Microcirculatory Perfusion during Volume Therapy

A Comparative Study Using Crystalloid or Colloid in Awake Animals

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Background: Because of the passage of water and salt molecules into the interstitial space, volume replacement with crystalloid solutions requires an amount at least four times that of lost blood. The resulting tissue edema may interfere with nutritive capillary perfusion and oxygen delivery. To prove this hypothesis, the effects of isovolemic hemodilution (hematocrit 30%) with Ringer’s lactate solution or dextran 60 on tissue perfusion and oxygenation were investigated in awake Syrian golden hamsters.

Methods: Experiments were performed by using a chronic dorsal skinfold window giving access to skeletal muscle tissue (musculus cutaneus) with in vivo microscopy, quantitative video image analysis, and surface oxygen partial pressure electrodes. Central venous and arterial pressures were measured by means of chronically implanted jugular venous and carotid catheters.

Results: Isovolemic exchange of blood with dextran caused no significant changes in arterial or central venous pressure, heart rate, capillary flow velocity, functional capillary density, or surface oxygen partial pressure during the 1-h observation period. A volume of Ringer’s solution equal to four times the amount of blood lost maintained arterial pressure and heart rate when central venous pressure was kept at predilution control values. However, tissue perfusion determined by counting perfused capillaries per terminal arteriole was reduced by 62%, and mean tissue oxygen partial pressure decreased from 19 to 8 mmHg.

Conclusions: In this model, volume replacement with artificial colloids yielded hemodynamic stability and adequate tissue oxygen supply, whereas administration of crystalloids alone jeopardized tissue perfusion and oxygenation. (Key words: Fluid therapy; colloids; crystalloids; dextran. Measurement techniques: in vivo microscopy; surface oxygen electrodes. Microcirculation: capillary perfusion; oxygenation.)

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Materials and Methods

To exclude any alterations of the microcirculation that might be caused by even transitory hypovolemia, we used an experimental model in which an acute hemodilution limited to a final hematocrit (Hct) of 30% was produced in two or three steps. After governmental ethics committee approval, the study was performed in 60 awake Syrian golden hamsters (body weight approximately 70 g). For chronic instrumentation, general anesthesia was induced with pentobarbital (50 mg/kg intraperitoneally). Additional pentobarbital was administered intraperitoneally if necessary. A transparent aluminum chamber was implanted for access to the microcirculation. Two symmetric Teflon-coated aluminum frames were placed on a dorsal skinfold so that the double-layered skinfold was secured between the two frames. One layer of the skin was completely removed in a circular area of 15 mm in diameter. The underlying layer consisting of skeletal muscle, subcutaneous tissue, and cutis was covered by a removable glass cover slip. This cover slip was incorporated into one of the frames (fig. 1). Neither antibiotics nor antiinflammatory drugs were used topically or systemically. Permanent catheters, filled with heparin-containing saline (50 IU/ml), were passed from the dorsum to the ventral side of the neck. A carotid artery and jugular vein were cannulated and the catheter tips advanced into the aortic arch and the superior vena cava, respectively. Correct position of the catheters was confirmed by continuous pressure recording.

After 48 h, the viability of the tissue in the chamber was evaluated before randomization by the same observer (VB) by using the following established criteria:

1. absence of petechial hemorrhage
2. absence of macroscopic edema
3. no signs of inflammation such as leukocyte rolling or sticking at venular walls, increasing vasodilation or neovascularization
4. blood cell velocity in collecting venules greater than 0.3 mm/s
5. presence of spontaneous arteriolar vasomotion

For observation, the awake animals were trained to crawl into a tube (methylmethacrylate ester polymer). This tube minimized movements by the animal. Within 5–10 min the animals became accustomed to the restricted movement. Blood pressure recordings and a blood gas analysis (volume withdrawn 0.1 ml) were then performed. The following criteria were used: mean arterial blood pressure greater than 80 mmHg, central venous pressure (CVP) −2 to +6 mmHg, heart rate 340–480 beats/min, arterial oxygen partial pressure greater than 60 mmHg, arterial carbon dioxide partial pressure 35–45 mmHg, and pH 7.28–7.42. All values were within these criteria and the animals were randomly assigned to one of two studies.

