Blood Hyperosmolality and Pulmonary Vascular Resistance in the Cat

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ABSTRACT

Blood osmolality rises during general muscle exercise. The purpose of this work was to investigate the effect of similar slow, graded rises of blood osmolality on pulmonary vascular resistance. Hyperosmolar solutions of sodium chloride, mannitol, urea, glucose, thiourea and ethylene glycol were infused into the left lower lobe pulmonary arterial branch in the cat. Lobe blood flow, pulmonary arterial, left atrial and systemic arterial pressures were recorded. With the exception of ethylene glycol, all the test solutions caused dose-dependent, reversible reductions in lobe vascular resistance (LVR). Maximal reduction in LVR was 30% of initial value. A rise of blood osmolality of 25 milliosmols/liter, comparable with levels found during exercise, caused a 10% reduction in LVR. Hyperosmolar solutions of ethylene glycol, which has the highest rate of cell wall penetration of the test substances, caused no change in LVR. Bolus injections of 1M solutions of sodium chloride caused rapid transient rises in LVR. It appears that the resistance vessels of the lungs react to graded rises of blood osmolality in a way qualitatively similar to that seen in the resistance vessels of skeletal muscle.

KEY WORDS pulmonary blood flow pulmonary arterial pressure plasma osmolality vascular smooth muscle vasodilatation general muscle exercise

Various types of experimental results have shown that alterations in blood and tissue fluid osmolality can markedly affect vascular smooth muscle. Intravenous infusion of hypertonic solutions elicits dilatation of the resistance vessels in skeletal muscle (1, 2). It has also been shown that the osmolality of venous blood from skeletal muscle rises during exercise (3). The possibility therefore exists that plasma or interstitial fluid hyperosmolality, at least in part, mediates exercise hyperventilation.

During heavy muscular exercise, arterial plasma osmolality can rise by as much as 25 milliosmols/liter (4). The osmolality of mixed venous blood must presumably be elevated even more in this situation. We found it particularly interesting that hyperosmolar solutions have been reported to produce pulmonary arterial hypertension. Two recent reviews (5, 6) state that a rise in the osmolality of the pulmonary arterial blood causes increased vascular resistance in the lung. Experimental results of this type have usually been obtained by rapid injection into the pulmonary artery or into central veins of a 20% sodium chloride solution. West et al. (7) found that hyperosmotic urea caused a fall in pulmonary vascular resistance when infused into the vascular bed of a blood-perfused isolated dog lung with perivascular edema. Hyperosmotic solutions of mannitol, sucrose, and sodium chloride, however, caused a rise in pulmonary vascular resistance in this preparation. In all these experiments, very high levels of osmolality (1000 milliosmols or more) were applied, so we decided to reexamine the effects of this type of stimulus on the pulmonary vascular resistance, taking care to create slow, graded rises of pulmonary arterial osmolality. Test substances of different chemical nature and with differences in membrane permeability were chosen.

It was found that slow, graded rises of
Methods
Seventeen cats weighing from 2.5 to 4.5 kg were anesthetized by intraperitoneal injections of sodium pentobarbital (30 mg/kg). Tracheostomy was performed, and intermittent positive-pressure breathing started at 19 strokes/min with an Ideal respiration pump, model 10/24 (C. F. Palmer, London). The end-tidal pressures were kept constant at approximately +9 and +3 cm H₂O by water seals. Systemic arterial pressure was recorded with a strain gauge (Statham P23Db) on a direct-writing polygraph (Sanborn 7700) from a heparin-saline-filled catheter in the femoral artery. A slow drip into a femoral vein of 5% glucose in saline was also started.

The chest was widely opened, using a sternum-splitting incision. The ribs on the left side were retracted, the left upper lobe removed and the hilus of the lower lobe cleaned. Catheters were placed in the main pulmonary artery through the right ventricular outflow track and in the left atrium through its appendage, and the pressures were recorded on the polygraph by appropriate pressure transducers (Statham P23Gb and P23De). Zero levels for the pressure transducers relative to air were set at the level of the left atrium. A thin catheter (P.P. 50) was also introduced into the remainder of one of the arterial side branches to the left upper lobe, and from there advanced into the left lower lobe pulmonary artery. This catheter was later used for infusion of hyperosmolar solutions into the lobe from syringes mounted in a constant-flow infusion pump (Harvard model 947). The period of infusion (usually 1 minute) was kept constant for each test series. Different blood concentrations were obtained by changing the used speed of the infusion pump. Knowing the hematocrit and lobe blood flow, we could calculate the initial change in plasma osmolality for each test.

Blood flow through the lobe was measured from a 2-mm or 2K-mm (i.d.) wraparound, gated, square-wave electromagnetic flow transducer placed on the left lower lobe pulmonary artery. The flowmeter model was Nycotron, type 372 M.

The animal was kept on a heated table and enclosed in a transparent polyethylene tent through which warmed, humidified air was flushed. By these means we were able to maintain deep rectal and lung surface temperatures constant and within normal range. The preparation is a modification of the one described by Hauge and Staub (8).

