Response of the Limb Vascular Bed in Man to Intrabrachial Arterial Infusions of Hypertonic Dextrose or Hypertonic Sodium Chloride Solutions

By Henry W. Overbeck, M.D., Ph.D., and George J. Grega, Ph.D.

With the Assistance of Michael C. Fick, M.A.

ABSTRACT

Infusions of hypertonic dextrose or NaCl solutions reduce resistance in several vascular beds of experimental animals. To study the response in man, 60 intrabrachial arterial jet infusions of hypertonic dextrose solution or hypertonic NaCl solution, each at 3 dose levels (1, 2, and 4 milliosmols/min), were made in 19 male student volunteers aged 21 to 29 years. Limb blood flow was measured by continuous infusion indicator-dilution, and vascular resistance calculated as mm Hg/ml flow/100 cm³ limb vol/min. Measured increases in ipsilateral cephalic venous plasma osmolarity and serum dextrose and sodium concentrations during hypertonic infusions ranged from 7 to 30 milliosmols/liter, 153 to 481 mg/100 ml and 4 to 19 mEq/liter, respectively. Measured limb venous blood hematocrit during hypertonic infusions was similar to that during control isotonic infusions. All 60 hypertonic infusions evoked an increase in limb blood flow and decrease in limb vascular resistance as compared to "resting" values during paired control isotonic NaCl infusions. There was a significant (P<.01) positive linear correlation between level of initial vascular resistance and magnitude of response to all hypertonic infusions. At each dose level, neither regression coefficient nor regression adjusted mean response to dextrose was significantly different from that to hypertonic NaCl (P>.05).

The results of these studies indicate that the local vascular response to hypertonicity in the limb of man is a decrease in resistance, the magnitude of which is a function of the level of plasma osmolarity and the level of initial limb resistance. The steady-state responses to hypertonic dextrose are quantitatively similar to those to hypertonic NaCl.

ADDITIONAL KEY WORDS sodium ion skeletal muscle skin viscosity vascular resistance wall-lumen ratio exercise hyperemia indicator-dilution hyperosmolar shock

Intra-arterial infusions of hypertonic dextrose or hypertonic NaCl solutions reduce resistance in several mammalian vascular beds; this response to increased plasma osmolarity has been demonstrated by many investigators in experimental animals (1-10). Several authors have recently reported the occurrence of shock in hyperosmolar clinical states in man (11-13). In addition, plasma hypertonicity occurs during skeletal muscle exercise, and it has recently been proposed that local hyperosmolarity may play an important role in hyperemia caused by exercise (10). Finally, radiopaque hypertonic solutions are frequently injected into patients for diagnostic purposes. Study of the hemodynamic effects of hypertonicity in man should thus not only increase knowledge of human
vascular physiology but also improve understanding of the mechanisms of hyperosmolar shock, help to define the role of osmolarity in local regulation of blood flow in man, and aid interpretation of the results of certain diagnostic procedures.

The present study was undertaken to define the response of the vascular bed of the forearm and hand in man to local changes in plasma osmolarity. Increases in plasma osmolarity were produced by intrabrachial arterial infusions of hypertonic dextrose or sodium chloride solutions. Limb blood flow responses were measured by an indicator-dilution technique (14, 15).

**Methods**

All 28 subjects were healthy, young (21 to 29 years), male Caucasian students at Michigan State University and were fully informed of the purposes, procedures, and hazards of the experiment. Written consent was obtained. An attempt, apparently unsuccessful in five subjects, was made to exclude subjects having anomalous bifurcation of the brachial artery by palpating the antecubital fossa. One subject was studied twice, once with infusions of hypertonic dextrose, once with hypertonic NaCl. Twenty experiments in 19 subjects were considered technically satisfactory by the criteria defined below. Mean ages, body weights, and forearm volumes of groups receiving hypertonic dextrose and hypertonic NaCl were 24 and 24, 170 and 166, and 1600 and 1580 ml, respectively.

These volunteers were studied in the resting, postabsorptive state in an air-conditioned laboratory, with ambient temperature ranging from 24° to 27°C. Prior to study, the volume of the arm distal to the level of the intercondylar line at the elbow was measured by water displacement. Figure 1 is a diagram of the experimental procedure. With the subject comfortable in the supine position and his arms supported at a 45° angle from the long axis of the body, 16-gauge hypodermic needles were inserted in an upstream direction into the basilic vein, the cephalic vein, and an antecubital vein of one arm ("ipsilateral" arm) distal to the elbow. Thin-walled Teflon catheters, i.d. .027 inches, o.d. .039 inches (Becton, Dickinson and Co., Rutherford, N. J.), were then introduced into these three veins through the hypodermic needles, the needles withdrawn, and the Teflon catheters connected to either a dye-cuvette (see below) or to a stopcock manifold by Silastic rubber tubing. The ipsilateral and contralateral brachial arteries were also cannulated in an upstream direction with 20-gauge Riley arterial needles. All venous and arterial punctures were performed under local procaine (Procaine HCl, Cutter Laboratories) anesthesia. To improve mixing of infused brachial arterial blood a jet-injector needle (Kimray, Inc., Oklahoma City, Oklahoma) previously described (14) was used for the intrarterial infusions. Infusion rate was 8.2 ml/min. This jet-injection system improves mixing of infused substances with brachial arterial blood at infusate kinetic energies too low to cause significant hemolysis (14). The jet needle was introduced into the brachial artery through the Riley needle, an adapter on the jet needle hub locking into the hub of the Riley needle. The tip of the jet needle usually protruded up to but not proximal to the intercondylar line at the elbow. To center the jet in the arterial lumen, the position of the jet needle was manipulated to obtain the lowest possible infusion pressure, usually not more than 200 mm Hg above pressure during jet infusion into air.

