall in the calculated dead space (V_D). V_D fell from 642 ± 135 ml to 204 ± 129 ml ($p < 05$) (Fig. 4). Since total ventilation was held constant by the mechanical ventilator, the decrease in dead space resulting from mannitol infusion produced a corresponding increase in alveolar ventilation.

There was a decrease in intrapulmonary shunt in 8 of 11 studies at five minutes, but the change was not significant (Table 3). The arterial Po_2 rose in the majority of patients but the change was not significant.

The hemoglobin concentration fell from 10.8 ± 0.7

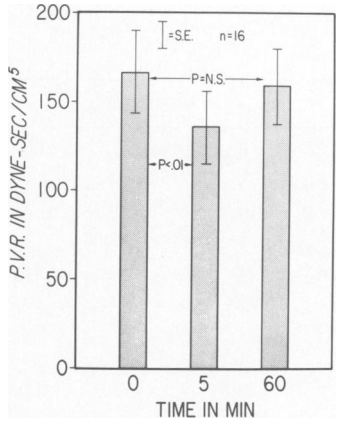

FIG. 2. Changes in pulmonary vascular resistance at five minutes and one hour following administration of hypertonic mannitol.

gm% to 10.1 ± 0.5 gm% ($p < .02$). At the same time the serum sodium fell from 137 ± 2 m Eq/L to 134 ± 3 m Eq/L ($p < .02$). These values returned to the control level after one hour.

There were no significant changes in any parameter measured following administration of furosemide.

Discussion

The principal pulmonary hemodynamic alteration in both experimental shock[4] and in post-traumatic respiratory distress in an increase in the calculated pulmonary vascular resistance.[18] Intravascular aggregation of platelets or other microparticles, local release of vasoactive compounds[16] and mechanical infolding of capillaries adjacent to regions of alveolar collapse[2] have been implicated in the increase in pulmonary vascular resistance. Local hypoperfusion of well ventilated regions of the lung produce and increase in respiratory dead space as evidenced by an increased arterial-to-end-tidal CO_2 gradient. Hypoxic vasoconstriction of the pulmonary microcirculation through regions of reduced ventilation may also contribute to the increased pulmonary vascular resistance but will tend to normalize the local ventilation-perfusion ratio and thereby limit the alveolar-arterial Po_2 gradient. In the extreme example of complete occlusion of capillaries surrounding non-ventilated alveoli, such alveolar-capillary units will have no effect on gas exchange. Therapeutic interventions resulting in a decrease in pulmonary vascular resistance will have quite opposite effects depending on whether the increased perfusion passes through regions that are well-ventilated or regions with poor to absent ventilation. In the former case, there will be an increase in alveolar ventilation, a decrease in dead space and an overall improvement in gas exchange whereas an increased perfusion of non-ventilated alveoli will increase the intrapulmonary shunt and produce a fall in arterial Po_2. The use of mannitol in the present study resulted in an increased alveolar ventilation suggesting that some improved perfusion took place through well ventilated areas. These studies are in agreement with those of Williams[22] who studied the effects of hypertonic mannitol during *in vivo* lung perfusion. Pulmonary edema was produced by acute elevations of left atrial pressure. This was associated with an increase in pulmonary vascular resistance and a fall in arterial Po_2. Perfusion of the lung with hypertonic mannitol resulted in a return of both pulmonary vascular resistance and arterial Po_2 to a normal range. Shunt and dead space ventilation were not measured in their study so the mechanism of the increased Po_2 could not be determined.

Other agents, such as a rapid bolus injection of methylprednisolone may reduce pulmonary vascular resistance by dilating constricted vessels in non-ventilated alveoli.[12,14] This drug produced a transiently increased shunt with a fall in arterial Po_2. On the other hand, mannitol produced no change in the shunt frac-

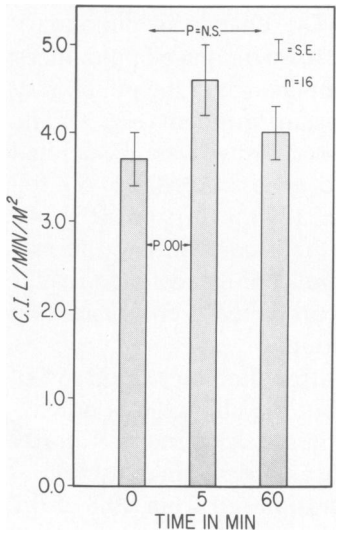

FIG. 3. Change in cardiac index at five minutes and one hour following administration of hypertonic manitol.

