

The Hypotensive Response to Rapid Intravenous Administration of Hypertonic Solutions in Man and in the Rabbit

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Transient hypotension has been observed in patients after rapid intravenous administration of mannitol, 25 per cent, in clinical doses. These studies were conducted to determine the mechanism for the hypotension, to determine dose and rate of injection response curves in rabbits, and to determine which vascular beds were most reactive. Studies in six patients showed mean decreases in blood pressure of 23 ± 6.0 per cent (\pm SE) and in total peripheral resistance of 38 ± 7 per cent after infusion of mannitol. Studies in 18 patients during cardiopulmonary bypass with mechanically fixed cardiac output demonstrated decreases in mean blood pressure of 30 ± 5 to 40 ± 3 per cent, depending on dose and rate of administration of mannitol. Patients not on bypass compensated for large decreases in total peripheral resistance by increases in cardiac output ($3.6 \pm .4$ at baseline to $4.4 \pm .4$ l/min) during mannitol-induced hypotension with no change in heart rate. Serum osmolality increased as blood pressure decreased. Significant but clinically unimportant decreases in sodium and potassium ions, hemoglobin, pH, and base excess values were observed. Studies in 18 rabbits showed that the greater the dose or rate of injection of mannitol the greater the decrease in blood pressure. Injection of radiolabeled microspheres in rabbits demonstrated a near doubling of blood flow to skeletal muscle tissue during the hypotension. This occurred with both equiosmotic hypertonic glucose (17 ± 3 to 32 ± 7 per cent) and mannitol (17 ± 1 to 31 ± 5 per cent), but not after isotonic saline solution. Changes in blood flow to other organ beds were variable and unimportant. The results suggest that hypotension following the intravenous administration of hyperosmotic solutions is due primarily to vasodilation in skeletal muscle. (Key words: Blood; glucose; serum osmolality. Blood pressure: hypotension; peripheral vascular resistance. Heart: cardiac output. Kidney: diuretics, mannitol. Muscle, skeletal: blood flow.)

HYPERTONIC SOLUTIONS such as mannitol, 25 per cent (1,600 mOsm/l), glucose, 50 per cent (2,523 mOsm/l), and sodium bicarbonate, 7.5 per cent (1,786 mOsm/l), are often administered rapidly to patients in critical care settings. We have observed transient hypotension in patients following the rapid intravenous injection

of mannitol, 25 per cent, and therefore undertook studies in patients and rabbits in order to quantitate this response and determine its characteristics.

Methods and Materials

HUMAN STUDY

Informed consent was obtained from 24 patients scheduled to undergo coronary-artery bypass grafting. All patients were anesthetized with halothane, nitrous oxide and oxygen. The lungs were ventilated mechanically via an endotracheal tube. Measurements of body temperature, electrocardiogram, and radial arterial and central venous pressures were made; a flow-directed thermodilution catheter (Edwards Laboratories) was used in six patients for measurement of cardiac output. All patients were free of surgical stimulation at the time of study and had had stable mean arterial blood pressures for at least 5 min prior to the study period. Group I consisted of six patients studied before bypass; each received mannitol, 25 per cent, 0.125 g/kg (Invenex—Division of Mogul Corp.) at a mean rate of 0.016 g/kg/sec via peripheral venous catheter. Groups II, III, and IV consisted of six patients each; Group II received 0.125 g/kg at a mean rate of 0.017 g/kg/sec, Group III received 0.25 g/kg at 0.014 g/kg/sec, and Group IV received 0.25 g/kg at 0.008 g/kg/sec via the central venous catheter or the pump reservoir during cardiopulmonary bypass. All patients were normothermic, and had not received a vasodilator or vasopressor drug for at least 10 min.