Limb blood flow was measured by indicator-dilution. Two indicators were used simultaneously: IHSAl (131I-labeled human serum albumin in isotonic sodium chloride solution, Albumotope, Squibb, New Brunswick, N. J.) and indocyanine green dye (Cardiogreen). All infusions, control and hypertonic, in a given subject contained the same concentrations of each of these two...
indications: approximately 0.06 μCi 131I/ml and 0.05 mg dye/ml. During intrabrachial-arterial infusions, ipsilateral antecubital venous blood was constantly withdrawn at 2.25 ml/min by a withdrawal pump (Model 2302, Harvard Apparatus Company, Dover, Mass.) through a cuvette-denstometer system (Model DTL, Gilson Medical Electronics, Middleton, Wis.). Optical density of venous blood was thereby continuously monitored on a strip chart recorder (Model 7100B, Hewlett Packard Company, Waltham, Mass.). This system has been previously described in detail (15) and allows continuous monitoring of ipsilateral venous concentrations of indocyanine green and thereby limb blood flow. In this series of experiments the dye system was used to detect steady-state blood flow. Previous experiments have indicated that the concentration of indicator in antecubital venous blood lies within the range of the concentrations in the cephalic and basilic veins and that a steady state of indicator concentration in the antecubital vein is paralleled by a steady state in the other veins (14). At the time of steady state, ipsilateral cephalic and basilic venous and contralateral brachial arterial blood was simultaneously sampled for determination of IHSA concentrations, from which blood flow was calculated. During blood sampling for IHSA concentrations, the catheters were first flushed by drawing and discarding 1 ml of blood, a volume at least three times the volume of the catheters. Actual drawing of samples, each 1.5 ml in volume, immediately followed, and these samples were placed in glass test tubes containing two drops of concentrated heparin solution. The tubes containing samples were rotated for at least 3 minutes, and then 1 ml aliquots were pipetted into plastic tubes for radioisotope counting on an automatic gamma scintillation system (Model 4230, Nuclear-Chicago Corporation, Des Plaines, Ill.).

To prevent the mild discomfort of the vessel punctures and the transient oscillations in the diameter of the punctured brachial artery from affecting the results, there was a resting period of at least 30 minutes after the punctures were completed before proceeding with the experiment. For study of vascular responses to hypertonic solutions, paired infusions at equal infusion rates were made: first an isotonic NaCl solution, then the hypertonic dextrose solution or the hypertonic NaCl solution. Thus resistance during the hypertonic infusions was compared to resting resistance measured during the isotonic control infusion. All infusions were maintained at approximately 37°C. The hypertonic solutions were prepared by adding 50% dextrose (50% Dextrose Injection, USP, Cutter Laboratories) or 5% NaCl (5% NaCl Solution, USP, Cutter Laboratories) to isotonic NaCl solution to achieve osmolarities of 393, 512, and 750 milliosmols/liter.

VASCULAR RESPONSES TO HYPERTONIC INFUSIONS

In this series of experiments the dye system was used to detect steady-state blood flow. Previous experiments have indicated that the concentration of indicator in antecubital venous blood lies within the range of the concentrations in the cephalic and basilic veins and that a steady state of indicator concentration in the antecubital vein is paralleled by a steady state in the other veins (14). At the time of steady state, ipsilateral cephalic and basilic venous and contralateral brachial arterial blood was simultaneously sampled for determination of IHSA concentrations, from which blood flow was calculated. During blood sampling for IHSA concentrations, the catheters were first flushed by drawing and discarding 1 ml of blood, a volume at least three times the volume of the catheters. Actual drawing of samples, each 1.5 ml in volume, immediately followed, and these samples were placed in glass test tubes containing two drops of concentrated heparin solution. The tubes containing samples were rotated for at least 3 minutes, and then 1 ml aliquots were pipetted into plastic tubes for radioisotope counting on an automatic gamma scintillation system (Model 4230, Nuclear-Chicago Corporation, Des Plaines, Ill.).

To prevent the mild discomfort of the vessel punctures and the transient oscillations in the diameter of the punctured brachial artery from affecting the results, there was a resting period of at least 30 minutes after the punctures were completed before proceeding with the experiment. For study of vascular responses to hypertonic solutions, paired infusions at equal infusion rates were made: first an isotonic NaCl solution, then the hypertonic dextrose solution or the hypertonic NaCl solution. Thus resistance during the hypertonic infusions was compared to resting resistance measured during the isotonic control infusion. All infusions were maintained at approximately 37°C. The hypertonic solutions were prepared by adding 50% dextrose (50% Dextrose Injection, USP, Cutter Laboratories) or 5% NaCl (5% NaCl Solution, USP, Cutter Laboratories) to isotonic NaCl solution to achieve osmolarities of 393, 512, and 750 milliosmols/liter. As compared to the control isotonic NaCl infusions (which added approximately 2.2 milliosmols of solute to brachial arterial blood per minute), these hypertonic infusions added an additional 1.02, 2.03, and 4.06 milliosmols of solute to brachial arterial blood per minute, respectively. The three dosage levels of one hypertonic agent were used in each subject; thus each subject received a total of six infusions, three of the hypertonic solution and three of the paired isotonic NaCl control solution. The hypertonic solutions were always administered in order of increasing dose. Duration of each infusion was as long as necessary to establish a steady blood flow or 13 minutes, whichever occurred first. Approximately 1000 ml of solution was infused and approximately 300 ml of blood was withdrawn during experiments with an average duration of 136 minutes; associated with these fluid changes was an average decrease in arterial hematocrit of 0.8 vol% over the course of the experiments. There was occasionally a short pause (up to 8 minutes) between the hypertonic infusion and the following control infusion to allow limb resistance to return toward resting level. During infusions, pressures in the ipsilateral cephalic and basilic veins and contralateral brachial artery were recorded in turn immediately before blood was sampled for IHSA concentrations. Recordings were made with pressure transducers (Models P23BB and P235B, Statham Industries, Hato Rey, Puerto Rico) and an oscillographic recording machine (Model 7714A, Sanborn Division, Hewlett Packard Company, Waltham, Mass.).

