Oxygen transport by low and normal oxygen affinity hemoglobin vesicles in extreme hemodilution

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The oxygen transport capacity of phospholipid vesicles encapsulating purified Hb (HbV) produced with a P50 at which Hb is 50% saturated (P50) of 8 (HbV8) and 29 mmHg (HbV29) was investigated in the hamster chamber window model by using microvascular measurements to determine oxygen delivery during extreme hemodilution. Two isoosmotic hemodilution steps were performed with 5% recombinant albumin (rHSA) until Hct was 35% of baseline. Isoosmotic exchange was continued until HbV suspended in rHSA solution to a total [Hb] of 5.7 g/dl in blood. P50 was modified by coencapsulating pyridoxal 5’-phosphate. Final Hct was 11% for the HbV groups, with a plasma [Hb] of 2.1 ± 0.1 g/dl after exchange with HbV8 or HbV29. A reference group was hemodiluted to Hct 11% with only rHSA. All groups showed stable blood pressure and heart rate. Arterial oxygen tensions were significantly higher than baseline for the HbV groups and the rHSA group and significantly lower for the HbV groups compared with the rHSA group. Blood pressure was significantly higher for the HbV8 group compared with the HbV29 group. Arteriolar and venular blood flows were significantly higher than baseline for the HbV groups. Microvascular oxygen delivery and extraction were similar for the HbV groups but lower for the rHSA group (P < 0.05); Venular and tissue PO2 were statistically higher for the HbV8 vs. the HbV29 and rHSA groups (P < 0.05). Improved tissue PO2 is obtained when red blood cells deliver oxygen in combination with a high- rather than low-affinity oxygen carrier.

oxygen-carrying capacity; blood substitutes; tissue oxygen; hemoglobin oxygen affinity

PHOSPHOLIPID VESICLES encapsulating concentrated hemoglobin (Hb) solution [Hb vesicles (HbV) or liposome-encapsulated Hb] provide oxygen-carrying capacity to plasma expanders, reproducing several of the characteristics of red blood cells (RBC) suspended in plasma. HbV contain Hb at a high concentration within a cell membrane-like structure. Their oxygen dissociation curve can be adjusted by varying the concentration of pyridoxal 5’-phosphate (PLP). A widely accepted premise for designing a blood substitute is that its Hb should have an oxygen dissociation curve like that of RBC or one that is right shifted, i.e., having a high P50 to facilitate the unloading of oxygen (P50 is the partial pressure of oxygen at which the Hb molecule is 50% saturated). In a previous study by Sakai et al. (16), vesicles were formulated with P50 values set at 9, 16, and 30 mmHg. The study showed that optimal tissue oxygen conditions were obtained when 80% of the circulating blood was substituted with HbV whose P50 was 16 mmHg, a value considerably lower than the usual value of 28 mmHg for normal blood (16). Oxygen-carrying capacity was found to be well above the oxygen supply limitation.

Recent developments in the field of oxygen-carrying plasma expanders (OCPE) based on molecular Hb solutions reported by Tsai et al. (22) show that the addition of comparatively small amounts of a significantly left-shifted polyethylene glycol-conjugated oxygen carrier (P50 ~5 mmHg) to blood in extreme hemodilution leads to baseline microvascular and systemic conditions. This result could not be obtained in identical extreme hemodilution experiments with the use of a right-shifted molecular Hb solution at a considerably higher concentration (19).

Extreme hemodilution in the hamster window chamber model to a hematocrit (Hct) level of ~11% is a powerful tool to test the efficacy of OCPEs in restoring microvascular function and systemic conditions. This Hct is below the threshold at which the organism becomes oxygen supply limited (5, 22, 23). In this scenario, the effects of a blood substitute became magnified upon introduction into the circulation. Furthermore, by encapsulating Hb, a phospholipid vesicle eliminates the problem of Hb extravasation and provides a setting in which the biophysical properties of the infusion solution can be rigorously controlled while allowing for the change in P50. Therefore, experimenting with vesicles that encapsulate Hb formulated with different P50 values provides the unique opportunity to investigate how oxygen affinity regulates oxygen delivery to the tissue by the microcirculation, a value not attainable by lowering RBC Hb P50 by the administration of sodium cyanate, which may introduce changes in tissue metabolism (7). In addition, RBC and HbV are different in size, flow pattern, homogeneous distribution in the plasma phase, and the mechanism of oxygen unloading in capillaries, and direct comparison between RBC and HbV is impossible. All these conditions indicate that the optimal P50 should be different in HbV and RBC.