Hemoglobin (Fisher Scientific Co. Digiglobin Model 255), plasma ionized calcium (Orion Biomedical, Model SS-20), potassium, sodium (Orion Biomedical, Model SS-30), serum osmolality (Advanced Instruments) and blood pH, P_{O_2} , P_{CO_2} , and base excess values (Instrumentation Laboratory) were determined before and 30, 60, 90, 120, 180, 240, and 300 sec after the beginning of injection of mannitol. All studies during cardiopulmonary bypass were conducted when the cardiac output was at a flow of 2.2 l/m² as measured with an electromagnetic flowmeter on the inflow line. Cardiac output was determined by thermodilution in Group I every 60 sec during the study period; duplicate measurements were made at baseline and at 5 min (Edwards Laboratories, Model-9510-A). Statham 231D transducers were used for all re-

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cordings. Viscosity of blood was determined in duplicate in 1-ml samples from six patients during cardiopulmonary bypass by use of a Brookfield micro cone-plate viscometer (Brookfield Engineering Laboratories, Model LVT) modified for shear rates from 230 to 1.15 sec⁻¹ as previously described.¹ Total peripheral resistance was calculated using the standard formula.

RABBIT STUDY

Twenty-five male New Zealand rabbits (2.2–2.7 kg) were anesthetized with halothane, 0.8–1.2 per cent, in oxygen, and allowed to breathe spontaneously. A tracheostomy was performed and 20-gauge catheters were inserted into the right femoral artery and vein. Mean arterial blood pressure was recorded with a Statham 23d transducer and Grass polygraph (Model 7 B Grass Instrument Co.) for a total of 60 injections. The rabbits were anesthetized for a minimum of 30 min and mean blood pressure was stable for at least 5 min prior to each injection. Mannitol, 25 per cent, was injected into the femoral vein via a syringe pump; maximal mannitol dose per rabbit was 1.5 g/kg.

Five additional rabbits were studied during controlled ventilation; Pa_{CO₂} was altered by the addition of carbon dioxide. Each rabbit acted as his own control and received 1 g/kg at 0.1235 g/sec during both hypocarbia (Pa_{CO₂} 20–30 torr) and hypercarbia (Pa_{CO₂} 50–60 torr). Three rabbits had the first injection during hypocarbia and two, during hypercarbia.

Another 18 similar rabbits were anesthetized and prepared as described above. Additionally, a 19-gauge medium Intracath (Deseret Pharmaceutical Co.) was inserted via the right carotid artery into the left ventricle and its position confirmed by the continuous pressure tracing obtained. The rabbits were divided into three groups of six per group. Group I received mannitol, 25 per cent, 1 g/kg (4 ml/kg, 1,600 mOsm/l); Group II received glucose, 31.7 per cent (4 ml/kg, osmolality approximately 1,600 mOsm/l). Group III received isotonic saline solution, 4 ml/kg. All injections were made at 0.495 ml/sec (equivalent to 0.1235 g/kg/sec mannitol, 25 per cent) into the femoral vein via an infusion pump. The rabbits were anesthetized for at least 40 min and the blood pressure had been stable for at least 5 min prior to study. One cubic centimeter of ¹⁴¹Ce-labeled microspheres 15 μm in diameter (2.5 μCi/ml) (Minnesota Mining & Manufacturing Co.) in a tuberculin syringe was manually injected via the carotid catheter into the left ventricle over 60 sec. Exactly 5 min after the beginning of the first injection one of the solutions (glucose, mannitol, or saline), chosen at random, was injected. As soon

TABLE 1. Seconds from Injection of Mannitol, 25 Per Cent, to Peak Blood Pressure Decrease*

	Time to Peak Decrease (Sec)	Time to Return to Baseline (Sec)
Pre-bypass 0.125 g/kg 0.016 g/kg/sec	50 ± 3	83 ± 8
Bypass 0.125 g/kg 0.017 g/kg/sec	60 ± 16	116 ± 26
0.25 g/kg 0.014 g/kg/sec	50 ± 5	[Not all returned to baseline]
0.25 g/kg 0.008 g/kg/sec	47 ± 6	90 ± 19

* Mean ± SE from 24 human subjects.

as mean blood pressure had decreased to below baseline or 15 sec had elapsed, 1 cc of ⁶⁵Cr-labeled microspheres (7.5 μCi/ml) was injected into the left ventricle over 15–30 sec. Ten minutes later, 1 cc of ⁸⁵Sr-labeled microspheres (2.5 μCi/ml) was injected over 60 sec. Five minutes later the left ventricular catheter was pulled back into the carotid artery in order to reconfirm ventricular position and the animal was sacrificed with an overdose of barbiturate.