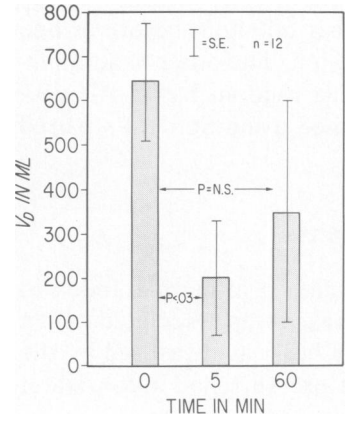

FIG. 4. change in respiratory dead space at five minutes and one hour following administration of hypertonic mannitol. The number of patients in whom respiratory dead space is reported above was reduced to 10. One patient was excluded who had a calculated change in dead space that was greater than his tidal volume.

tion in spite of an overall increase in pulmonary blood flow.

A decrease in vascular resistance in the kidneys of dogs suffering from traumatic shock was noted by us following the use of hypertonic mannitol.[9] This response did not occur following the administration of equal volumes of crystalloid solution.[11] The decrease in renal vascular resistance was confirmed by Berman who studied unilateral infusion of hypertonic mannitol and noted a decrease in renal vascular resistance limited to the ipsilateral kidney.[3] Flores compared the effects of hypertonic mannitol with isotonic mannitol and noted that only the hypertonic solution was effective in reducing renal vascular resistance.[6]

The osmotic effect of hypertonic mannitol is most probably extended across the cell membrane. The T ½ of mannitol in the vascular bed is less than 30 sec and about 80% has left the circulation by one minute.[15] Measurement of the hemoglobin concentration five minutes after the infusion of hypertonic mannitol in the present study showed a significant drop indicating an expansion of the plasma volume. Concurrently, there was a fall in the serum sodium concentration suggesting an expansion of the extracellular space, presumably resulting from withdrawal of water from the intracellular compartment. Cellular volume is normally maintained by the continuous, active removel of serum from the interior of the cell by means of an energy-requiring sodium pump. When the supply of metabolic energy is reduced as might occur following a prolonged period of hypoperfusion, sodium will accumulate in the cell and water will diffuse across the cell membrane to maintain osmotic equilibrium. Cellular swelling may than reduce blood flow by compression of adjacent microvasculature or by reducing the vessel lumen secondary to swelling of the endothelium.[10] Elevation of the extracellular osmolarity will reduce cell swelling and improve the microcirculation. This hypothesis for the observed effects of mannitol has been recently reviewed by Powell.[17] In addition, Willerson[21] has noted a decrease in vascular resistance in non-ischemic portions of the myocardium following mannitol infusion. These studies of ischemic myocardium parallel our findings in the pulmonary vascular bed.

Diuretics have been advocated in the management of the respiratory distress syndrome, especially when associated with evidence of "fluid overload".[5] The possibility that the beneficial effects of mannitol observed in this study might be due to a non-specific result of diuresis was tested by comparing the effects of mannitol with a potent loop diuretic, furosemide. Pulmonary vascular resistance and cardiac index did not change. These observations lend support to the concept that the effects of mannitol are due to its osmolarity and lack of penetration of the cell membrane.

The present study demonstrates that hypertonic mannitol, when administered to patients with acute respiratory distress, results in an increase in cardiac output associated with an increase in effective alveolar ventilation. The result is an improvement in overall gas exchange. We suggest that further efforts directed at improving the distribution of perfusion should be added to present methods directed at improving the distribution of ventilation in these patients.

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Discussion

Dr. Watts R. Webb (Syracuse, New York): (Slide) I would like to emphasize that you get an increase in peripheral resistance not only with the so-called shock lung syndrome, or adult respiratory distress syndrome, but with any period of hypovolemia, as shown here. In animals, where the pressure is reduced over 40% of the normal, maintained for a couple of hours, stroke volume is down, cardiac output is down, but note that peripheral resistance goes up, and also the pulmonary vascular resistance may arise four or fivefold.

And the important thing about this is that restoration of the blood volume returns these toward normal, but does not return it completely to normal. The most important thing, has been pointed out by Tom Shires and his co-workers for a long time, is that you not only have to restore the blood, you have to restore a good deal more than just the blood.

And so what I'm wondering is whether we have seen, truly, the respiratory distress syndrome, or just a response to hypovolemia, where there always is an increase in pulmonary vascular resistance. This is normalized primarily by restoration of blood volume, and, in fact, to more than a normal blood volume.