Plasma osmolality was measured with a Knorr (Berlin) osmometer, and hematocrit was measured using an International microcapillary centrifuge, model MB.

The following test solutions were used: sodium chloride 1 M, mannitol 1 M, glucose 2 M, urea 2 M, thiourea 2 M, ethylene glycol 2 M.

Mean lobe vascular resistance (LV) was calculated as the difference between mean pulmonary arterial and mean left atrial pressures divided by mean lobe blood flow.

Results
In each of 15 cats, two or more of the solutions of sodium chloride, mannitol, urea, and glucose were tested. The solutions were infused into the lobar artery to give initial increments of lobe plasma osmolality in the range of 10 to 200 milliosmols/liter plasma.

![Figure 1](http://circres.ahajournals.org/content/28/3/372/suppl/DC1)

**FIGURE 1**

Effect on lobe blood flow of a rise in blood osmolality of 40 milliosmols/liter. Arrows mark infusion of urea.

Qlobe = flow through left lower lobe; P̄PA = mean pulmonary arterial pressure; P̄LA = mean left atrial pressure; P̄FA = femoral arterial pressure.
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Figure 2

Effect on lobe blood flow of a rise in blood osmolality of 81 milliosmols/liter. The small vertical bars mark infusion of mannitol. Symbols and abbreviations as in Figure 1.

Both the on- and off-effects were quite rapid when this substance was used. In three experiments, lobe blood flow started to fall toward control level before the urea infusion was finished. In two experiments with urea infusion, a slight rebound effect was seen. It consisted of a transient rise in resistance, which was evident just after the end of the infusion. In contrast, when mannitol was used, the off-effect was slow and gradual, as demonstrated in Figure 2. Increments in calculated lobe plasma osmolality above 75 milliosmols/liter in one-third of the tests caused some changes also in vascular pressures, as demonstrated in this figure. The pulmonary arterial pressure rise never exceeded 3 mm Hg; the left atrial pressure rise never exceeded 2 mm Hg. When a solution of 0.9% sodium chloride was infused at the same rates and with the same volumes, no vascular responses were seen.

Figure 3 is a composite diagram covering all the data from this set of experiments. The calculated initial rise in plasma osmolality for each substance is plotted against the change in LVR, expressed as percent of pretreatment value. Although the four substances are chemically different, no systematic difference in their ability to reduce LVR could be detected. There was, however, a wide variation between individuals in the sensitivity of the preparations to hyperosmolar solutions. The maximal effect obtained was a 30% reduction in LVR. Such a response was obtained with a calculated elevation of plasma osmolality of about 200 milliosmols/liter.

In Figure 4 the vascular responses to the four test substances are pooled, and a common dose-response curve combining all the tests performed is given. Mean reductions of LVR are plotted against rising levels of osmolality. Vertical bars give standard error of the mean.

Throughout this work we used calculated osmolality as reference instead of measured venous lobar blood osmolality. The reason for this is that sampling of lobar venous blood during infusions would by itself cause changes...
Calculated rise in plasma osmolality

(ΔmOsm/L)

0 100 200

15 20 25

50 100 150

0

Measured ΔmOsm/L

Calculated ΔmOsm/L

50 100 150

Calculated rises in lobe plasma osmolality caused by the in vivo infusions of hyperosmolar solutions plotted against measured rises in plasma osmolality caused by similar in vitro additions of hyperosmolar solutions to samples of whole blood. Because of water flux out of the red cells, the measured values are lower than the calculated ones.

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in LVR, since the outflow pressure from the lobe would be affected. As an alternative to such direct sampling we carried out a series of measurements of cat plasma osmolality before and after in vitro additions of hyperosmolar solutions of the four test substances.

Freshly drawn heparinized blood had osmolality levels of 318, 323, and 310 milliosmols/liter, respectively. Each figure is the mean of four measurements, the variation between individual measurements being less than ±5 milliosmols/liter. To samples of 3 ml whole blood from each cat were added 0.1, 0.3, and 0.6 ml of our standard solutions of glucose, mannitol, urea and sodium chloride. After such an addition, the blood samples were centrifuged and the new plasma osmolality measured. By subtracting the initial plasma osmolality the rise in osmolality was found.

The time elapsing from the in vitro additions of hyperosmolar solutions to separation of the plasma fraction varied from ½ to 3 minutes.

Expected rise in plasma osmolality upon these in vitro additions of the hyperosmolar solutions was also calculated. The initial hematocrit was here taken into account, and flux of water across the red cell membranes was ignored in these calculations. Calculated and measured rises in plasma osmolality are plotted in Figure 5. Not unexpectedly, measured values were systematically lower (15% to 25%) than the corresponding calculated ones. This indicates that the stimuli actually presented to the pulmonary vascular bed in the in vivo experiments were somewhat smaller than the calculated values given. This must be primarily due to water flux across the red cell membranes in transit from the infusion catheter to the resistance vessels.