The rabbits were then dissected into 11 specimens: approximately 90 per cent of the skin, 10–15 per cent of the muscle mass (always the entire proximal musculature of the left leg and both triceps muscles of the forelegs), the liver, kidneys, spleen, heart, lungs, mesentery, brain, large intestine, and the small intestine taken together with the stomach. All specimens were washed, blotted dry, and the wet weights recorded. All tissues were digested in 1 N potassium hydroxide by heating to 50 C for 24–48 hours. The microspheres in each organ were then separated from the digestate by centrifugation and the ¹⁴¹Ce, ⁵¹Cr, and ⁸⁵Sr contents determined by discrimination of their gamma emissions using a well-type scintillation counter. Comparison with appropriate standards allowed the calculation of fractional blood flow to each organ.

All human and animal data were analyzed using Student's t tests for paired and unpaired data and analysis of variance where appropriate. Differences were considered significant when P was less than 0.05. Values are presented as means ± SE.

Results

HUMAN STUDY

The Group I patients (pre-bypass) showed significant decreases in mean blood pressure (22 ± 5 torr) and

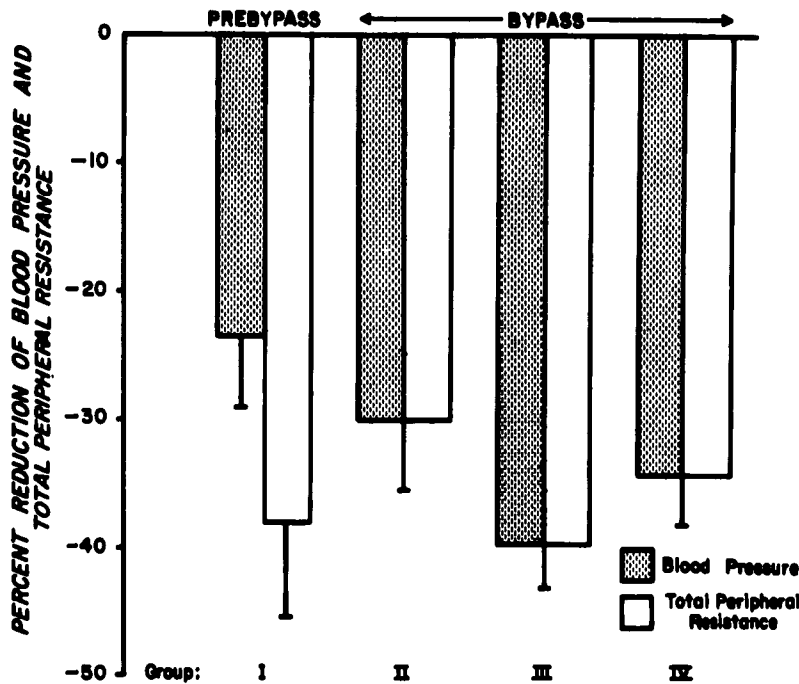


FIG. 1. Percentage decreases in mean arterial blood pressure and total peripheral resistance (mean \pm SE). Group I = pre-bypass patients given mannitol, 25 per cent, 0.125 g/kg, at the rate of 0.016 g/kg/sec; Group II, 0.125 g/kg at the rate of 0.017 g/kg/sec; Group III, 0.25 g/kg at the rate of 0.014 g/kg/sec; Group IV, 0.25 g/kg at the rate of 0.008 g/kg/sec, all during cardiopulmonary bypass. $N = 6$ in each group. Group I patients had a marked decrease in total peripheral resistance compared with blood pressure. The changes in blood pressure and total peripheral resistance were the same in Groups II, III, and IV because cardiac output was mechanically fixed.