In the present study, we investigated the microvascular effects of restoring oxygen-carrying capacity in conditions of extreme hemodilution, introducing by exchange transfusion identical amounts of Hb-carrying vesicles in which oxygen affinity was specifically controlled so that P50 was either 8 or 29 mmHg. The P50 value of 8 mmHg was chosen because it is...
similar to that of a recently developed oxygen carrier that is effective at a low concentration (2–4, 22). In these experiments, the hemodilution protocols were performed using a recombinant albumin solution (13) as the plasma expander.

**METHODS**

Investigations were performed in male golden Syrian hamsters (55–65 g body wt) fitted with a dorsal skinfold chamber window (6). This model has been used extensively for investigations of the intact microvasculature of adipose and subcutaneous tissue and skeletal muscle in conscious animals for extended periods. Pentobarbital sodium (50 mg/kg ip) was used for window implantation and for carotid artery and jugular vein catheterization. The microvasculature was examined 4–5 days after the initial surgery, and only animals passing an established systemic and microcirculatory inclusion criteria, which included having tissue void of low perfusion, inflammation, and edema (21), were entered into the study. Animal handling and care followed the NIH Guide for the Care and Use of Laboratory Animals. The experimental protocol was approved by the local animal care committee.

**Preparation of HbV with different P50**. HbV were prepared under sterile conditions as previously reported (12, 15). Hb was purified from outdated donated blood provided by the Hokkaido Red Cross Blood Center (Sapporo, Japan) and the Japanese Red Cross Society (Tokyo, Japan). The encapsulated purified Hb (38 g/dl) contained 0 or 25%, 1.4 ml; Nipro, Osaka, Japan) to regulate the rHSA concentration mixed with a solution of recombinant human serum albumin (rHSA (5%) 0.98, 20

**Acute isovolemic exchange-transfusion (hemodilution) protocol**. Progressive hemodilution to a final systemic Hct level of 11% was accomplished with three isovolemic exchange steps. This protocol, leading to extreme hemodilution while maintaining stable hemodynamic conditions, is described in detail in a previous report by Tsai (19). Briefly, the volume of each exchange-transfusion step was calculated as a percentage of the blood volume, estimated as 7% of the body weight. An acute anemic state was induced by lowering systemic Hct by 60% with two steps of progressive isovolemic hemodilution using 5% rHSA, referred to as exchange levels 1 and 2. Level 1 exchange was 40% of blood volume, and level 2 and 3 exchanges were 35% of blood volume, respectively.

After level 2, the animals were randomly divided into three experimental groups by being assigned to an experimental group according to a sorting scheme based on a list of random numbers (1). Level 2 exchange was followed by level 3 exchange. Hemodilution with 5% rHSA solution was continued with one group of the experimental groups by being assigned to an experimental group according to the NIH Guide for the Care and Use of Laboratory Animals. The experimental protocol was approved by the local animal care committee.

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**Blood chemistry and biophysical properties**. Arterial blood was collected in heparinized glass capillaries (0.05 ml) and immediately acquired.

![Fig. 1. Oxygen dissociation curves for phospholipid vesicles encapsulating purified Hb (HbV) produced with a P50 at which Hb is 50% saturated (P50) of 8 (HbV8) and 29 mmHg (HbV29) vs. the dissociation curve for hamster blood (P50 = 32 mmHg).](http://ajpheart.physiology.org/)

**Table 1. Physical characteristics of solutions**

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Viscosity, cp</th>
<th>COP, mmHg</th>
<th>P50, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>rHSA (5%)</td>
<td>0.98</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>HbV8 (10 g Hb/dl)</td>
<td>2.92</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>HbV29 (10 g Hb/dl)</td>
<td>2.96</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>HbV29/rHSA (8.6 g Hb/dl)</td>
<td>2.87</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>HbV8/rHSA (8.6 g Hb/dl)</td>
<td>2.90</td>
<td>20</td>
<td>29</td>
</tr>
</tbody>
</table>

