THE EFFECT OF HYDROXYETHYLSTARCH 6% 130/0.4 IN A BALANCED ELECTROLYTE SOLUTION (VOLULYTE®) COMPARED TO GELATINE (GELOPLASMA®) ON TISSUE OXYGEN SATURATION AND MICROVASCULAR REACTIVITY DURING HAEMODILUTION MEASURED WITH NEAR-INFRARED SPECTROSCOPY.

Cathérine VAN EECKHOUT

Promotor: Dr. Anneliese MOERMAN

Co-promotor: Prof. Dr. Stefan DE HERT

Masterproef voorgedragen in de master in de specialistische geneeskunde

Anesthesie en Reanimatie
THE EFFECT OF HYDROXYETHYLSTARCH 6% 130/0.4 IN A BALANCED ELECTROLYTE SOLUTION (VOLULYTE®) COMPARED TO GELATINE (GELOPLASMA®) ON TISSUE OXYGEN SATURATION AND MICROVASCULAR REACTIVITY DURING HAEMODILUTION MEASURED WITH NEAR-INFRARED SPECTROSCOPY.

Cathérine VAN EECKHOUT

Promotor: Dr. Anneliese MOERMAN

Co-promotor: Prof. Dr. Stefan DE HERT

Masterproef voorgedragen in de master in de specialistische geneeskunde

Anesthesie en Reanimatie
Deze pagina is niet beschikbaar omdat ze persoonsgegevens bevat.
Universiteitsbibliotheek Gent, 2021.

This page is not available because it contains personal information.
Ghent University, Library, 2021.
| 1) Abstract                  | p.1 |
| 2) Background               | p.2 |
| 3) Methods                  | p.4 |
| 4) Results                  | p.7 |
| 5) Discussion               | p.10|
| 6) Conclusion               | p.13|
| 7) References               | p.14|
| 8) Summary (Dutch)          | p.18|
**Background and Goal of Study.** During acute haemodilution, blood viscosity and functional capillary density change considerably, leading to microscopic maldistribution of blood flow. It has been suggested that the latest generation colloids might enhance tissue perfusion. This is suggested by the improved rheology of the blood and by the attenuated responses to injury of the endothelial glycocalyx.

Therefore, we conducted a prospective, randomized, blinded study to evaluate the effect of hydroxyethylstarch (Volulyte®) as a priming solution of the cardiopulmonary bypass (CPB) on microvascular reactivity, and compared it with the standard CPB priming in our department, gelatine (Geloplasma®). The experimental hypothesis was that Volulyte® would provide better microcirculatory perfusion than Geloplasma®.

**Materials and Methods.** After ethical committee approval and informed consent, 40 elective cardiac surgery patients were randomized to receive either Volulyte® (n=20) or Geloplasma® (n=20) as the exclusive priming solution. Only crystalloid solutions were used before CPB was established. To evaluate microvascular reactivity, postocclusive reactive hyperaemia (PORH) measured with near-infrared spectroscopy (NIRO-200NX) was examined before and after CPB. PORH refers to the reproducible transient increase in blood flow after release of an arterial occlusion. The velocity and degree of flow restoration depend on the capacity of the microvasculature to recruit arterioles and capillaries, thereby reflecting the integrity of the microcirculation. Recovery times and rate of recovery were determined. Data were compared using the t-test, chi-square test, two-way ANOVA and Mann-Whitney U test, as appropriate.

**Results and Discussion.** After CPB, recovery times were significantly shorter in the Volulyte® group (tM 36 sec [24,104] vs 44 sec [22,81] in the Geloplasma® group, p=0.02). Rate of recovery increased in the Volulyte® group with 31%/min, while it decreased in the Geloplasma® group (-34 %/min), p=0.02 between the 2 groups.

**Conclusion.** The shorter recovery times and increased rate of recovery indicate that Volulyte® might provide better microcirculatory perfusion than Geloplasma®.
BACKGROUND

Volulyte® is a third generation starch containing 6% hydroxyethyl starch (HES 130/0.4) in an isotonic solution, with the electrolyte content adapted to the principal ionic constituents of normal plasma. Several studies demonstrate that colloids improve oxygen transport and tissue oxygenation.\textsuperscript{1-3} The latest generation synthetic colloid solutions might offer further superiority regarding their ability to improve tissue perfusion. This is suggested by the improved rheology of the blood and by the attenuated responses to injury of the glycocalyx.\textsuperscript{1}

Improved rheology of the blood
During acute haemodilution, blood viscosity and functional capillary density (FCD, capillaries with red blood cell transit per unit surface) change considerably, jeopardizing tissue survival because of local microscopic maldistribution of blood flow.\textsuperscript{4} Restoration of blood rheology is a key component in the management of tissue perfusion and oxygenation, independently of the restitution of oxygen carrying capacity.\textsuperscript{5}

The effects of various synthetic colloids and lactated ringer’s solution at various ratios have been evaluated on hemorheological parameters in vitro.\textsuperscript{6} Gelatine significantly accelerated the erythrocyte aggregation and elevated the plasma viscosity compared to hydroxyethyl starch. HES did not change the erythrocyte aggregation compared to the control.