total peripheral resistance (783 ± 226 dynes/sec/cm⁻⁵) (fig. 1). Maximal blood pressure changes and times of nadir after injection were constant within this group. The extent and duration of hypotension were less and the cardiac output increased ($3.6 \pm .4$ to $4.4 \pm .4$ l/min) 60 sec after injection compared with the other three groups of patients; there was no change in heart rate. Changes in serum osmolality, Na⁺, K⁺, plasma ionized calcium, blood hemoglobin, pH, and base excess values were similar in direction though nearly double those found in any of the other groups.†

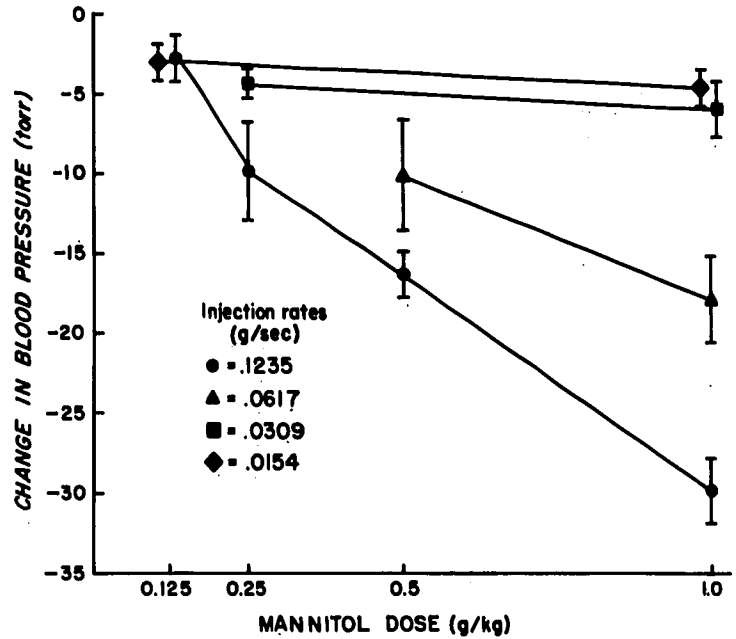
The three groups of patients studied during cardiopulmonary bypass experienced different extents and durations of hypotension. The maximal blood pressure changes and times to the nadir after injection were similarly variable but relatively constant within each group (table 1). Group II showed a decrease in mean blood pressure of 22 ± 5 torr, Group III, a decrease of 36 ± 5 torr, and Group IV, a decrease of 26 ± 4 torr (fig. 1). Changes in total peripheral resistance were of the same magnitudes as the changes

in blood pressure since cardiac output was mechanically fixed.

Changes in serum osmolality occurred following injection of mannitol, and these varied with the dose and the duration of injection, as well as with the volume of dilution. The samples analyzed 0.5 to 5 min after injection showed changes in osmolality that reached a peak and then decreased approximately exponentially as mixing and fluid shifts stabilized. For purposes of comparison, therefore, the zero-time intercepts were obtained from semilogarithmic plots of the changes in serum osmolality. These values were: Group I = 20.1, Group II = 14, Group III = 21.1, Group IV = 22.7 mOsm/l. The differences in these values and in the changes in mean blood pressure between Groups I and II reflect dilutional effects, those between Groups II and III reflect dose effects, whereas those between Groups III and IV resulted from the different rates of injection. Significant changes in osmolality were found in all groups from 30 to 240 sec; the times of nadir in blood pressure corresponded well to the rapid increases in serum osmolality, and were strikingly similar in all groups (table 1). Durations of statistically significant though clinically insignificant decreases in plasma Na⁺, K⁺, blood hemoglobin, pH and base excess values corresponded to the doses and rates of mannitol administered. There was no significant change in plasma ionized calcium, P_{O₂} or P_{CO₂} values in any of the groups. Blood viscosity studies revealed statistically significant,

† See NAPS Document #03375 for 19 pages of supplementary material. Order from ASIS/NAPS, Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, New York 10017. Remit in advance \$3.00 for microfiche copy or for photocopy, \$5.00 up to 20 pages plus 25¢ for each additional page. All orders must be prepaid. Institutions and Organizations may order by purchase order. However, there is a billing and handling charge for this service. Foreign orders add \$3.00 for postage and handling.