The calculating equation for limb blood flow was adapted from that suggested by Andres et al. (16): limb (forearm plus hand) blood flow = cpm IHSA infused per minute into brachial artery ÷ (mean cpm per ml venous blood − cpm per ml contralateral brachial arterial blood). The mean IHSA concentration of the paired venous samples was used in calculation of blood flow. The calculated blood flows and vascular resistances presented in Table 1 and Figures 3 and 4 were not adjusted for the intrabrachial arterial infusion rate of 8.2 ml/min for reasons previously discussed (14), although there is evidence that the infusate forms a simple additive to preexisting limb blood flow. However, duplicate calculations were made using adjusted blood flows to ensure that conclusions would not be changed. Relative difference (rd), the percent by which a concentration of indicator in either cephalic or basilic vein differs from their mean concentration, a measure of degree of mixing of infusate with limb blood (16), was also calculated.
additive to preexisting limb blood flow. In the case of the electrolytes, plasma flow rather than blood flow was used in the above equation and was calculated as: plasma flow = limb blood flow \times \left(102 - \text{cephalic venous hematocrit}\right)/100. In this equation, all values were based on samples obtained from the ipsilateral cephalic vein because venous electrolyte output concentrations were measured only in cephalic venous serum. The calculation was also adjusted for 2% trapped plasma.

Student's t-test, simple linear correlation and regression, and Duncan's new multiple range test were used for statistical analyses.

Results

Sixty control isotonic NaCl and sixty hypertonic intrabrachial arterial infusions were made in twenty technically satisfactory experiments in the 28 subjects. Experiments were considered technically satisfactory if the following four criteria were met: (1) The relative difference between indicator concentrations in the basilic and cephalic veins did not exceed 20%. Andres et al. (16) believe that relative differences exceeding 20% suggest anomalous high bifurcation of the brachial artery. In the presence of this anomaly, limb blood flow cannot be measured with confidence by this indicator-dilution technique, and in addition, mixing of the vasoactive substance with limb blood is probably inadequate for reliable response studies. (2) To avoid excessive infusate kinetic energies and hemolysis, jet infusion pressure during intrabrachial infusion did not exceed pressure during infusion into air by more than 200 mm Hg or there was no evidence of hemolysis and vasodilatation during the infusions. Previous experiments in the dog forelimb indicate that under these conditions no significant hemolysis is produced by the jet infusion (14). In 15 experiments jet infusion pressure remained within 200 mm Hg of infusion pressure into air. In five experiments infusion pressure gradually rose during the course of the experiments, possibly due to fibrin accumulation in the jet orifices or partial obstruction of an orifice by the vessel wall. (In no case did intra-arterial infusion pressure exceed infusion pressure into air by more than 400 mm Hg.)

In these subjects, resting blood flow during
the repeated control isotonic NaCl infusions did not rise, and additionally, in one subject orthotolidine testing of serial dilutions of serum indicated that free hemoglobin concentration in ipsilateral venous blood was similar to that in contralateral arterial blood during the ipsilateral intrabrachial-arterial jet infusions. This was considered good evidence that no significant hemolysis and vasodilatation had occurred in these 5 subjects. (3) Blood flow following each hypertonic infusion returned to either the pre-existing resting level or to a new steady state, usually close to the preexisting level. (4) The subject was able to remain reasonably quiet with minimal limb movement. In nine experiments these criteria were not satisfied and the data were discarded; in five of these experiments the mean of the relative differences exceeded 20%.

Steady-state limb blood flow was regularly achieved during the control isotonic NaCl infusions. During the hypertonic infusions, a gradually damping oscillation of blood flow was usually noted, probably due in part to the reciprocal relationship between blood flow and concentration of the vasoactive agent, as previously described (18). In most subjects, however, a reasonably steady-state blood flow was ultimately achieved during the hypertonic infusions. Rate of achievement of the steady state appeared to be fairly similar for the two hypertonic agents and similar to that previously reported for other vasodilator agents in the limb of man (18). Figure 2 is a record of the changes detected by the cuvette-densitometer in optical density of ipsilateral antecubital venous blood during infusions of isotonic NaCl and hypertonic dextrose solutions in one subject.

