Systemic hemodynamics and renal function in hemorrhaged dogs resuscitated with cross-linked hemoglobin

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Stulak, John M., Luis A. Juncos, John A. Haas, and J. Carlos Romero. Systemic hemodynamics and renal function in hemorrhaged dogs resuscitated with cross-linked hemoglobin. Am. J. Physiol. Regulatory Integrative Comp. Physiol. 278: R28–R33, 2000.—Cross-linked hemoglobin (XL-Hb) infused into dogs increases mean arterial pressure (MAP) but decreases blood flow to the renal (RBF), mesenteric (MBF), and iliac (IBF) circulations. These actions differ markedly from dextran infusion (which increases RBF, MBF, and IBF without altering MAP) and may be due to scavenging of nitric oxide by XL-Hb. However, because the hormonal milieu regulating regional circulation is altered during hemorrhage (when XL-Hb may be used), we studied whether systemic hemodynamics, RBF, MBF, IBF, and renal excretory function in hemorrhaged dogs was altered when resuscitated with XL-Hb compared with dextran (n = 6 each). Hemorrhage decreased MAP by 25% due to a 75% decline in cardiac output. RBF, MBF, and IBF all fell by 33, 64, and 72%, respectively (P < 0.05 each). There was also a fall in glomerular filtration rate (GFR), urinary flow, and sodium excretion (P < 0.05 each). After resuscitation, MAP, cardiac output, RBF, MBF, IBF, and GFR all recovered to basal values with either XL-Hb or dextran. Urinary flow and sodium excretion increased to above basal levels with dextran (both by 3.5-fold; P < 0.05) or XL-Hb (by 7.5- and 10-fold, respectively; P < 0.05). We conclude that resuscitation with XL-Hb after hemorrhage not only increases MAP, but also restores RBF, MBF, IBF, GFR, and urinary sodium and volume excretion analogously to dextran. The results contrast with those in normal dogs and suggest that nitric oxide inhibition does not impair hemodynamic and renal function recovery during hemorrhage.

renal hemodynamics; nitric oxide; natriuresis; diuresis

IN RECENT YEARS, THE SYNTHESIS of different forms of stroma-free polymerized hemoglobin has been developed for several therapeutic uses including resuscitation of hemorrhagic shock (6, 16, 18, 22, 23). Among them, diaspirin cross-linked hemoglobin (XL-Hb; Baxter Health Care) is one of the most frequently used. However, despite its efficacy in elevating blood pressure, it may not improve visceral or peripheral perfusion because it also possesses vasoconstrictor properties. In fact, we (1) and others (8, 25) have shown that infusion of XL-Hb into normal dogs decreases blood flow to the renal (RBF), mesenteric (MBF), and iliac vascular (IBF) beds, although mean arterial pressure (MAP) was increased. Also of interest was our observation that the increases in MAP were not accompanied by the expected pressure-induced natriuresis, rather there was a decrease in sodium excretion (1).

One property of XL-Hb that may possibly explain both, the decrease in perfusion and sodium excretion, is its ability to scavenge nitric oxide (NO) (2, 11, 13). That is, because NO exerts a tonic renal vasodilator action (14, 19, 20) and inhibits sodium and water transport (4, 14, 19, 27, 28), then XL-Hb (by scavenging NO), may decrease the intrarenal NO levels and thus lead to renal vasoconstriction and sodium retention. Indeed, this has been suggested to be the case in normal animals (1, 11, 21, 25) and thus raises significant concerns about using XL-Hb during hemorrhagic shock, a setting in which visceral and peripheral blood flow is already compromised, because it could potentially worsen hypoperfusion. However, because the regulation of regional perfusion is altered during hemorrhagic hypovolemic shock, it is possible that increases in pressure and/or volume may be more important than NO in maintaining regional perfusion in these situations. Furthermore, little is known concerning the consequences of the potential NO scavenging effect of XL-Hb on renal excretory function during volume resuscitation after hemorrhage. Therefore, in the present study, we measured the changes in systemic hemodynamics, RBF, MBF, IBF, and renal excretory function in dogs during moderately severe hemorrhage and then determined whether recovery of these parameters was impaired when the dogs were resuscitated with XL-Hb compared with dextran (an osmotically equivalent, biologically neutral, volume expander that does not quench NO).