Study A

The microcirculation of the skeletal muscle tissue in the chamber of 30 awake hamsters was observed by intravital microscopy. To obtain an Hct of approximately 30%, isovolemic hemodilution was performed in 12 hamsters using dextran 60 (6%, 60,000 Da) administered in two or three steps with intermittent Hct determinations. The exchange volume was 19.1 ± 1.5 ml/kg (mean ± SD). In 12 hamsters hemodilution was performed in increments using Ringer’s lactate solution; 20.3 ± 4.3 ml/kg of blood were exchanged for 79.5 ± 15.9 ml/kg Ringer’s solution. To ensure normovolemia and to maintain CVP at predilution values, the crystalloid was infused during the 1-h observation. Hemodilution was not performed in 6 control animals. The system used for video microscopy consisted of a modified Orthoplan microscope (Leitz, Wetzlar, Germany) equipped with an epillumination system (Ploemopak, Leitz, Wetzlar, Germany) and a blue filter Block for fluorescence measurement by 0.2 ml of 150,000 Da, in COHU, San Diego, California, Sony-Denmark Instruments were done using figure 2:

- vessel diameter
- erythrocyte velocity between the skinfold and the vessel over a distance of 150 μm
- functional capillary density (i.e., all capillaries per arteriole)

Study B

In 30 awake male hamsters as described above, control and experimental groups were determined on the basis of age. For measurement purposes, warm isotonic saline was perfused through a platinum surface microelectrode carefully avoided using a micromanipulator. 80–120 measurements were taken from the mean and percent hypoxic ranges.

Both studies included 30 min of stabilization, and hemodilution was then performed with 30 and 60 min of hypoxia in the animals of each group. For all other treatment all the animals were exposed to hypoxia for 48 h. From these values were obtained the cerebral perfusion pressure (CPP) values.

Statistics

Because of the lack of normality of the variables (vessel diameters, functiona...
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block for fluorescence microscopy (contrast enhancement by 0.2 ml 5% fluorescein isothiocyanate-dextran, 150,000 Da, intravenously; Pharmacia AB, Uppsala, Sweden). The images obtained by the microscope were recorded with a low-light-level camera (COHU 4410, COHU, San Diego, CA) and stored on video tape (Umatic, Sony-Deutschland, Koeln, Germany). Measurements were done off line and included, as shown in figure 2:

- vessel diameters (by video image shearing)
- erythrocyte velocity (by computation of delay between the signals of two videodensitometers positioned over a blood vessel)
- functional capillary density (by counting of erythrocyte-perfused capillaries of a microcirculatory unit [i.e. all capillaries branching from the same terminal arteriole])

Study B

In 30 awake hamsters hemodilution was performed as described above (dextran n = 12, Ringer’s n = 12, and control n = 6). Oxygen partial pressure was determined on the surface of the tissue in the chamber. For measurements, the cover glass was replaced with warm isotonic saline (30°C). A calibrated eight-wire platinum surface electrode (head diameter 2.4 mm) was positioned randomly over 10–15 different areas using a micromanipulator. Tissue compression was carefully avoided. A single determination consisted of 80–120 values that were recorded within 10 min. The measurements were displayed as a frequency distribution divided in subsets of 5 mmHg each. Arithmetic means and percentage of values in the lowest class (hypoxic range, 0–5 mmHg) were used to compare groups.

Both studies followed the same protocol. After 30 min of stabilization, control values were recorded, and then hemodilution was performed. Additional recordings were made immediately after hemodilution and 30 and 60 min later. After the experiment, half of the animals of each group were followed up without further treatment and with free access to food and water for 48 h. From the remaining animals, blood samples were obtained to determine plasma colloid osmotic pressure (COP) by membrane osmometry.

Statistics

Because of a lack of a normal distribution or inequality of variances (Levene’s test) in several subgroups of all parameters, significant differences were computed using Wilcoxon’s signed rank test within groups. Comparisons between groups were calculated by the Mann-Whitney rank test. For statistical analysis of the surface oxygen partial pressures, sum-histograms were compiled by averaging the frequencies in each class of 5 mmHg because the measuring device did not record numerical values of single platinum wires. The arithmetic means of the individual histograms and the percentage of values in the lowest class also were compared by nonparametric tests. Testing of skewness and kurtosis was not possible because of the lack of single numerical values, and thus the shape of the histograms was evaluated only in a descriptive way. Differences in survival were analyzed with the chi-square test. Statistical calculations were done using a commercial software package (SPSS Inc., Chicago, IL).