Table 1 lists duration of infusions and mean changes in limb blood flow, pressures and calculated vascular resistance in response to the hypertonic infusions. The calculated mean levels of resting blood flow and vascular resistance in the 19 subjects were 71.1 ml/min and 21.8 mm Hg/ml/100 cm³/min, respectively. Calculated mean resting plasma flow was 45.5 ml/min. Calculated on the basis of this resting plasma flow, mean initial increases in arterial plasma osmolalities for the three dose levels of hypertonic solutions were 22.4, 44.8, and 89.6 milliosmols/liter. Calculated on the basis of the plasma flow measured at the time of steady-state response, increases in arterial plasma osmolalities were 18.9, 32.7, and 45.6 milliosmols/liter. Durations of hypertonic dextrose infusions were similar to durations of hypertonic NaCl infusions. Rate of return to resting blood flow levels following cessation of the hypertonic dextrose infusions was also
TABLE 1

Limb Hemodynamic Changes in Response to Hypertonicity

<table>
<thead>
<tr>
<th>Dose (milliosmols/min)</th>
<th>Min of infusion</th>
<th>Limb blood flow</th>
<th>Vascular resistance</th>
<th>Change in resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total (ml/min)</td>
<td>Per 100 cm² (ml/min)</td>
<td>(mm Hg)</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>12.2 ± 1.6</td>
<td>66.8 ± 20.3</td>
<td>90.8 ± 8.3</td>
</tr>
<tr>
<td>Hypertonic NaCl</td>
<td>1.02</td>
<td>9.7 ± 1.1</td>
<td>126.0 ± 22.6</td>
<td>94.6 ± 9.1</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>14.1 ± 4.1</td>
<td>155.6 ± 32.2</td>
<td>99.1 ± 7.2</td>
</tr>
<tr>
<td>Hypertonic NaCl</td>
<td>4.06</td>
<td>9.4 ± 1.0</td>
<td>155.6 ± 32.2</td>
<td>99.1 ± 7.2</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>12.2 ± 2.5</td>
<td>75.8 ± 37.4</td>
<td>91.7 ± 6.4</td>
</tr>
<tr>
<td>Hypertonic dextrose</td>
<td>1.02</td>
<td>9.9 ± 1.0</td>
<td>87.6 ± 44.7</td>
<td>92.5 ± 6.1</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>12.7 ± 3.7</td>
<td>78.1 ± 40.9</td>
<td>94.7 ± 7.2</td>
</tr>
<tr>
<td>Hypertonic dextrose</td>
<td>2.03</td>
<td>9.1 ± 2.0</td>
<td>103.7 ± 41.0</td>
<td>96.1 ± 7.3</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>12.2 ± 3.0</td>
<td>74.2 ± 38.3</td>
<td>98.9 ± 6.6</td>
</tr>
<tr>
<td>Hypertonic dextrose</td>
<td>4.00</td>
<td>9.2 ± 1.8</td>
<td>131.1 ± 12.0</td>
<td>100.4 ± 2.5</td>
</tr>
</tbody>
</table>

Values are means (of 10 measurements) ± sd. Control values are for paired infusions of isotonic NaCl. $P_A$ = mean brachial arterial pressure; $P_{LV}$ = mean basilic or cephalic venous pressure. Values for hypertonic infusions were during steady-state response.

*Statistically highly significant ($P < .01$).
TABLE 2
Limb Input Concentration minus Output Concentration during Isotonic and Hypertonic Infusions

<table>
<thead>
<tr>
<th>Dose (milliosmols/min)</th>
<th>Hematocrit (vol %)</th>
<th>Plasma osmolarity (milliosmols/L)</th>
<th>Serum dextrose (mg/100 ml)</th>
<th>Serum Na⁺ (mEq/L)</th>
<th>Serum K⁺ (mEq/L)</th>
<th>Serum Ca²⁺ (mEq/L)</th>
<th>Serum Mg²⁺ (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotonic NaCl (Pooled Data)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 0.17 ± 0.09</td>
<td></td>
<td>+ 1.73 ± 0.71*</td>
<td>+ 2.73 ± 0.60†</td>
<td>- 0.32 ± 0.09†</td>
<td>- 0.19 ± 0.06†</td>
<td>- 0.09 ± 0.03†</td>
<td></td>
</tr>
<tr>
<td>(48)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertonic NaCl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.02</td>
<td>+ 0.91 ± 0.19†</td>
<td>+ 11.1 ± 1.6†</td>
<td>+ 6.1 ± 1.6†</td>
<td>- 0.08 ± 0.04</td>
<td>+ 0.01 ± 0.05</td>
<td>- 0.004 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>(9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.03</td>
<td>+ 1.74 ± 0.07†</td>
<td>+ 15.4 ± 3.9†</td>
<td>+ 10.0 ± 1.8†</td>
<td>- 0.04 ± 0.04</td>
<td>+ 0.05 ± 0.12</td>
<td>+ 0.03 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>(9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.06</td>
<td>+ 2.37 ± 0.21†</td>
<td>+ 22.2 ± 3.9†</td>
<td>+ 13.6 ± 3.4†</td>
<td>+ 0.10 ± 0.05</td>
<td>+ 0.25 ± 0.08*</td>
<td>+ 0.06 ± 0.01†</td>
<td></td>
</tr>
<tr>
<td>(9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertonic Dextrose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.02</td>
<td>+ 0.14 ± 0.28</td>
<td>+ 9.6 ± 2.7*</td>
<td>+ 185.5 ± 46.0</td>
<td>- 0.02 ± 0.07</td>
<td>+ 0.03 ± 0.03</td>
<td>- 0.03 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>(7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.03</td>
<td>+ 0.41 ± 0.27</td>
<td>+ 14.5 ± 2.9†</td>
<td>+ 287.0 ± 46.0*</td>
<td>- 0.16 ± 0.08</td>
<td>+ 0.12 ± 0.02†</td>
<td>- 0.02 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>(7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.06</td>
<td>+ 0.84 ± 0.32*</td>
<td>+ 23.0 ± 5.1†</td>
<td>+ 445.3 ± 31.4†</td>
<td>- 2.0 ± 4.6</td>
<td>+ 0.15 ± 0.11</td>
<td>+ 0.05 ± 0.10</td>
<td>- 0.06 ± 0.03</td>
</tr>
<tr>
<td>(7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means of differences ± the appropriate standard deviation. Number in parentheses is number of measurements for value above.
*Statistically significant (P < .05). †Statistically highly significant (P < .01).
similar to that following cessation of hypertonic NaCl and roughly 13 minutes. Mean limb blood flows and resistances following the first two hypertonic infusions were not significantly different from values preceding those infusions; thus it is unlikely that the order of infusions significantly affected results. There was a slight continuous rise in mean arterial pressure during the total course of the experiments, possibly attributable to an increase in plasma volume due to the infusions. However, arterial pressures during the hypertonic infusions were similar to those during the paired isotonic control infusions. A slight increase also occurred in the cephalic and basilic venous pressures during the experiments.