FIG. 2. Dose-response curves for 60 injections of mannitol, 25 per cent, in rabbits (mean \pm SE). Four dose-and-rate of injection schedules are presented. The lowest dose and slowest rate of injection had minimal effects on mean arterial blood pressure. N = 6 in each group.



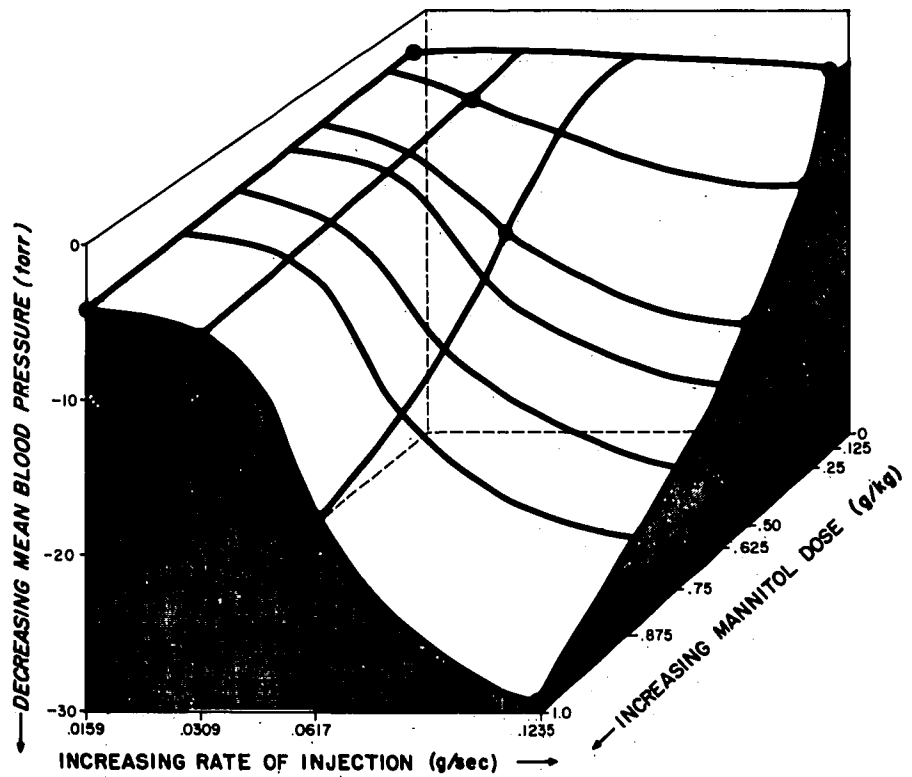
but clinically insignificant, decreases 30 sec after injection only. §

RABBIT STUDY

Most rabbits had small, transient (2-8-sec) increases in mean blood pressure (1-5 torr), followed by

marked decreases, then sustained increases, in blood pressure. This triphasic response was most pronounced in those rabbits receiving the largest dose and the most rapid rate of injection; only an occasional initial increase was seen at the lower rates of injection. All blood pressures returned to baseline

FIG. 3. Three-dimensional plot illustrating that both total osmotic load and rate of injection were important determinants of the change in blood pressure. Actual data points are indicated by large black dots. N = 6 for each data point.