Results

Macrocirculation

Mean arterial pressure and heart rate were unchanged in the two studies throughout the experiment. In the crystalloid, in which 20.3 ± 4.3 ml/kg blood had been replaced by 79.7 ± 15.9 ml/kg crystalloid, an additional 60.9 ± 31.9 ml/kg Ringer’s had to be infused during the observation period to maintain CVP at predilution values. In this group, COP decreased

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significantly compared with that in the undiluted control animals (26.4 ± 4.4 vs. 13.4 ± 2.5 cmH₂O, \( P < 0.001 \)), and body weight increased by 13%. These parameters did not change in dextran-treated animals. During hemodilution, there were no significant changes in arterial oxygen partial pressure or arterial carbon dioxide partial pressure.

**Microcirculation**

In all three experimental groups no statistically significant change in the diameters of the terminal arterioles, capillaries, and collecting venules was observed. In control and colloid-treated animals, capillary erythrocyte velocity (table 1) remained at predilution values. In contrast, a statistically significant decrease in mean capillary erythrocyte velocity was observed in the crystalloid group. Figure 3 shows the velocity distribution profile in the dextran group mean capillary erythrocyte velocity was unchanged until 60 min after dilution. The profile for the Ringer’s group was bimodal: in 70 of the 109 vessels flow had ceased, whereas the erythrocyte velocity in the perfused capillaries remained in the predilution range. The reduced functional capillary density (\( P < 0.01 \), table 1) also indicated heterogeneity of perfusion during crystalloid dilution. Erythrocyte velocity and functional capillary density did not change in control or colloid-treated animals.

**Surface Oxygen Partial Pressures**

In all three groups tissue surface oxygen partial pressures were distributed in a bell-shaped, physiologic histogram during the predilution phase (fig. 4). The apparent distribution of oxygen partial pressure remained unchanged in control and colloid-treated animals, indicating homogeneous tissue oxygenation during colloid dilution. The mean values did not change significantly (table 1). In contrast, the histogram of the crystalloid-treated animals appeared shifted to the left 60 min after dilution. Mean surface oxygen partial pressure was markedly reduced at this time, and 56% of the values were in the hypoxic range of 0–5 mmHg (\( P < 0.01 \); table 1).

**Table 1. Hematocrit (Hct), RBC Velocity (vRBC), Functional Capillary Density (FCD), Mean Surface \( P_a \), and Percentage of \( P_a \) Values in the Lowest Class (Hypoxic Range) during Control Experiments (Control) and before, Immediately, and 60 Minutes after Hemodilution (HD) with Dextran 60 (Dx) or Ringer’s Lactate Solution (RL)**

<table>
<thead>
<tr>
<th></th>
<th>Before HD</th>
<th>End of HD</th>
<th>60 Min Later</th>
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<tbody>
<tr>
<td><strong>Hct (%)</strong></td>
<td></td>
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<tr>
<td>Ctrl (n = 12)</td>
<td>49 ± 2</td>
<td>48 ± 2</td>
<td>48 ± 2</td>
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<tr>
<td>Dx (n = 22)</td>
<td>46 ± 3</td>
<td>29 ± 6</td>
<td>30 ± 1</td>
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<tr>
<td>RL (n = 22)</td>
<td>46 ± 3</td>
<td>30 ± 1</td>
<td>30 ± 1</td>
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<tr>
<td><strong>vRBC (mm/s)</strong></td>
<td></td>
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<tr>
<td>Ctrl (74 caps)</td>
<td>0.34 ± 0.1</td>
<td>0.37 ± 0.1</td>
<td>0.34 ± 0.2</td>
</tr>
<tr>
<td>Dx (96 caps)</td>
<td>0.34 ± 0.1</td>
<td>0.35 ± 0.1</td>
<td>0.30 ± 0.2</td>
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<tr>
<td>RL (105 caps)</td>
<td>0.35 ± 0.1</td>
<td>0.30 ± 0.2</td>
<td>0.10 ± 0.2†</td>
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<tr>
<td><strong>FCD (n/unit)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Ctrl (n = 6)</td>
<td>8 ± 2</td>
<td>8 ± 2</td>
<td>8 ± 2</td>
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<tr>
<td>Dx (n = 10)</td>
<td>9 ± 3</td>
<td>9 ± 3</td>
<td>7 ± 4</td>
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<tr>
<td>RL (n = 10)</td>
<td>11 ± 6</td>
<td>9 ± 5</td>
<td>3 ± 3†§</td>
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<tr>
<td><strong>( P_a ) (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ctrl (n = 6)</td>
<td>19 ± 3</td>
<td>19 ± 4</td>
<td>19 ± 4</td>
</tr>
<tr>
<td>Dx (n = 12)</td>
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<td>19 ± 4</td>
<td>18 ± 4</td>
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<tr>
<td>RL (n = 12)</td>
<td>20 ± 4</td>
<td>15 ± 3†</td>
<td>8 ± 3†§</td>
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<td><strong>Hypoxic range (%)</strong></td>
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<tr>
<td>Ctrl (n = 6)</td>
<td>0 ± 1</td>
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<td>0 ± 1</td>
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<tr>
<td>Dx (n = 12)</td>
<td>0 ± 1</td>
<td>1 ± 1</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>RL (n = 12)</td>
<td>1 ± 1</td>
<td>2 ± 3</td>
<td>35 ± 20†§</td>
</tr>
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</table>