Viscosity was measured at a shear rate of 160 s⁻¹ at 37°C. COP, colloid osmotic pressure measured at 27°C; P50, partial pressure of oxygen at which Hb is 50% saturated; rHSA, recombinant human serum albumin; HbV8 and HbV29, Hb vesicles with a P50 of 8 and 29 mmHg, respectively.
analyzed for arterial \( \text{PO}_2 \) (\( \text{PaO}_2 \)), arterial \( \text{PCO}_2 \) (\( \text{PaCO}_2 \)), base excess (BE), and pH (Blood Chemistry Analyzer 248; Bayer, Norwood, MA). The comparatively low \( \text{PaCO}_2 \) and high \( \text{PaO}_2 \) values of these animals is a consequence of their adaptation to a fossorial environment. Blood samples for viscosity and colloid osmotic pressure measurements were quickly withdrawn from the animal with a heparinized 5-ml syringe at the end of the experiment for immediate analysis.

Viscosity was measured in a cone/plate viscometer (DV-II+) with a cone spindle (CPE-40; both from Brookfield Engineering Laboratories, Middleboro, MA) at a shear rate of 160 s\(^{-1}\). Colloid osmotic pressure (COP) was measured using the Wescor 4420 colloid osmometer (23).

**Functional capillary density.** Functional capillary density (FCD; in cm\(^{-1}\)) is the total length of RBC-perfused capillaries divided by the area of the microscopic field of view (21). Capillary segments were considered functional if RBC were observed to transit over a 30-s period. FCD was tabulated from the capillary lengths with RBC flow in an area comprising 10 successive microscopic fields (420 \( \times \) 320 \( \mu \)m). Detailed mosaics were made of the chamber vasculature to study the same microvessels throughout the experiment.

**Microhemodynamic parameters.** Arteriolar and venular blood flow velocities were measured online using the photodiode cross-correlation technique (8) (Fiber Optic Photo Diode and Velocity Tracker Correlator model 102B; Vista Electronics, Ramona, CA). The centerline velocity (\( V \)) was corrected according to vessel size to obtain the mean RBC velocity (11). The video image shearing technique was used to measure vessel diameter (\( D \)) online. Blood flow was calculated from the measured parameters as
\[
Q = V\pi(D/2)^2
\]

**Microvascular \( \text{PO}_2 \) distribution.** High-resolution microvascular \( \text{PO}_2 \) measurements were made using phosphorescence-quenching microscopy (18), a method based on the oxygen-dependent quenching of phosphorescence emitted by albumin-bound metallocorphyrin complex after pulsed light excitation. Phosphorescence microscopy is not dependent on the level of dye within the tissue, and the decay time is inversely proportional to the \( \text{PO}_2 \) level. The phosphorescence decay curves were converted to oxygen tensions by using a fluorescence decay curve fitter (model 802; Vista Electronics) (9). This technique has been used in this animal preparation and others for both intravascular and extravascular oxygen tension measurements, because albumin exchange between plasma and tissue allows for sufficient concentrations of albumin-bound dye within the interstitium to achieve an adequate signal-to-noise ratio. Animals received a slow intravenous injection of 15 mg/kg body wt at a concentration of 10.1 mg/ml of a palladium-meso-tetra(4-carboxyphenyl)porphyrin (Porphyrin Products, Logan, UT). \( \text{PO}_2 \) measurements were made 20 min after porphyrin injection, allowing it to be distributed to all the tissues.

In our system, intravascular measurements are made by placing an optical rectangular window (5 \( \times \) 40 \( \mu \)m) within the vessel of interest, with the longest side of the rectangular slit positioned parallel to the vessel wall. Tissue \( \text{PO}_2 \) is measured in regions void of large vessels with the longest side of the rectangular slit positioned parallel to the vessel wall. Tissue \( \text{PO}_2 \) is measured in regions void of large vessels with the longest side of the rectangular slit positioned parallel to the vessel wall. Tissue \( \text{PO}_2 \) is measured in regions void of large vessels with the longest side of the rectangular slit positioned parallel to the vessel wall. Tissue \( \text{PO}_2 \) is measured in regions void of large vessels with the longest side of the rectangular slit positioned parallel to the vessel wall. Tissue \( \text{PO}_2 \) is measured in regions void of large vessels with the longest side of the rectangular slit positioned parallel to the vessel wall.
Data analysis. Results are presented as means ± SD unless otherwise noted. All data are presented as absolute values and ratios relative to baseline values. A ratio of 1.0 signifies no change from baseline, whereas lower and higher ratios are indicative of changes proportionally higher or lower than baseline. The same vessels and functional capillary fields were followed so that direct comparisons to their baseline levels could be performed, allowing for more robust statistics for small sample populations. For repeated measurements, time-related changes were assessed by analysis of variance (ANOVA). Data within each group were analyzed using ANOVA for nonparametric repeated measurement, and when appropriate, post hoc analyses were performed with the Dunn’s multiple comparison tests. For level 3 exchange, groups were analyzed using one-way ANOVA, and post hoc analyses were performed with the Bonferroni post tests. All statistics were calculated using GraphPad Prism 4.01 (GraphPad Software, San Diego, CA). Changes were considered statistically significant if P < 0.05.