Table 2 presents limb arteriovenous osmolarity, [dextrose], and [Na+] gradients measured during the intrabrachial arterial isotonic and hypertonic infusions. Arterial plasma osmolarity, serum [dextrose] and serum [Na+] did not change significantly over the course of the experiments. Measured increase in ipsilateral cephalic venous plasma osmolarity during infusion of hypertonic dextrose was similar to that during infusion of a comparable dose level of hypertonic NaCl; increases ranged from 7 to 30 milliosmols/liter. Measured increase in ipsilateral cephalic venous serum [dextrose] during infusion of hypertonic dextrose ranged from 153 to 481 mg/100 ml. Measured increase in ipsilateral cephalic venous serum [Na+] during infusion of hypertonic NaCl ranged from 4 to 19 mEq/liter.

All 60 hypertonic infusions evoked an increase in limb blood flow and decrease in limb vascular resistance, as compared to resting flow and resistance during the paired control isotonic infusions. The increase in blood flow and decrease in resistance in response to each hypertonic agent and dose were highly significant by paired Student's t-test ($P < .01$). For each dose level of each hypertonic agent, there was a significant ($P < .05$) linear correlation between resting limb vascular resistance and magnitude of response to the hypertonic infusions. Hence,
VASCULAR RESPONSES TO HYPERTONIC INFUSIONS

725

variations in level of resting limb vascular resistance in these subjects added significantly to the variation of the response measurements. To reduce this source of experimental variation, regression coefficients were calculated for the relation between magnitude of response and resting resistance for each dose level of each hypertonic agent. Individual data points were then adjusted to the mean level of resting resistance. The adjusted response points were used for comparison of responses to the two hypertonic agents and for constructing a dose-response curve. Figures 3a, b, and c thus present the correlation coefficients and the responses to the three dosage levels of the hypertonic agents plotted against the level of resting resistance. Response points and regression lines were drawn independently for each hypertonic agent. At each dosage level the regression coefficient for hypertonic dextrose was homogeneous with that for hypertonic NaCl (P > .3). The adjusted responses for hypertonic dextrose were not statistically dissimilar from those for hypertonic NaCl (P > .05). Duplicate calculations of correlation and regression coefficients and adjusted responses, using blood flows from which the infusion rate of 8.2 ml/min had been subtracted gave similar results. It was therefore concluded that the responses to hypertonic dextrose were similar to the responses to equally hypertonic NaCl.

At each dose level, the response data for both agents adjusted to the overall mean level of resting vascular resistance (21.83 mm Hg/ml/100 cm³/min) were consequently pooled. Figure 4 presents the dose-response relation for these pooled data. Doses were expressed in terms of the steady-state level of measured limb cephalic venous plasma osmolarity. Duncan's new multiple range test indicated that the three points on the curve were statistically dissimilar (P < .01). A fairly good logarithmic relation was obtained for the dose-response relation. The regression equation was Y = -26.20 log X + 23.65 (the regression equation for blood flow data from which infusion rate was subtracted was Y = -31.96 log X + 28.24 [corresponding overall mean level of resting vascular resistance 25.74 mm Hg/ml/100 cm³/min]).

Contralateral arterial serum [K⁺], [Ca²⁺], and [Mg²⁺] and blood hematocrit did not change significantly over the course of the experiments. Mean ipsilateral cephalic venous serum [K⁺], [Ca²⁺], [Mg²⁺], and blood hematocrit during control infusions of isotonic NaCl were 3.46 mEq/liter, 3.41 mEq/liter, 1.79 mEq/liter, and 37.7 vol%, respectively. Corresponding values during infusions of hypertonic dextrose were 3.36 mEq/liter, 3.78 mEq/liter, 1.75 mEq/liter, and 38.5 vol%. Corresponding values during infusions of hypertonic NaCl were 3.36 mEq/liter, 3.56 mEq/liter, and 38.5 vol%.