Values are mean ± SD.
CAPS = total number of registered capillaries in each group.

\* \( P < 0.05 \), within group.
\( \dagger \) \( P < 0.001 \), within group.
\( \ddagger \) \( P < 0.05 \), Dx versus RL.
\( \ddagger \) \( P < 0.05 \), Dx versus RL.

**Fig. 3. Distribution profiles of capillary erythrocyte velocities before, immediately after, and 60 min after hemodilution with dextran or Ringer’s solution. For each study, the histograms combine n single determinations performed in 12 animals in each group. Values (x) are given as means ± standard deviation.**

**Survival**

All of the control (n = 12) animals survived. In contrast, only 7 of 10 animals in the solution were alive after 24 h; 6 of these died within 48 h, only one survived after 48 h, and all had a final body weight of less than 0.01. No signs of anemia were noted on microscopic examination of the blood samples, and no deaths were attributed to the hemodilution procedure.

**Discussion**

Despite much fanfare, there is no agreement on the best performance fluid. Fluids such as saline and Hartmann’s solution are still the colloid of choice. The present study demonstrated that the best performing fluid is colloid and the best colloid is dextran. As far as the authors are concerned, dextran is the best colloid. The advantage of colloid is that it is more effective in maintaining intravascular volume than crystalloid, which is lower in oncotic pressure. In fact, it is the only fluid that can replace interstitial fluid by as much as 40% of the body weight. However, dextran is not the best colloid for all situations. For example, in patients with renal failure, dextran should be avoided because of its potential nephrotoxicity. In patients with sepsis, dextran should be avoided because of its potential proinflammatory effects. In patients with cardiac failure, dextran should be avoided because of its potential to increase cardiac workload. In patients with liver failure, dextran should be avoided because of its potential to increase portal venous pressure.

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Fig. 4. Distribution profiles of surface oxygen pressures before, immediately after, and 60 minutes after hemodilution with dextran or Ringer’s solution. For each study, the histograms combine single determinations performed in 6 control animals and 12 animals in each experimental group; x is the arithmetic mean value.

Survival

All of the control (n = 6) and colloid-treated (n = 12) animals survived the 48-h observation period. In contrast, only 7 of the 12 hamsters treated with Ringer’s solution were alive 24 h (P < 0.05) after dilution. After 48 h, only 2 animals in this group were alive (P < 0.01). No signs of pulmonary edema could be found on macroscopic section. In 1 animal (Ringer’s group, death on the 2nd day), the venous catheter had perforated the vena cava. All other catheters were positioned satisfactorily.

Discussion

Despite much discussion over the past two decades, there is no agreement on whether volume resuscitation is best performed with exclusively crystalloid solutions, such as saline and Ringer’s, or a combination of crystalloids and colloids, such as hydroxyethylstarch or dextran. As far as pulmonary function is concerned, most investigators agree that neither the crystalloid nor the colloid regimen has specific advantages or disadvantages. In fact, the lungs remain unaffected by large amounts of fluid and a wide variation in COP, perhaps because of their capacity to increase lymphatic drainage by as much as 400%.11 The adjustment of transcapillary osmotic gradients by redistribution of interstitial albumin may be an additional mechanism of pulmonary adaptation to large volume or COP shifts.12-14 However, function of tissues other than the lungs, where these mechanisms are less effective, might be compromised by large volume or COP shifts.