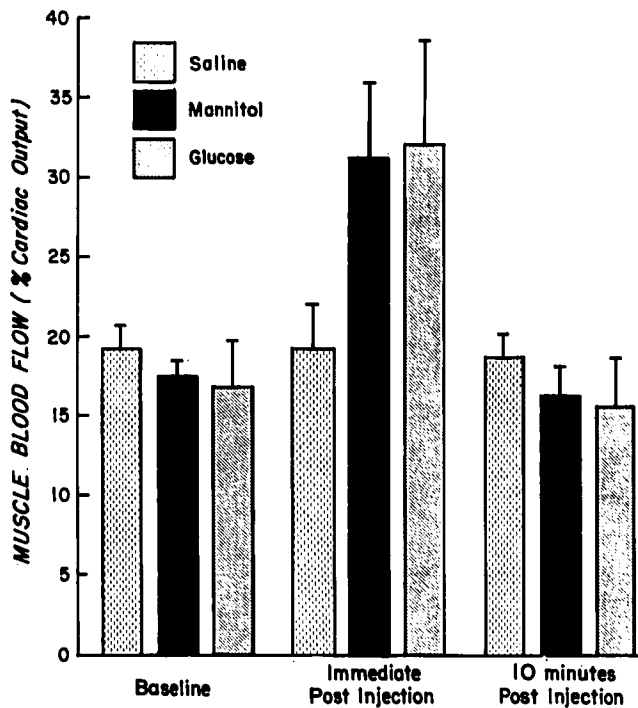


FIG. 4. Muscle blood flows expressed as percentages of cardiac output (mean \pm SE) at baseline and nadir after injection of equal volumes at the same rate of injection of mannitol, 25 per cent, glucose, 31.7 per cent, and physiologic saline solution. Blood flow to skeletal muscle nearly doubled after both equiosmotic, hypertonic solutions but not after physiologic saline solution. $N = 6$ for each group.

within 10 min after mannitol injection. Mannitol, 1 g/kg, caused statistically significant decreases in blood pressure at all rates of injection, whereas 1.0, 0.5, and 0.25, but not 0.125, g/kg at the most rapid rate of injection caused statistically significant decreases in blood pressure (fig. 2). When either rate of injection or osmotic load was decreased, the decrease in blood pressure was proportionally less (fig. 3). The times at which the blood pressure reached its nadir were most constant with the highest osmotic load and most rapid rate of administration, and the mean time was 12.5 ± 0.5 sec after injection. Blood pressures began to decrease approximately 7 sec after the start of injection; the times for return to baseline ranged from 65 to 250 sec with the highest dose and most rapid rate of injection. For this reason, the dose of 1 g/kg mannitol 25 per cent at 0.1235 g/sec was chosen for the blood flow study, and microspheres were administered 15 sec after the end of the mannitol injection when no change in blood pressure was observed. Clinically important decreases in blood pressure (>10 torr) occurred only at the highest doses and most rapid rates of administration.

In five rabbits, the mean P_{aCO_2} during spontaneous ventilation was 47 ± 4 torr, during hypocarbia 24 ± 5 torr, and during hypercarbia 58 ± 2 torr. The blood

pressure changes were 16 ± 3 torr during hypocarbia and 20 ± 4 torr during hypercarbia.

At equiosmotic concentrations and equal volumes, mannitol and glucose produced nearly identical decreases in blood pressure (36 ± 3 and 34 ± 2 per cent, respectively), at nearly identical times (15 ± 1 and 14 ± 0.4 sec) after injection. Both changes were significant when compared with baseline and with the control group given isotonic saline solution.

There were significant changes in the distribution of cardiac output in several organs within each subgroup. However, when compared with the control group given saline solution, muscle blood flow was the only organ bed to demonstrate significant changes with mannitol and glucose. Muscle blood flow with mannitol increased from 17 ± 1 per cent at baseline to 31 ± 5 per cent during hypotension and returned to 16 ± 4 per cent when blood pressure returned to normal. Similarly, glucose infusion increased muscle blood flow from 17 ± 3 to 32 ± 7 per cent during hypotension, and it returned to 16 ± 3 per cent at a normal blood pressure. The saline-treated control group did not show any change in blood pressure or blood flow to skeletal muscle.