Table 2 presents ipsilateral limb input concentrations and output concentrations for blood hematocrit and serum K⁺, Ca²⁺, and Mg²⁺ during the control isotonic and the hypertonic infusions. For the hematocrit there was no significant difference between input
and output concentrations during infusion of isotonic NaCl. However during infusions of both hypertonic agents input concentration significantly exceeded output concentration. For $K^+$, $Ca^{2+}$, and $Mg^{2+}$, output concentration significantly exceeded input concentration during the infusion of isotonic NaCl. In contrast, during infusion of both hypertonic agents either there was no significant difference between input and output concentrations or input concentration significantly exceeded output concentration.

**Discussion**

The techniques used in this study to measure limb blood flow (jet-infusion to improve mixing plus continuous monitoring of limb venous indicator concentrations) have not been previously combined in a study of vascular responses to a vasoactive agent. Twenty out of the 29 experiments in the present series were technically satisfactory by the defined criteria. Considering that in five of the nine unsuccessful experiments there was evidence for anomalous high bifurcation of the brachial artery, the proportion of successful experiments was acceptably high. As pointed out in earlier reports (14, 15), these techniques appear to offer major advantages in such vascular studies. Not only is mixing of indicator and vasoactive substances with blood upstream to the arteriole probably significantly improved, but the techniques also allow detection of inadequate mixing (such as that occurring with high bifurcation of the brachial artery). Such inadequate mixing occurred in five experiments and probably would not have been detected if blood flow had been measured by plethysmography rather than by indicator-dilution. An additional advantage is that the indicator-dilution technique measures blood flow changes in the same tissues reached by the vasoactive substance; this is often not the case with plethysmography. Finally, continuous monitoring of venous indocyanine green concentrations, and thereby blood flow, allows detection of steady-state blood flow and flexibility of experimental design. The advantages of these techniques in this type of response study seem to outweigh such disadvantages as the complexity of the techniques and the necessity for multiple vascular punctures.

Local hypertonic infusions evoke fluid shifts in the limb from the extravascular to the intravascular space (4). Solute shifts also occur. The fluid shifts pose theoretical problems in the interpretation of blood flow measurements by either plethysmography or by indicator-dilution. With plethysmography, a progressive decrease in the extravascular space of the limb would be erroneously interpreted as a progressive decrease in limb blood flow and an increase in limb vascular resistance. With indicator-dilution, similar fluid shifts would cause limb venous outflow to exceed limb arterial inflow; thus, strictly speaking, one necessary condition for accurate indicator-dilution measurements would be violated. Furthermore, these fluid shifts occur primarily at the capillary, downstream to the arteriole, the main site of vascular resistance. Thus calculated increase in total limb blood flow would exceed actual increase in blood flow through the arterioles; accordingly, calculated decrease in limb vascular resistance would be greater than actual decrease in arteriolar resistance.

Data from the present experiments indicate that fluid and solute shifts occurred. Calculated steady-state increases in arterial plasma osmolarities for the three dose levels of hypertonic solutions were 18.9, 32.7, and 45.6 milliosmols/liter. In contrast, measured steady-state cephalic venous plasma osmolarities increased by only 10.4, 15.0, and 22.6 milliosmols/liter (pooled data for both hypertonic solutions), suggesting a combination of diffusion of solute out of plasma and water into plasma. These data, however, give no indication of the relative proportions of solute and fluid shifts.

Some indication of the magnitude of fluid shifts may be inferred from the effect of the isotonic and hypertonic infusions on limb hematocrit values. Calculated input hematocrit agreed closely with measured output.
hematocrit during the isotonic infusions, suggesting that the isotonic infusions formed a simple additive to preexisting limb blood flow. In contrast, calculated input hematocrit significantly exceeded measured output hematocrit during most of the hypertonic infusions. This finding suggests that, as would be expected, the plasma hyperosmolarity decreased erythrocyte size or resulted in shifts of fluid from the extravascular to the intravascular space of the limb, or both. If one neglects erythrocyte shrinkage as a factor, one may use these data to calculate the maximum amount of fluid that could have been shifted. Such calculations indicate that the net influx into plasma during infusion of hypertonic dextrose could not have exceeded 3 ml/min (or 0.19 ml/100 cm³ limb vol/min in a limb of 1600 cm³ vol). Similar calculations indicate that the net influx into plasma during infusion of hypertonic NaCl could not have exceeded 9 ml/min (or 0.56 ml/100 cm³ limb vol/min in a limb of 1800 cm³ vol).

Data from the isolated perfused dog forelimb (S. Gazitua, unpublished observations) may also offer some indication of the magnitude of fluid shifts accompanying local plasma hypertonicity. Intrabrachial arterial infusions of hypertonic dextrose producing changes in arterial plasma osmolarity similar to the maximum changes in the present experiments evoked a constant decrease in dog forelimb weight over the course of a 10-minute infusion averaging 3 g/100 g limb weight. Thus limb venous outflow probably exceeded arterial inflow by 0.3 ml/100 cm³ limb vol/min. Similarly, during infusions of equally hypertonic NaCl, venous outflow probably exceeded arterial inflow by an average of 0.2 ml/100 cm³ limb vol/min. Thus these data from the dog limb agree fairly well with data from the human limb in the present experiments and would suggest that the maximum amount of excess outflow per minute in the limb of man may have been so small as to be negligible in calculations of blood flow by indicator-dilution. However, the significant progressive decrease in limb weight, which in a human forearm and hand of 1600-cm³ volume could amount to as much as 30 to 50 g/10-min hypertonic infusion, would introduce a very significant error in plethysmographic measurements of blood flow.