The leaky capillary syndrome occurs if there is protracted hypovolemia, or if the various tissue factors, such as serotonin or histamine and the various bradykinins are released. The catecholamines in response to fat embolism and certainly to septicemia play a role. It's protected primarily by restoration of volume, but also protected, as we've found in our own work, by denervation, which prevents the increased vascular resistance, or lowers it toward normal. Steroids, antiserotonin agents, methasergide, for example, aid, and more recently we have shown the lung to be protected very markedly by prostaglandin E_2.

We have thought that the increased pulmonary vascular resistance is due primarily to an increased venous tone and to interstitial edema, much more than to the edema of the endothelial cells. I wonder if what we have seen in Dr. Power's study is that just mannitol has given an increased volume, somewhat comparable to the infusion of, perhaps 500 to 1000 cc of lactated Ringer's.

We have seen this same effect in our shocked animals from increased volume, which gives immediately a decrease in peripheral resistance, a decrease in pulmonary vascular resistance, and an increase in cardiac output, just as was demonstrated here in the patients.

Lasix has no effect in the shocked animal. If you give this comparable volume of mannitol to the normal animal, there is an immediate rise in cardiac output, and a fall in the pulmonary vascular resistance, just as if you had given any other plasma expander, whether it be lactated Ringer's or serum albumin or plasma.

Lasix in the normal has no hemodynamic effect, and, obviously, one wouldn't expect it, until it had time for a rather massive diuresis. So I wonder if what we have seen has not been primarily just the administration of an adequate amount of fluid to patients who had been rather underinfused, rather than patients who had the true leaky capillary syndrome, and had been overinfused.

Dr. Arnold G. Diethelm (Birmingham, Alabama): This is really an old concept now applied to the lung. The concept, basically, involves the fact that an obstructed vascular lumen in the kidney, the heart, and the brain, when reopened with reflow of blood into the obstructed organ will initially be patent, but then subsequently become obstructed. This observation, made by two British pathologists, Sheehan and Davis, in the late 1950's was termed the no reflow phenomenon, and this was substantiated by Ames and colleagues at the Massachusetts General Hospital, relating to the brain, using the rabbit as the experimental animal. Subsequently, Leaf and colleagues and others have confirmed the no reflow phenomenon in the kidney.

Parallel to these observations Sacks and colleagues, in California, observed that a hypertonic, hyperosmolar solution might be satisfactory to preserve kidneys and emphasized the role of cell dehydration; specifically, the endothelial cell.

The present paper is of particular interest because, to my knowledge, the concept of cell dehydration applied to the endothelial cell has not yet been confirmed in the lung. The paper suggests that the resistance of the pulmonary vasculature does not diminish after a bolus administration of mannitol. But one question comes to mind, and that is: Mannitol, when given to the kidney or the brain, has to be given immediately after the occlusion. Therefore, dehydration must take place at the same time or prior to the reflow of blood.

The circumstances here are quite different. The clinical situation presents itself with a patient with pulmonary trauma, four to 6 to 8 hours pass by, and then the bolus of mannitol is given.

Therefore, the question is whether or not the endothelial cell completely occludes the lumen of the pulmonary vasculature, or is it markedly narrowed? If it is completely occluding the lumen, then only the lead point of the lumen of the vessel would be exposed to the mannitol. Everything distal would receive no mannitol.

On the other hand, it's possible that the lumen is not completely occluded, but only partially occluded. If that were the case, then the entire lumen (the endothelial cells along the entire lumen) would have exposure to the hypertonic solution. So the first question to Dr. Powers: What is his concept in regards to this?

There are several other very brief questions. Is there really enough lung water to account for the dilution of serum sodium? It would seem that this would be a very large amount of water to be immediately placed into the intravascular space to cause sodium dilution.

The last question is: Have you been able, or had the opportunity to confirm these observations with the ventilation perfusion scan before and after the administration of mannitol?

Dr. Lazar H. Greenfield (Richmond, Virginia): I rise to bring up some observations that reflect our interests, which go back several years, when we became attracted to the experimental model of an isolated lung subjected to injury. It was obvious that one of the first physiological approaches should be to recruit water from the lung made edematous. In early use of mannitol, howver, we were very discouraged by the fact that it seemed to want to reside on the wrong side of the capillary bed, and, in fact, to perpetuate edema and cause hemorrhage in the lung.

On the basis of this, we were reluctant to apply it to patients. However, in more recent clinical studies at the Medical College of Virginia within the past year, patients with head injury received large-bolus infusions of mannitol. Our observations confirm Dr. Powers' hemodynamic reports, showing that there were, in fact, sig-