By increasing extracellular osmolality in a cat portal vein Johansson and Jonsson (9) showed that the occurrence of a fall in the smooth muscle cell volume was accompanied by inhibition of its electrical and mechanical activity. According to their findings, the smooth muscle fibers act as an osmometer. The effect of various hyperosmotic solutions will therefore depend on the ability of the solutes to penetrate the smooth muscle wall.
To obtain information on this particular point, we carried out four additional experiments using thiourea and ethylene glycol as test substances. Both substances have a considerably higher ability to penetrate smooth muscle cells than have the four test substances just described (10). Of the two additional substances, ethylene glycol has again the highest rate of cell wall penetration. Each of the two substances was tested on two preparations. The responses to thiourea were not detectably different from those to sodium chloride, urea, mannitol, and glucose. However, no response could be elicited when ethylene glycol was the test substance. The highest infusion rate used for this substance gave a calculated initial rise in plasma osmolality of 200 milliosmols/liter.

Finally, six rapid bolus injections of 0.5 to 2 ml of 1M sodium chloride were carried out in two cats. The effect of such injections was a rapid but transient rise in LVR.

Discussion

It is conceivable that the rise in lobar blood flow induced by hyperosmolar solutions results solely from shrinkage of red blood cells and thereby a change in the rheological properties of the blood going through the lobe. This possibility, however, is unlikely to be correct, since hyperosmolar solutions can induce a fall in pulmonary vascular resistance even in the absence of red blood cells. In a recent series of experiments (11) using isolated rabbit lungs perfused with plasma at constant volume inflow, we found that slow, graded rises in perfusate osmolality caused reductions in the inflow pressure.

Another possibility discussed by West et al. (7) is that hyperosmolar solutions may reduce pulmonary vascular resistance by dehydrating the lung. In an isolated, perfused dog lung they could demonstrate a fall in vascular resistance in the dependent edematous region after administration of urea. A perfusate osmolality of well above 3000 milliosmols/liter was created in this experiment. Since hyperosmolar solutions of mannitol, sucrose, and sodium chloride did not cause such a reduction in vascular resistance, their explanation of the urea effect is probably incorrect. There is no evidence of edema formation in the present experiments.

A third possibility is that the measured changes in lobar blood flow are recording artifacts caused by changes in perfusate conductivity. However, the similarity of effect of concentrated sodium chloride solution and glucose probably rule out this explanation.

We believe that changes in vascular smooth muscle tone were responsible for the observed rise in lobar blood flow. The large variation between preparations of the responses to a given rise in plasma osmolality most probably reflects variations in the basal tone of the vascular smooth muscle. Only when a substance which is known to penetrate smooth muscle cells very rapidly (ethylene glycol) was used did we observe a complete absence of a dilator response. This latter observation is in agreement with the findings of Johansson and Jonsson (9). Since ethylene glycol is the least osmotically active substance of those tested in the present experiments, it will also be the one least effective in reducing smooth muscle cell volume. If shrinking of the cells is associated with hyperpolarization and inhibition of their electrical and mechanical activity, then the lack of effect of ethylene glycol infusions can be explained as a result of the rapid cell wall penetration of this substance. Also, the rapid off-effects found when urea was used as a test substance most probably reflect the relatively high rate of cell wall penetration of this substance compared with, for example, mannitol.

A disadvantage of the present experimental design is that lobe plasma osmolality will change during infusion of a hyperosmolar test solution. After an initial rapid rise in plasma osmolality, a gradual reduction will follow as a consequence of the increased lobar blood flow induced. The response itself will reduce the strength of the stimulus. This is the reason initial rises in osmolality have been used as reference. As shown by the in vitro studies, flux of water across the red cell membranes will also change the plasma osmolality in such
a way that our dose-response data will give an underestimate of the potency of hyperosmolarity as a vasodilator stimulus.

Since cardiac output in an anesthetized cat is about 130 ml/kg and total blood volume is about 70 ml/kg (12), some recirculation of test solutions therefore must take place during the last one-third of the 1 minute infusion periods. Because of dilution of the small volumes of test solutions in the total blood volume and because of equilibration with the tissues, any secondary rise in osmolality of the blood going through the left lower lobe must, however, be very small indeed.

The maximal fall in LVR which could be obtained in the present tests never exceeded 30% of initial resistance. Rises of plasma osmolality within the range occurring during muscular exercise could reduce LVR by about 10%. Such a blood change may thus conceivably contribute to the fall in pulmonary vascular resistance observed during physical exercise. In this connection it is of interest that moderate rises in plasma osmolality have a positive inotropic effect on the heart (13).

The rapid rise in LVR observed after bolus injections of 1M NaCl solution is most likely a phenomenon of a completely different nature. This particular effect of hyperosmolar solutions has attracted considerable interest, and there is good evidence that it is caused by transient aggregation of blood cells (14, 15).

In conclusion, it appears that the resistance vessels of the lungs react to graded rises of blood osmolality in a way qualitatively similar to that seen in the resistance vessels of skeletal muscle.

References
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