Most previous investigations that studied organ perfusion during fluid resuscitation used models of severe circulatory shock. In these models, the capillary endothelium may have been altered before the onset of volume therapy by persistent ischemia and hypoxia or circulating toxins. However, clinical practice is different: hypovolemia can be caused by an increase in vascular volume in the capacitance system (vasodilating anesthetics,15,16 or ventilation using positive end-expiratory pressure17), fluid redistribution into a “third space,” blood loss during surgery, or trauma. These are situations where early fluid substitution is intended to maintain normovolemia in patients with an intact vascular system. Moreover, previous studies comparing the crystalloid and colloid treatment regimens did not investigate the effect of fluid composition on nutritive capillary perfusion, which is crucial for organ function and tissue viability.

The most direct method to investigate the microcirculation is by in vitro microscopy.18 With our technique, the microvessels in the hamster skinfold chamber could be studied in the awake animal without acute surgical trauma. This technique also avoids the side effects of anesthesia, controlled ventilation, and trauma-induced acute inflammation that are inevitable accompaniments of other microcirculation models.19,20 Electron-microscopic studies demonstrated the structural integrity of this chronic preparation.21 The observations in the current study were confined to the microcirculation of a bundle of skeletal muscle from the dorsal midline of the skin to the anterolateral thorax (musculus cutaneus), but the results may be representative for skeletal muscle tissue.

A protocol using incremental isovolemic hemodilution was chosen to minimize endothelial trauma, activation of mediator cascades, and baroreceptor reflexes that may occur even during transitory hypovolemia. The exchange volume of approximately 19.5 ml/kg is comparable to an acute blood loss of 1,300 ml in an adult human. In accordance with previous studies,1,12 a four times larger volume of crystalloids was infused to maintain the intravascular fluid volume as estimated by measuring CVP despite the rapid transcapillary equilibration of these solutions. In a shock model used by Wang and coworkers,21 a rapid infusion of four times
of the volume lost increased CVP to nearly 200% of preshock level, but microcirculatory blood flow as measured by laser Doppler flowmetry could not be restored. In the animals of the colloid group no further fluid therapy was necessary to maintain CVP at predilution values.

During hemodilution systemic oxygen delivery is maintained by increasing cardiac output to compensate for the decreased Hct. The increased flow results in a greater organ perfusion as measured by the radioactive microsphere technique or by electromagnetic flowmeters (for review, see Messmer25). This increase in perfusion is usually attributed to capillary recruitment24 (an increase in perfused capillaries per tissue volume). However, in our study functional capillary density remained constant. Another possible consequence of increased organ perfusion could be an increase in capillary erythrocyte velocity, which also remained unchanged in our study. Similar observations were reported in other models of isovolemic hemodilution in which erythrocyte velocity and erythrocyte flux (the number of erythrocytes passing a capillary per unit time) remained unchanged.24,25 These observations suggest a regulation of erythrocyte flux, which is constitutive for local oxygen delivery.6 During normal conditions the volume fraction (tube Hct) of erythrocytes in microvessels (diameter < 500 μm) is as much as 50% less than systemic Hct, mainly because of a fluid dynamic phenomenon, the Fahraeus effect26: blood cells in the center of the flow profile travel up to two times faster than the marginal plasma layer. Thus, the constancy of capillary erythrocyte flux and velocity (local oxygen transport capacity) during hemodilution with dextran despite an increased organ blood flow may be the result of an increase in capillary plasma velocity. This would be equivalent to a reduction of the Fahraeus effect. Unfortunately, capillary plasma velocity cannot be quantified with current techniques. However, this hypothesis is confirmed by experiments showing that erythrocyte flow fraction (discharge Hct) of biologic capillaries approximates systemic Hct at various degrees of hemodilution.28 In addition, an increased ratio of tube to systemic Hct during progressive hemodilution has been shown.25 Both observations agree with an increase in capillary plasma velocity while erythrocyte velocity remains unchanged.