RESULTS

Exchange transfusion. Twenty-four animals (55–65 g body wt) entered into the exchange-transfusion (hemodilution) protocol, and all tolerated the experiment without any visible discomfort. Microvascular studies were completed in six preparations for each test material, namely, the level 2 rHSA, HbV8, and HbV29. The data were analyzed using a model for computing oxygen delivery to the tissue at the microscopic level.

Hematological changes. The exchange-transfusion protocol resulted in a final Hct ranging from 11.0 ± 0.5 to 11.4 ± 0.6%. The HbV8 and HbV29 groups had a final plasma Hb concentration of 2.1 ± 0.1 g/dl, which increased the total Hb concentration in blood (RBC + Hb in plasma) to 5.7 ± 0.2–0.3 g/dl after completion of the level 3 exchange transfusion. Thus oxygen-carrying capacities at this level were similar to those found at level 2, where total blood Hb concentration was 5.7 ± 0.3 g/dl (Hct 18.1 ± 0.7) (Table 2).

Systemic and blood gas parameters. Changes in the systemic parameters are presented in Fig. 3. Mean arterial pressure was statistically lower for the extreme hemodilution tests with rHSA and the HbV29 group and attained the highest value with HbV8 viscosity. Heart rate after hemodilution followed by exchange transfusion with the HbV solutions was ~10% higher than baseline at the level 3 exchange. The slight increase in heart rate was not statistically different.

Analysis of arterial blood gases (Table 2) showed a statistical increase in P02 after hemodilution and exchange transfusion. PaCO2 was unchanged from baseline after hemodilution. Blood pH was not statistically changed. At level 3 exchange, BE was positive and not statistically different between HbV groups, but it was negative and statistically different from baseline for the HSA group (P < 0.05).

Colligative properties. Blood viscosities and COP after level 3 exchange were sampled at 1 h and 10 min after completion...
Table 3. Rheological properties and COP

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Blood Viscosity, cp</th>
<th>Plasma Viscosity, cp</th>
<th>COP, mmHg</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>4.2±0.7</td>
<td>1.2±0.1</td>
<td>17.6±0.7</td>
<td>6</td>
</tr>
<tr>
<td>Level 2 rHSA</td>
<td>2.0±0.2*</td>
<td>0.9±0.1</td>
<td>7.2±0.8</td>
<td>4</td>
</tr>
<tr>
<td>Level 3 rHSA</td>
<td>1.6±0.2*</td>
<td>0.9±0.1</td>
<td>17.4±1.1</td>
<td>5</td>
</tr>
<tr>
<td>Level 3 HbV8</td>
<td>1.9±0.3*</td>
<td>1.0±0.1</td>
<td>17.3±0.8</td>
<td>6</td>
</tr>
<tr>
<td>Level 3 HbV29</td>
<td>2.0±0.4*</td>
<td>1.0±0.1</td>
<td>17.8±1.0</td>
<td>5</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = no. of animals studied. Viscosity was measured at a shear rate of 160 s⁻¹ at 37°C. COP was measured at 27°C. Hct are presented in Table 2. *P < 0.05 compared with nondiluted blood.

of the exchange. Table 3 shows that blood viscosity ranges from 1.6 cp (plasma 0.9 cp) for rHSA to 2.0 cp (plasma 1.0 cp) for the HbV groups.

All test materials caused COP to maintain the value for normal blood for this species (5), namely, 17.6 ± 0.7 mmHg at 1 h after the last exchange, showing that introduction of bulk solutions into the circulation caused minor fluid shifts.