MATERIALS AND METHODS

Twelve mongrel dogs (15–20 kg) were anesthetized with 30 mg/kg of intravenous pentobarbital sodium and then intubated and ventilated according to Kleinman and Radford's nomogram (12). We catheterized the 1) femoral artery to monitor MAP, perform hemorrhage, and collect blood samples, 2) femoral vein for infusion of creatinine (20 mg/min), additional anesthetic, and the XL-Hb or dextran, and 3) left ureter to collect urine samples and measure urine output. Via a left flank incision, we placed Transonic flow probes on the proximal segments of the renal, mesenteric, and iliac arteries for monitoring of RBF, MBF, and IBF. A pulmonary artery catheter was placed to measure cardiac output (CO), right
atrial pressure (RAP), pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP).

After anesthetizing and instrumenting (before hemorrhaging) the dog, a 30-min equilibration period was allowed followed by a 15-min period (basal period) during which we collected the baseline blood flow data. On completion of these basal determinations, the dogs were hemorrhaged by removing blood from the femoral arterial catheter at a rate of 0.8 ml·kg⁻¹·min⁻¹ until MAP had decreased by 25%. Another 15-min equilibration period was allowed, after which we collected blood flow data for 15 min (hemorrhage period). The dogs were then resuscitated by infusing either 6% dextran or XL-Hb into the femoral vein catheter at the same rate as hemorrhage until the exact volume that was lost during hemorrhage was replaced. After this resuscitation, another 15-min equilibration period was allowed. Blood flow data were then collected again after 20 and 40 min had elapsed (recovery periods at 20 and 60 min) to evaluate the effects of XL-Hb and dextran resuscitations. Urine samples were collected during each clearance period to measure urine flow, total and fractional Na⁺ excretion rates, total K⁺ excretion rate, and creatinine levels. Blood samples were obtained at the midpoint of each clearance period to measure electrolytes and creatinine levels. We measured MAP, RAP, PAP, PCWP, and CO during each clearance period. Vascular resistances for the systemic (SVR), pulmonary, renal, mesenteric, and iliac circulations were calculated for each period from the measured data. We assessed the dynamics of blood flow changes to each vascular bed during hemorrhage, called deterioration dynamics: (basal value – hemorrhage value)/time period; and resuscitation, called recovery dynamics: (basal – hemorrhage)/time period. Measurements from both groups (those to receive dextran or XL-Hb) were pooled together when we calculated the deterioration dynamics of each vascular bed.

Plasma and urine creatinine concentrations were measured with a Beckman creatinine analyzer, and creatinine clearance was used to estimate glomerular filtration rate (GFR). Sodium and K⁺ concentrations were measured with a flame photometer (Instrumentation Lab. I. L943).

Statistical analysis. Results are expressed as means ± SE. Results from the control periods were compared with the posthemorrhage period, and the results from the postresuscitation periods were compared with the control and posthemorrhage periods with a randomized block analysis of variance. When the F value yielded a value of P < 0.05, differences between clearances were determined by Newman-Keuls multiple range test. Differences between XL-Hb and dextran groups were evaluated by an unpaired Student’s t-test.

RESULTS

Cardiovascular. Systemic hemodynamic data during the basal, hemorrhage, and resuscitation periods are shown in Fig. 1 and Table 1. Hemorrhage decreased MAP in both groups by ~25% (from 137 ± 4 to 100 ± 5 and 130 ± 3 to 100 ± 4 mmHg for the dextran and XL-Hb groups, respectively). This decrease in MAP was characterized by a decrease in CO of ~75% (from 3.3 ± 0.4 to 1.3 ± 0.1 and from 3.7 ± 0.5 to 1.5 ± 0.2 l/min, respectively) and an increase in SVR of 76–85%. These parameters were accompanied by the expected reductions in PAP and PCWP.

Full volume resuscitation with XL-Hb restored MAP to basal levels within the first 20-min period (130 ± 3 mmHg), and this remained stable throughout the remainder of the experiment (136 ± 3 mmHg at 60 min of resuscitation). This was initially induced by an increase in CO, which reached basal values at 20 min postresuscitation (3.5 ± 0.3 l/min), accompanied by an appropriate decrease in SVR (from 185% to 98% of basal). However, at 60 min postresuscitation, CO had declined to below basal values (2.9 ± 0.3 l/min) and MAP was maintained at the expense of an increase in SVR to 128% of basal values. XL-Hb also increased PAP and PCWP to basal values.