The mechanism of the presumed increase in capillary plasma velocity remains difficult to understand because dextran does not increase plasma fluidity. (Hemodilution increases whole-blood fluidity by diluting the blood cells, which generate most of blood's viscosity.) However, dextran has recently been shown to form a 50–100 nm–thick layer on the luminal surface of capillary endothelium thereby reducing negatively and positively charged domains.29 It may be that plasma flow is facilitated by reduced interaction of endothelial receptors with specific plasma proteins (e.g., procoagulatory factors or albumin).

The decreases in capillary perfusion and tissue oxygenation in the animals hemodiluted with Ringer's occurred progressively. This finding suggests that a slow process initiated by Ringer's lactate infusion rather than rheologic properties of that solution caused the changes in our study. The progressive formation of tissue edema may be the underlying mechanism of these changes. In the Ringer's group, gradual worsening of the quality of the microscopic pictures (blurring of cellular and vascular boundaries) was observed 30–60 min after dilution and may have been caused by the increasing tissue edema. Because of the nearly unrestricted passage of Ringer's into the interstitial space, the Starling forces establish a new pressure balance across the capillary wall: interstitial hydrostatic pressure increases by fluid accumulation, and the increasing dilution lowers interstitial oncotic pressure to a greater extent than intravascular oncotic pressure. The resulting inward forces increase intraluminal hydrostatic pressures in capillaries and collecting venules and reduce the arteriolar-to-venular pressure difference. The compensation for increased filtration by lymphatic drainage as in the pulmonary system is insufficient in soft tissues.30 At the same time, endothelial and erythrocyte edema also occur.31 Both factors increase hindrance to capillary perfusion. This is reflected in our data by the decrease in capillary erythrocyte velocity and functional capillary density. The resulting tissue hypoxia may cause or perpetuate metabolic acidosis as demonstrated during crystalloid resuscitation by Brueckner et al.34

Our findings agree with theoretical calculations by Mirashemi et al.35 Their computer model of total body circulation consists of both series and parallel coupled vascular compartments and a constant pressure and flow source. In their model the lower whole-blood viscosity increases arteriolar pressure and thus the arteriolar-to-venular pressure difference. However, this benefit of hemodilution is only preserved when solutions that are isoncotic to plasma.

The severity of the complications after crystalloid therapy is highlighted by the low survival rates among

References
the hamsters treated with Ringer's solution in our study. Within hours after the experiment, the animals showed loss of appetite and drowsiness, which we interpreted as signs of circulatory failure. Because the change of oxygen-carrying capacity was kept within the range usually considered to be tolerable and was identical in the dextran group, the high mortality is likely to be a consequence of a primary lesion of the terminal vascular bed.

The reduction in oxygen transport capacity in our hamster model is comparable to an acute blood loss of 19.5 mg/kg. When normovolemic conditions are maintained by cell-free substitutes, this reduction is compensated for by an increase in cardiac output. With colloid-containing solutions this compensation is achieved without compromising peripheral oxygen delivery. In contrast, the large volume of colloids needed to maintain normovolemia caused severe edema in skeletal muscle and presumably in other soft tissues. It has been demonstrated in humans in comparable conditions that the resulting malperfusion and hypoxia jeopardize the outcome by increasing the incidence of adult respiratory distress syndrome. Our results add to the evidence that volume therapy should include artificial colloids with their long-lasting, beneficial effect on microvascular perfusion and tissue oxygenation.

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References


pH-Stat Metabolic Hypothesis: A Study of Multiple Trauma

Bradley J. Hindman

Background: Our purpose was to determine if pH-stat or lactate-stat increase the brain tissue oxygen content better by examining the metabolic effect of lowering brain pH by profound hyperventilation or increasing arterial carbon dioxide levels to achieve metabolic suppression.

Methods: New Zealand White rabbits were randomly assigned to A, n = 9) or pH-Stat groups (A, n = 9) or pH-Stat groups. Differences of brain tissue oxygen tension, CBF, metabolic rate for oxygen, and cerebral venous blood flow (CBF) were measured. Control animals at 65 mm Hg arterial pressure had a baseline arterial pressure of 65 mm Hg and 70% of the group was kept at 60 mm Hg arterial pressure. CBF was determined with a flow probe and arterial pressure was increased to 85 mm Hg with aortic catheters. Baseline values were determined in the two groups before control CBF arterial pressure.

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