Data from the present experiments may also give some indication of the nature of solute shifts occurring in response to the isotonic and hypertonic infusions. Output concentration of K⁺, Ca²⁺, and Mg²⁺ significantly exceeded input concentration during the isotonic control infusions. In contrast, during hypertonic infusions, input concentration of these electrolytes exceeded output concentration (Table 2). Possible effects of these solute shifts on limb vascular resistance are discussed below.

The indocyanine green dye system was not used for quantitative measurement of blood flow in the present experiments because in one patient it was found that in the presence of plasma hypertonicity dye-calculated blood flows were systematically higher than blood flows calculated by ¹³¹I-labeled human serum albumin. This discrepancy might have been due to hypertonic shrinkage of the erythrocytes, decreasing hematocrit and thus lowering blood optical density. Another possibility is that the plasma hypertonicity decreased optical density of the dye, possible by aggregating the dye-labeled albumin molecules. The decreased optical density would be interpreted as a decreased dye concentration and an increased blood flow. This type of artifact should also be considered by those who measure cardiac output by indocyanine green dilution in the presence of plasma hyperosmolality such as produced by radiologic contrast media or hyperosmolar clinical states.

Mass, and therefore kinetic energy, of the hypertonic infusates exceeded mass and kinetic energy of the control isotonic infusates. Infusate kinetic energies greater than 10,000 g cm² sec⁻² have been shown to cause hemolysis and vasodilatation (16). Calculations, however, indicate that at the two lower dose levels of hypertonicity, infusate kinetic energy did not exceed 8500 g cm² sec⁻² and therefore probably did not create hemolysis. At the highest dose level, infusate kinetic energy was approximately 12,000 g cm² sec⁻², and slight
hemolysis may have contributed to some of the increases in blood flow in some subjects.

Considering these possible sources of technical error, the results of the present experiments indicate that the local response to hypertonic dextrose or hypertonic NaCl in the vascular bed of the limb of man is a decrease in vascular resistance, the magnitude of which is a function of the level of plasma osmolarity. An increase in calculated limb blood flow and decrease in calculated limb vascular resistance occurred in response to all 60 hypertonic dextrose or hypertonic NaCl infusions. Hence the response in the limb of man to these agents is similar to responses in most vascular beds of other mammals, including dog hindlimb (1, 2), forelimb (3-5), kidney (6), brain (7), ileum (J. Dabney and C. C. Chou, unpublished observations), skeletal (8) and heart (1, 9) muscle, and cat skeletal muscle (10). Exceptions are the dog lung, where hypertonic dextrose (and many other vasoactive agents) elicits no response (19), and the dog kidney, where hypertonic NaCl solution only transiently decreases resistance (6).

The mechanism of the decrease in vascular resistance evoked by hypertonicity is uncertain and may involve combinations of increases in vessel caliber and changes in blood viscosity. Changes in blood viscosity might be due to decreased concentration, decreased size, increased aggregation, or deformity of erythrocytes. In the present experiments, hematocrit of limb venous blood measured during hypertonic infusions was similar to that during control isotonic infusions, indirect evidence suggesting that changes in blood viscosity due to decreased concentration of erythrocytes contributed little to the response observed. Other available evidence suggests that changes in viscosity do not significantly contribute to the decrease in vascular resistance. In the dog forelimb in vivo, hyperosmolarity increases the viscosity of whole human blood measured at low shear (20). An increase in viscosity would increase vascular resistance, an effect opposite to that observed in the present experiments.

Hypertonic infusions may increase vessel caliber by passive vasodilatation due to interstitial space dehydration, decrease in extravascular pressure and resulting increase in transmural pressure. Dog forelimb weight decreases during intrabrachial arterial hypertonic infusions in the face of reduced vascular resistance, indicating movement of fluid from the extravascular to the intravascular space and extraluminal dehydration (4). The present experiments do not provide information about the role of this mechanism, but other available evidence suggests that it has only a minor part in the response to plasma hypertonicity; it has been reported that renal lymphatic vessel pressure and venous resistance undergo only minor changes during intrarenal arterial infusions of hypertonic dextrose (6).

Hypertonic infusions may also increase vessel caliber passively by dehydrating vessel walls. This possibility is more difficult to investigate, and the published data have been recently reviewed (6).

Active vasodilatation most likely plays an important role in the vascular response to increases in plasma tonicity. There are reports indicating that hypertonicity produces negative chronotropic, dromotropic, and inotropic effects on isolated vascular smooth muscle (10, 21). These active effects may be due in part to changes in cell membrane permeability attributable to cellular shrinkage and reduction in size of cell membrane "pores" (21). Active effects might also be due to changes in the gradient of potassium or other electrolytes across the cell membrane (10). These changes in gradients might occur as the result of changes in intracellular, serum, or interstitial electrolyte concentrations resulting from fluid shifts or ion movements in response to hypertonicity. In the present study it was found that venous serum [K⁺] and [Ca²⁺] occurring during the hypertonic infusions were slightly lower than venous serum [K⁺]

Circulation Research, Vol. XXVI, June 1970
and \([\text{Ca}^{2+}]\) during the control infusions of isotonic NaCl. A lower \([\text{Ca}^{2+}]\) might evoke vasodilatation but the lower \([\text{K}^+]\) would tend to evoke vasoconstriction, changes tending to cancel each other. Hence, assuming that venous concentrations reflect interstitial fluid concentrations, net changes in interstitial fluid concentrations of \(\text{Ca}^{2+}\), \(\text{Mg}^{2+}\), and \(\text{K}^+\) probably did not contribute significantly to the vasoactivity observed in the present experiments.