Dextran resuscitation also restored MAP within the first 20-min period (135 ± 4 mmHg), and this remained stable until termination of the experiment (139 ± 4 mmHg at 60 min). As with the XL-Hb resuscitation, the increased MAP was a product of an increase in CO, which was well above basal levels at 20 min (5.1 l/min) but declined to near basal values at 60 min (4.1 l/min). These changes in CO were accompanied by the corresponding decrease, and then increase, in SVR at 20 and 60 min, respectively. Dextran resuscitation also increased PAP and PCWP to basal values.

Regional blood flows. As shown in Figs. 2 and 3, hemorrhage decreased RBF (from 165 ± 14 to 106 ± 11 and 143 ± 8 to 87 ± 10 ml/min in the XL-Hb and dextran groups, respectively), MBF (from 281 ± 31 to 120 ± 12 and 203 ± 16 to 66 ± 5 ml/min, respectively), and I BF (from 173 ± 23 to 52 ± 13 and 148 ± 22 to 87 ± 10 ml/min, respectively). XL-Hb increased flow to all three vasculatures to basal levels by 20 min (151 ± 14, 320 ± 38, and 200 ± 31 ml/min for RBF, MBF, and I BF, respectively), which remained stable at 60 min (140 ± 14, 297 ± 35, and 149 ± 14 ml/min, respectively). Dextran increased the flow to all three vasculatures to above basal levels at 20 min (192 ± 24, 306 ± 41, and 267 ± 35 ml/min, respectively), and, despite dropping
somewhat, they remained at control values at 60 min (146 ± 20, 256 ± 30, and 181 ± 21, respectively).

Renal excretory function. As seen in Fig. 4, GFR fell in the dextran group after hemorrhage (from 24 ± 4.1 to 10 ± 2.7 ml/min). It then increased from the hemorrhage value at 20 min after dextran resuscitation (41 ± 6.6 ml/min) and was restored to near control values after 60 min (30 ± 5.0 ml/min). GFR also tended to decrease but did not reach statistical significance in the XL-Hb group with hemorrhage (from 22 ± 2.7 to 15 ± 4.0 ml/min); however, XL-Hb resuscitation significantly increased it at both 20 and 60 min (32 ± 6.2 ml/min).

Urinary flow rate also decreased with hemorrhage in the dextran group from 0.14 ± 0.02 to 0.07 ± 0.01 ml/min (Fig. 4), and increased (to above basal levels) after dextran resuscitation to 0.62 ± 0.13 and 0.52 ± 0.12 ml/min at 20 and 60 min, respectively. Urinary flow tended to decrease with hemorrhage in the XL-Hb group (albeit not quite reaching statistical significance: from 0.12 ± 0.02 to 0.08 ± 0.01 ml/min, P = 0.09), and then also increased to above basal values with XL-Hb infusion (to 0.70 ± 0.25 and 0.87 ± 0.26 ml/min at 20 and 60 min, respectively).

Changes in urinary sodium excretion (UNaV; Fig. 4) mimicked those in urinary flow rate, decreasing after hemorrhage in the dextran group (from 19 ± 3t o2 ± 1 µEq/min) and increasing markedly to greater than basal levels with dextran resuscitation (to 53 ± 22 and 67 ± 21 µEq/min at 20 and 60 min, respectively). In the

### Table 1. Systemic hemodynamics before and after hemorrhage and 20 and 60 min after full-volume resuscitation with either dextran or XL-Hb