Microhemodynamics. After level 3 exchange, arteriolar and venular diameters were not statistically different from baseline for any of the groups. Arteriolar flow velocities attained the highest value for the HbV8 group, being 1.90 relative to baseline. Arteriolar flow velocities attained the highest value for the HbV8 group, being 1.90 relative to baseline. Venular diameters were not statistically different from baseline.

The same effect of the exchange caused significantly higher blood flow velocities in the arteriolar and venular microcirculation (Fig. 4).

Combining data for the RBC flow velocity and diameter allowed calculation of the arteriolar and venular blood flows (Fig. 5). The results of this calculation showed that all exchanges caused blood flow to increase. Arteriolar and venular blood flows at level 3 exchange with the use of rHSA were significantly higher than those at baseline. However, continuing hemodilution with this material to level 3 exchange did not sustain the increase, and arteriolar and venular blood flow, although showing a tendency to remain elevated, were not statistically different from baseline values.

Level 3 exchange transfusion with HbV8 and HbV29 caused blood flow to be significantly higher than baseline. Furthermore, the HbV8 group showed consistently higher blood flows than the HbV29 group; however, the trend was not statistically significant.

Functional capillary density. The number of capillaries with RBC passage upon level 3 hemodilution in the rHSA, HbV8, and HbV29 groups was 62 ± 9, 76 ± 12, and 72 ± 13% of baseline, respectively. These values were statistically different from baseline but not statistically different with respect to each other (Fig. 6).

Microvascular oxygen distribution. Oxygen tension measured using phosphorescence microscopy after level 3 exchange transfusion in the rHSA, HbV8, and HbV29 groups showed that these materials produced virtually identical distributions of arteriolar microvascular PO₂ (arterioles averaged 49.5 mmHg), although HbV8 tended to be higher (Fig. 7). The decrease of RBC from level 2 to level 3 did not decrease the arteriolar PO₂. Venular PO₂ after level 3 was significantly lower than at level 2 exchange in all cases (rHSA, 7.2 ± 3.2 mmHg; HbV8, 15.1 ± 3.7 mmHg; HbV29, 9.6 ± 4.2 mmHg).

Tissue PO₂ values at level 3 exchange were consistently lower than those at level 2 exchange (20.1 ± 2.2 mmHg), with the difference being statistically significant. The highest was attained by the HbV8 group, being 14.0 ± 2.2 mmHg. By comparison, tissue PO₂ for the HbV29 group was 9.2 ± 2.7 mmHg and for the rHSA group, 2.6 ± 1.4 mmHg, which was significantly lower compared with the HbV8 and HbV29 groups (Fig. 7).

Oxygen delivery and extraction. Figure 8 shows the results of the analysis for delivery and release of oxygen by the
Fig. 5. Arteriolar and venular flow (nl/s, means ± SD, n = no. of vessels studied) in each animal group were as follows. Baseline: arterioles (A), 14.8 ± 7.1, n = 76; venules (V), 5.0 ± 2.9, n = 76. Level 1 with rHSA: A, 21.9 ± 9.7; V, 5.8 ± 3.6. Level 2 with rHSA: A, 27.2 ± 16.1; V, 8.3 ± 4.2. Level 3 with rHSA: A, 16.9 ± 6.8, n = 20; V, 5.4 ± 4.8, n = 20. Level 3 with HbV6: A, 23.4 ± 8.1, n = 18; V, 9.9 ± 5.1, n = 18. Level 3 with HbV29: A, 21.0 ± 8.0, n = 18; V, 8.3 ± 5.2, n = 18.

microcirculation. It is apparent that exchanging RBC for HbV₈ maintains oxygen delivery to the tissue, whereas HbV₂₉ reduces this by ~20%, and continued hemodilution with a non-oxygen-carrying material significantly depresses oxygen delivery to the tissue, reducing this to half of that attained at the level 2 hemodilution.

DISCUSSION

The principal finding of this study is that under identical extreme hemodilution conditions, with the use of vesicles encapsulating Hb with normal P₅₀ (HbV₂₉ = 29 mmHg) and low P₅₀ (HbV₈ = 8 mmHg), tissue PO₂ is statistically significantly higher when the high oxygen affinity material is used, namely, 14.0 ± 2.2 vs. 9.2 ± 2.7 mmHg. The significantly increased tissue PO₂ attained with HbV₉ appears to be due to a series of incremental improvements in microvascular and macrovascular hemodynamics comprising the increase of arteriolar blood flow and mean arterial blood pressure, which was significantly higher (P < 0.05) for HbV₈ than for HbV₂₉.