Active arteriolar dilatation in response to hypertonicity may also be evoked by changes in plasma or cellular concentrations of other vasoactive chemicals. These changes might be produced by alterations in equilibria between active and inactive forms of certain chemicals (e.g., polypeptides) secondary to changes in ionic strength of plasma or cellular fluid. However, there are little or no data to support this possibility.

Data from the present experiments indicate a significant positive linear correlation between the magnitude of the decrease in limb vascular resistance and the level of resting or initial limb vascular resistance. This relation was considered in data interpretation. A similar relation between initial resistance and response to hypertonicity also exists in the pump-perfused forelimb of the dog (22). Additionally, a correlation between change in resistance and initial resistance has been reported in man for a number of other vasoactive agents, both vasodilators (14) and vasoconstrictors (23). The mechanism of this relationship may be in part related to changes in the wall-to-lumen ratio (24) and in part attributed to the inverse relation between limb blood flow and concentration of vasoactive agent (18).

Results of the present experiments suggest that steady-state limb vascular responses to hypertonic dextrose and hypertonic NaCl are similar in man.\(^2\) This similarity in steady-state response to dextrose and NaCl has also been reported in the dog forelimb (4 and S. Gazitúa, unpublished observations). The similarity of the vascular responses to equally hypertonic dextrose and NaCl in the limb of man fails to support the view that the sodium ion has a specific vascular effect in man. However, there is a possibility that an increase in viscosity produced by hypertonic dextrose and not by hypertonic NaCl (4) may have masked a difference in effect of the two agents on vessel geometry. In addition, the greater shift of fluid into plasma during infusion of hypertonic NaCl may also have obscured a difference in effect of the two agents on arteriolar resistance. A more conclusive statement about specific vascular effects of the sodium ion might be made if the experiments had allowed observation of the response to changes in the concentration of the sodium ion alone in the absence of possible interaction with changes in plasma osmolarity. Unfortunately, it is impossible to increase serum sodium concentration significantly without significantly increasing plasma tonicity unless some other serum constituent is simultaneously removed, and such removal might also produce vasoactive effects or interaction. Other data from man (25), although also not conclusive, additionally fail to support the view that the sodium ion has specific vascular effects. In view of lack of evidence of a specific vascular effect of the sodium ion in man, it seems unjustified to attribute the vasoconstriction seen in hypertension to direct action of the sodium ion on contractile mechanisms in vascular smooth muscle. Instead of acting directly, the sodium ion may act indirectly on blood vessels in hypertension through changes in response to circulating norarterenol (26), through osmotically induced shifts in water between the intra- and extracellular spaces and passive vasoconstriction (27), or through shifts in water and resulting alterations in

\[^2\]In this regard it is interesting to note that subjective responses to the two agents differed. The infusion of hypertonic dextrose resulted in a transient mild warm sensation in the forearm and hand. In contrast, the infusion of hypertonic NaCl evoked a transient mild sensation characterized as a feeling of aching or numbness and heaviness, especially in the hand and fingers. In no subject were these sensations sufficiently uncomfortable to cause anxiety and changes in blood pressure.
concentration gradients of other vasoactive chemicals, including ions (28).

The present experiments indicate that small increases in limb venous plasma (and thus probably interstitial fluid) osmolarity are accompanied by large increases in limb blood flow. Although the present experiments acutely altered plasma osmolarities, these data suggest that profound decreases in resistance in the limb vascular beds may occur in clinical hyperosmolar states, in which venous plasma osmolarities as high as 424 milliosmols/kg have been reported (12). Although generalized changes in vascular resistance produced by hypertonicity in these conditions would probably be buffered by baroreceptor reflex activity, the shock reported in some of these patients may be attributable in part to the peripheral vasodilatation evoked by plasma hypertonicity.

Mellander et al. (10) found levels of hypertonicity in local venous blood during skeletal muscle exercise in the cat limb which are of sufficient magnitude to account for the arteriolar dilatation. They have suggested that regional hyperosmolarity may play an important role in exercise hyperemia. Calculations made by extrapolation from the dose-response curve (Fig. 4) prepared from the present data indicate that the vascular response to hypertonicity in the limb of man may be slightly less than the response in the limb of the cat reported by Mellander et al. However, the effect in man of hyperosmolarity is compatible with the suggestion of Mellander et al., assuming that skeletal muscle exercise in man is accompanied by increments in venous plasma osmolarity similar to those occurring in the cat limb.

Acknowledgment

The authors are grateful to Drs. Francis J. Haddy and Jerry B. Scott for their helpful suggestions and encouragement. Dr. Roger A. Wolthuis assisted us in some of the initial studies and in the development of the techniques used. The technical assistance of Irwin B. Kirkpatrick, Josephine Johnston, and Linda Risner is greatly appreciated.

References

VASCULAR RESPONSES TO HYPTERTONIC INFUSIONS


Response of the Limb Vascular Bed in Man to Intrabrachial Arterial Infusions of Hypertonic Dextrose or Hypertonic Sodium Chloride Solutions
HENRY W. OVERBECK and GEORGE J. GREGA

Circ Res. 1970;26:717-731
doi: 10.1161/01.RES.26.6.717

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1970 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

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/26/6/717

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/