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basal</th>
<th>Hemorrhage</th>
<th>20 min Posthemorrhage</th>
<th>60 min Posthemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR, mmHg·l⁻¹·min⁻¹</td>
<td></td>
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<tr>
<td>Dextran</td>
<td>45 ± 5.6</td>
<td>79 ± 4.0*</td>
<td>30 ± 4.7†</td>
<td>38 ± 7.0*</td>
</tr>
<tr>
<td>XL-Hb</td>
<td>40 ± 6.6</td>
<td>74 ± 9.6*</td>
<td>39 ± 2.9†</td>
<td>51 ± 6.9*</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>Dextran</td>
<td>2.7 ± 0.2</td>
<td>1.0 ± 0.6*</td>
<td>4.3 ± 0.5†</td>
</tr>
<tr>
<td></td>
<td>XL-Hb</td>
<td>4.4 ± 0.8</td>
<td>2.5 ± 0.7*</td>
<td>5.5 ± 0.5†</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>Dextran</td>
<td>11.5 ± 1.4</td>
<td>7.3 ± 1.0*</td>
<td>13.9 ± 1.5†</td>
</tr>
<tr>
<td></td>
<td>XL-Hb</td>
<td>12.9 ± 0.8</td>
<td>8.2 ± 0.6*</td>
<td>15.6 ± 1.6†</td>
</tr>
<tr>
<td>PVR, mmHg·l⁻¹·min⁻¹</td>
<td>Dextran</td>
<td>3.1 ± 0.3</td>
<td>4.9 ± 0.4*</td>
<td>2.4 ± 0.4†</td>
</tr>
<tr>
<td></td>
<td>XL-Hb</td>
<td>2.4 ± 0.4</td>
<td>4.0 ± 0.6*</td>
<td>3.0 ± 0.5†</td>
</tr>
</tbody>
</table>

Values are means ± SE. XL-Hb, cross-linked hemoglobin; SVR, systemic vascular resistance; PCWP, pulmonary capillary wedge pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance. *P < 0.05 vs. basal period, †P < 0.05 vs. hemorrhage period.
XL-Hb group, UNaV tended to fall with hemorrhage (10 ± 5 to 1 ± 0.3 µEq/min, P = 0.065) and then also increased to above basal levels with XL-Hb infusion (to 84 ± 27 and 105 ± 31 µEq/min at 20 and 60 min, respectively).

Urinary potassium excretion did not significantly decrease with hemorrhage in either the dextran (from 15 ± 3 to 4 ± 2 µEq/min) or XL-Hb groups (11 ± 4 to 6 ± 3 µEq/min). Resuscitation with dextran significantly increased potassium excretion at 20 min (to 42 ± 13 µEq/min, P < 0.05) but dropped back down to basal levels at 60 min (34 ± 10 µEq/min). Resuscitation with XL-Hb also increased potassium excretion at 20 min to 50 ± 12 meq/min (P < 0.05), and they remained elevated at 60 min (56 ± 12 meq/min, P < 0.05).

Deterioration hemodynamics. During hemorrhage, RBF, MBF, and IBF all decreased. RBF deteriorated the slowest (1.9 ± 0.4 ml·min⁻¹·min⁻¹) and the least (33 ± 8%). In contrast, MBF and IBF decreased much faster (5.6 ± 0.9 and 3.5 ± 0.6 ml·min⁻¹·min⁻¹, respectively) with maximum decreases of 64 ± 10% in MBF and 72 ± 16% in IBF.

Recovery hemodynamics. During resuscitation, RBF recovered at equivalent rates with either dextran or XL-Hb (3.7 ± 0.5 and 3.7 ± 0.8 ml·min⁻¹·min⁻¹, respectively). In contrast, recovery of MBF and IBF was faster with dextran than with XL-Hb. MBF rose by 6.4 ± 1.1 ml·min⁻¹·min⁻¹ with dextran compared with 5.5 ± 0.4 ml·min⁻¹·min⁻¹ with XL-Hb (P < 0.05), and IBF rose by 5.3 ± 1.0 ml·min⁻¹·min⁻¹ with dextran vs. 3.5 ± 0.7 ml·min⁻¹·min⁻¹ with XL-Hb (P < 0.05). Despite the differences in the rate of recovery, blood flow to all three vasculatures returned at least up to the basal levels with either dextran or XL-Hb (Figs. 2 and 3). Finally, whereas peak recovery tended to be greater with dextran in all three vascular beds, the differences were not statistically significant.