In the hemodilution procedures of this study, blood was exchanged with a rHSA solution as a colloidal plasma expander, which was the same suspending medium used for the Hb vesicles. Therefore, in these experiments, we can make a direct comparison between an oxygen-carrying and non-oxygen-carrying blood substitute, uncomplicated by the presence of additional materials. Our results show that the level 2 hemodilution with rHSA leads to maintained functional capillary density and significantly improved arteriolar and venular blood flow, although somewhat lowered central blood pressure. The latter finding is not necessarily negative and may reflect a lowered overall peripheral vascular resistance due to the decrease of blood viscosity after hemodilution. The fact that microvascular flow is significantly increased indicates that the level 2 hemodilution with rHSA provides the tissue with adequate microvascular perfusion and that this colloid is an adequate plasma expander.

Average oxygen delivery and extraction were somewhat greater for HbV₈ than for HbV₂₉. These are calculated values and are not statistically significantly different; however, the same difference was found in all micro and macro parameters measured in this study.

The level 2 hemodilution and the succeeding level 3 hemodilution with either HbV₈ and HbV₂₉ resulted in the same total Hb concentration in the circulation (5.7 and 5.8 g Hb/dl); however, oxygen delivery was lower with HbV₂₉ and lowest with rHSA, as might be expected due to the low Hb content (3.7 g Hb/dl) in the absence of plasma Hb for the rHSA group. Therefore, because all groups had the same Hct at the level 3 hemodilution, the sustained oxygen consumption and tissue PO₂ relative to the rHSA group clearly demonstrate that Hb vesicles release oxygen. However, the vesicles with the lowest P₅₀ provide an oxygen delivery capacity identical to that of blood at level 2 hemodilution, whereas vesicles with a high P₅₀ lower oxygen delivery at the microcirculatory level, an effect probably caused by the decreased blood flow associated with HbV₂₉.

The differences in tissue PO₂, mean arterial blood pressure, and arteriolar blood flow between HbV₈ and HbV₂₉ show that in designing a blood substitute, it is not sufficient to provide adequate oxygen-carrying capacity. Once a suitable oxygen carrier is available, it also must be able to maintain or enhance other circulatory transport parameters, particularly flow. The Hb vesicles used in this study are vasoactive, and the difference in P₅₀ appears to be a factor in improving flow condition that is not related to vasoactivity. An explanation for this may be related to the inherent variability of tissue PO₂ shown in this and other studies (4, 22), which may be enhanced in extreme hemodilution. This variability determines that if average tissue PO₂ is low, portions of the tissue may become anoxic. Introducing a small quantity of a low-P₅₀ Hb oxygen carrier into the circulation will deliver oxygen only to those parts of the tissue

Fig. 6. Functional capillary density after the level 1, level 2, and level 3 exchanges for the different test fluids. All values are relative to baseline levels. †P < 0.05 relative to baseline.
where the anoxic threshold is passed, thus eliminating the inherent variability of oxygen delivery shown by the variability of tissue PO2.

Considering the significantly improved blood pressure and the trend toward higher flow for HbV8 (in the absence of vasoconstriction and changes in the rheological properties of blood), it is possible that in conditions of extreme hemodilution the cardiac function should be improved because of the proposed more homogenous heart tissue oxygenation using HbV8 vs. HbV29.

In summary, the present results show that either HbV8 or HbV29 are efficient oxygen carriers that do not cause vasoactivity. The experiments were carried out using rHSA as a hemodiluent, and this material was adequate as a plasma volume substitute. Oxygen extraction was similar for both oxygen carriers; however, HbV8 appeared to be beneficial at the systemic level, because base excess remained at baseline levels, whereas it was decreased for HbV29. This finding suggests that improved tissue PO2 and microcirculatory oxygen delivery may be efficient in other tissues. The improvement obtained may be specific to the conditions of these experiments in which the vesicles were tested for their capacity to restore tissue PO2, FCD, and oxygen extraction in the microcirculation during extreme hemodilution. The significant differences in the tissue oxygen parameters produced by the presence of low-P50 Hbs vs. an identical oxygen carrier with normal P50 suggests that small amounts of Hbs with high oxygen affinity may have therapeutic effects in the treatment of ischemic conditions (6).

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