Discussion

The vasodilator properties of hypertonic solutions are well documented in the physiologic literature^{2,3}; less well known are the effects such solutions have on man.^{4,5} We studied patients undergoing coronary-artery bypass grafting, since mannitol is frequently administered as a diuretic and the normal conduct of anesthesia did not need to be altered. The dosage of 0.25 or 0.125 g/kg was chosen since this is the usual amount chosen for diuresis for adult patients. The mean percentage decreases in blood pressure were different in all groups of patients; the duration of hypotension was shorter and changes in total peripheral resistance greater in Group I (fig. 1) compared with the other groups. An increase in cardiac output secondary to increased inotropy, decreased afterload, or increased preload seemed to account for the brief duration and less profound hypotension in Group I, since there was no change in heart rate. Mannitol has been shown to have inotropic properties of its own⁶; we cannot conclude that this caused the increased cardiac output observed in our patients, since peripheral resistance (afterload), and preload also changed and systolic time intervals were not measured.

An accurate assessment of the duration of vasodilatation was not possible in Groups II, III, and IV since other variables, such as altered flow, impaired venous return, or administration of vasopressor or vasodilator drugs interfered with continuous recordings of the changes produced by mannitol. The mean

blood pressure clearly remained lower for a longer period in the patients in Group III, who received the larger dose and more rapid rate of injection. Interestingly, the percentage decreases in total peripheral resistance in Groups I and III were nearly identical. The times of nadir after injection also were nearly identical. Considering the relative increases in the circulating blood volumes of the patients in whom cardiopulmonary bypass was used, Groups I and III actually received very similar doses and rates of administration; the two groups had similar peak increases in serum osmolality. Serum osmolality thus correlated inversely with the decrease in total peripheral resistance and blood pressure; changes in Na^+ , K^+ , and hemoglobin values probably reflect movement of free water into the circulation⁷ and possible dehydration of erythrocytes.⁸ The ratio of hemoglobin to hematocrit did not confirm the latter possibility. The changes in blood pH and base excess values, although significant, were clinically unimportant and cannot be explained by the small acid load presented by mannitol itself. Transient dilution of plasma bicarbonate at a constant PaCO_2 , so-called dilutional acidosis, could account for these changes.⁹ The near-double incremental decreases in pH, base excess, Na^+ , K^+ , and hemoglobin values found in Group I compared with the other groups again reflect the smaller blood volumes in the Group I patients and thus represent nearly identical fluid shifts. The small changes in ionized calcium or in blood viscosity are insufficient to account for the hypotensive response.

Both rate of injection and total osmotic load are important determinants of blood pressure changes with mannitol (fig. 3). A vasodilator response to hypertonic solutions has been demonstrated in animals.^{2,3} Vasomotor responses and blood flows to individual organ beds have been examined, but no study has examined the animal *in toto* and the concomitant changes in distribution of cardiac output. Vasodilation of coronary and peripheral blood vessels in man has been found^{4,6}; a slight but significant decrease in blood pressure in newborns given hypertonic sodium bicarbonate therapy in the presence of normal acid-base status has been recorded.⁵

Injected radiolabeled microspheres accurately reflect the distribution of cardiac output of rabbits. The baseline distribution found in our study was comparable to that found by other investigators¹⁰; slight differences may be accounted for by variations in techniques and depths of anesthesia. Blood flow to muscle tissues nearly doubled during the hypotension induced by hypertonic glucose or mannitol (fig. 4). This did not occur with an equal volume of isotonic saline solution. Interestingly, the times to nadir and percentage decreases in blood pressure after injection were also nearly identical with glucose and mannitol.

Muscle blood flow has been demonstrated to be sensitive to changes in serum osmolality, and this might explain the marked shift in the distribution of cardiac output found in our study. The reason muscle arterioles respond preferentially to osmotic shifts is unclear, but this response may reflect a form of autoregulation. Changes in blood flow to other organs were variable; cardiac blood flow was unaltered while the cerebral blood flow changes found are of questionable value, since experimental technique required ligation of the right carotid artery.

The etiology of the vasodilator response to hypertonic solutions has not been clearly defined, and the basis for the major effect's being on the vasculature to skeletal muscle has not yet been explained. We conclude that clinically important hypotension may be avoided by slow administration of all hypertonic solutions.

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The protocol was approved by the Human Studies Committee of the University of Pennsylvania.

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