**DISCUSSION**

We previously found (1) that infusing XL-Hb into normal dogs increased MAP but decreased RBF, MBF, and IBF. Conversely, infusion of dextran did not alter MAP but markedly increased perfusion to the same three vascular beds. This finding was worrisome, because restoring perfusion, rather than increasing MAP, is a main goal during resuscitation. Thus we now studied whether volume replacement after moderately severe hemorrhage (rather than volume expansion in control dogs) with XL-Hb restores MAP and systemic hemodynamics without compromising RBF, MBF, and IBF. In addition, because XL-Hb may impair renal excretion of sodium (1), we also examined whether XL-Hb resuscitation would alter recovery of renal excretory function. We found that volume resuscitation with XL-Hb not only increased MAP, but also increased RBF, MBF, and IBF (in marked contrast to controls). In addition, we found that resuscitation with XL-Hb caused a striking increase in urinary volume and sodium excretion (to well above basal levels), which is also quite different from the response to XL-Hb seen in normal dogs.

We first established a model of moderately severe hemorrhage in which there is clear deterioration of MAP, but not to the degree in which rapid tissue death ensues. We achieved this by bleeding the dogs until their MAP dropped to 35–40 mmHg; this produced the expected hemodynamic changes; that is, CO fell by 75% with a 1.8-fold increase in SVR and a fall in PAP of ~27%. This degree of hemorrhage caused significant, yet not ominous decreases in RBF, MBF, and IBF. We used this model because little is known about the effects of XL-Hb during moderately severe hemorrhagic shock. On the other hand, others have evaluated the efficacy of hemoglobin solutions in restoring MAP, improving tissue perfusion and prolonging survival during very severe hemorrhage (6, 7, 16, 18, 22–24). These studies used models that exhibit extreme reductions in CO, MAP, and organ perfusion, leading to profound tissue ischemia (as manifested by the changes in oxygen consumption and acid-base equilibrium). For example, several studies (6, 7, 24) bled rats until their MAP dropped to 35–40 mmHg; this not only reduced blood flow to the kidneys (by 77%) but also to the heart and brain (by 40%). Whereas using these models is clearly very useful, the information obtained may not necessarily extrapolate to situations of less severe hypoperfusion, because with less severe hypoperfusion there is presumably less tissue damage and/or death, and thus cross-talk between adaptive mechanisms (e.g., increased renin-angiotensin and sympathetic activity) and local factors (e.g., NO or oxygen radicals) may not be the same.

With the use of the present model, we found that full volume replacement with either dextran or XL-Hb was...
very effective at restoring MAP and regional blood flows. The improvement with dextran was due to restoring volemia (and consequently CO) with the expected decrease in SVR. Somewhat surprisingly, however, the improvement in the XL-Hb group was also primarily due to restoration of CO (SVR decreased). This finding is consistent with the effects of XL-Hb during more severe hemorrhage (6, 7, 21–23) and is particularly interesting in view of the well-known vasoconstrictor action of XL-Hb in normal animals (1, 8, 9, 11, 21, 25). Indeed, because XL-Hb-induced vasoconstriction is thought to be (at least partially) due to NO scavenging and hemorrhagic shock is associated with enhanced NO synthesis (29), one might have expected XL-Hb to increase SVR (even more than in normal animals). Yet this was clearly not the case: SVR decreased, and RBF, MBF, and IBF all increased to similar levels as with dextran resuscitation, suggesting that volume restoration by XL-Hb accounts for most of its effectiveness in restoring regional blood flow and that NO scavenging by XL-Hb is not playing a major role. This is consistent with other studies that have reported that inhibiting NO in the absence of volume expansion (during hemorrhagic shock) does not improve hemodynamics (24, 29, 30). In any event, it seems clear that the vasopressor effect of XL-Hb does not aggravate the hemorrhage-induced decreases in regional blood flows.

Despite the similarities between dextran and XL-Hb in restoring systemic and regional hemodynamics, there were some differences. Dextran did increase CO and decrease SVR to a greater degree than XL-Hb. In fact, resuscitation with dextran caused CO to increase to higher than basal values, whereas XL-Hb only restored it to basal levels. Whereas it is tempting to speculate that this more “normal” response might be beneficial, we could not address this possibility in the present study. On the other hand, the differences between therapies in restoring RBF, MBF, and IBF were small, transient, and, with the exception of GFR, not statistically significant, which might argue against the above-mentioned difference in CO and its distribution being important. These possibilities clearly require further study.

Basal levels of RBF and GFR were rather low in the present study (likely due to anesthesia in the setting of volume depletion, as suggested by the low UNaV), but the trends in these parameters caused by the hemorrhage and resuscitation measures should still be valid. In fact, as expected, hemorrhage decreased RBF in all dogs and caused GFR to fall in all the dogs in the dextran group and in five of the six dogs in the XL-Hb group. Recoveries were somewhat different with XL-Hb resuscitation compared with dextran. Dextran caused both RBF and GFR to transiently increase to higher than basal levels, but there was no overshoot with XL-Hb resuscitation. The differences between the groups were transient and reached significance only with the GFR’s. The reasons for the different responses between the two treatment groups are unclear, but may be because the afferent arteriole is very sensitive to NO and thus may be more susceptible to the vasoconstrictor action of the XL-Hb than the remaining vasculature (10).

NO inhibits renal sodium and water reabsorption (4, 14, 19, 20, 27, 28), and, in fact, inhibiting NO with subpressor doses of NO inhibitors decreases the ability of the kidney to eliminate sodium and renders these animals salt sensitive (14, 15, 17, 19, 20). Infusion of XL-Hb into normal dogs also impairs sodium excretion (it increased MAP without increasing sodium excretion) and thus is consistent with its NO scavenging effect. However, in the present study, XL-Hb did not appear to impair UNaV or volume, because they both rose by similar magnitudes during resuscitation with either XL-Hb or dextran. In fact, both parameters increased to well above basal levels with XL-Hb or dextran. Therefore, as with the vascular effects of XL-Hb, it seems unlikely that NO scavenging is playing a role in this setting. Thus the mechanisms responsible for the increased urinary sodium and volume excretion remain obscure but may be due to one of the following possibilities. It may be simply related to the volume replenishment, because two nonrelated volume expanders caused similar increases in urinary sodium and volume excretion. However, whereas this explanation is supported by the increased urinary potassium excretion (consistent with increased bulk flow through the distal nephron), it is hard to explain why the urinary sodium and volume rose to well over basal levels; it is doubtful that redistribution of extracellular fluid could account for the dramatic increases in the sodium excretion rates seen. A second possibility is that hemorrhage may have increased endothelin to natriuretic levels (3), and thus, on replenishing volume (with either XL-Hb or dextran), the natriuresis became apparent. Alternatively, the high endothelin levels together with increased secretion of atrial natriuretic factor during resuscitation may have enhanced each other’s renal excretory actions in the proximal and distal nephron (3, 5, 26), thus leading to the exaggerated natriuresis. Finally, we cannot exclude that hemorrhage simply caused a “stunned kidney” with a transiently impaired reabsorptive capacity and, consequently, an increase in natriuresis.

In summary, we have shown that full-volume resuscitation with XL-Hb in dogs with moderately severe hemorrhage increases MAP (mainly by increasing CO), restores RBF, MBF, and IBF, and induces a marked diuresis and natriuresis. Furthermore, the effects of XL-Hb on regional perfusion and renal excretory function were similar to those seen with dextran resuscitation. Finally, NO scavenging by XL-Hb did not appear to impair recovery of systemic hemodynamics, regional perfusion, or renal excretory function in this model of hemorrhage.

Perspectives

Blood transfusions are a crucial aspect of medical therapeutics but have limitations such as availability, cost, limited shelf life, time-consuming, cross-matching, infectious risk, immunosuppressive effects, and transfusion reactions. These limitations have sparked
great efforts to develop alternatives to blood. Hemoglobin solutions are attractive alternatives to blood but have their own series of problems. Indeed, several of the hemoglobin solutions have vasopressor and renal effects that may be due to alterations in hormones (e.g., endothelin) or local factors (e.g., NO). We previously reported that XL-Hb had marked pressor and antinatriuretic effects in control animals that could be detrimental if they are also present in situations of impaired organ perfusion. However, we now report that XL-Hb in a model that has impaired perfusion does not decrease organ perfusion. In fact, we found that both the vascular and renal excretory effects were markedly different than in control animals, highlighting how a substance can have markedly different effects depending on the conditions. Whereas development of several of these hemoglobin solutions (including the one used in the present study) have now been halted due to concerns of patient safety, others (with similar characteristics) are in different stages of development. Our studies stress the need to further characterize the effects of these solutions in the pathologies in which they are most likely to be used.

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