HES 130/0.4 has been compared to conventional HES solutions in the setting of normovolemic haemodilution.\textsuperscript{1} HES 130 solution showed to have a better molecular size for improved rheology. This resulted in increased skeletal muscle oxygen tension.\textsuperscript{1} The authors demonstrated that increased viscosity maintained functional capillary density (FCD), which was found to be critical in sustaining tissue survival.\textsuperscript{7}

Attenuated responses to injury of the glycocalyx
The endothelial glycocalyx is the active interface between blood and the capillary wall, and is essential for the vascular barrier against fluid and protein extravasation. The glycocalyx is compromised during major surgery\textsuperscript{8}, leading to microvessel perfusion failure by loss of the vascular barrier function. The resulting extreme fluid extravasation increases capillary haematocrit. This causes an increase in blood viscosity and reduces red blood cell velocity, which goes along with a decrease in FCD.

It has been demonstrated that hydroxyethyl starch (HES) solutions might sustain vascular barrier function.\textsuperscript{9} A contributing mechanism for the observed protective effects is the
influence of HES on blood viscosity. HES is capable of interfering with the physiological bridging of red blood cells and thereby decreases aggregation.\textsuperscript{9,10} More microvessels are perfused with the use of HES, attenuating the responses to glycocalyx destruction.\textsuperscript{8,9} Also, tissue-perfusion inhomogeneity, which increases the risk of ischaemic regions, seems to be addressed with HES.

In this study we aimed to investigate the effect of Volulyte\textsuperscript{®} on tissue oxygen saturation ($S_O_2$) and microvascular reactivity during extreme haemodilution. Therefore, its effects were examined during CPB. There are many different solutions available for priming the CPB circuit. The current standard priming solution in our department is a gelatin plasma expander (Geloplasma\textsuperscript{®}, Fresenius Kabi, Schelle, Belgium). In this study we investigated the effects of Volulyte\textsuperscript{®} as a priming solution compared to Geloplasma\textsuperscript{®}, on $S_O_2$ and microvascular reactivity.

To measure $S_O_2$ and microvascular reactivity, near-infrared spectroscopy (NIRS) was used. The physical principles upon which NIRS is based have been described previously.\textsuperscript{11} In general terms, NIRS utilizes the absorption and reflectance spectra of near-infrared light to quantify oxygenation levels of tissues underlying the sensor. To evaluate microvascular reactivity, postocclusive reactive hyperemia (PORH) was examined. The velocity and degree of flow restoration after postocclusive ischaemia depend on the capacity of the microvasculature to recruit arterioles and capillaries, thereby reflecting the integrity of the microcirculation.\textsuperscript{12-14}

The experimental hypothesis of the present study is that Volulyte\textsuperscript{®} provides better microcirculatory perfusion than Geloplasma\textsuperscript{®}. Therefore, the effect of the priming solutions on $S_O_2$ and microvascular reactivity were evaluated. We hypothesize that Volulyte\textsuperscript{®} will demonstrate faster and better flow restoration after a period of ischaemic stress (PORH).
METHODS

Participants
We conducted a prospective, randomized, blinded study in 40 patients. This study was approved by the ethical committee. All patients provided written informed consent before inclusion. They were all recruited at the university hospital of Ghent. Including criteria were adult patients scheduled for elective coronary artery bypass grafting surgery on moderately hypothermic (> 32°C) CPB without blood transfusion. Exclusion criteria were an ejection fraction < 25%, a known allergy to HES, admission of HES or gelatines within the preceding 2 weeks, diabetes, renal insufficiency (creatinine > 2.0 mg/dl), significant hepatic disease (liver function tests > 3x upper limit of normal), history of cerebrovascular disease, significant carotid artery stenosis (> 60%), perioperative use of corticosteroids, and need for vasopressor or inotropic therapy before surgery. An expected haematocrit on CPB, calculated based on preoperative haematocrit, calculated blood volume and amount of cardioplegia, of < 23% was also considered an exclusion criterium. The patients were randomised into two groups and received either Volulyte® (n=20) or Geloplasma® (n=20) as the exclusive priming solution. The priming solutions were blinded by the perfusionist.

Protocol
All subjects needed to fasten 6 hours prior to anaesthesia and were asked to refrain from nicotine and extensive physical activity 6 hours before the study. On the morning of surgery, patients were allowed to take their routine medication, except for angiotensin-converting enzyme inhibitors and angiotensin II antagonists. Patients were premedicated with oral diazepam (5-10 mg).
Standard monitoring was used throughout the procedure, including ECG, pulse oximetry, end-tidal oxygen, carbon dioxide and sevoflurane concentrations, bispectral index (BIS), invasive arterial and central venous pressure measurement, and temperature measurement (Dräger Infinity C700, Dräger Medical GmbH, Lübeck, Germany). Arterial blood pressure was recorded continuously via the right radial artery catheter. Two disposable NIRS sensors (NIRO-200NX, Hamamatsu Photonics, Tokyo, Japan) were applied bilaterally on the patient’s forehead for continuous registration of cerebral oxygen saturation (S$_{cO_2}$), and two sensors were applied on each forearm in a circumferential orientation (over the brachioradialis
muscle, ~5 cm distal from the proximal head of the radius) for measurement of $S_tO_2$ and microvascular reactivity.

All patients received a standardized anaesthetic and CPB management. Anaesthesia was induced with fentanyl 5 µg kg$^{-1}$, diazepam 0.1 mg kg$^{-1}$, and rocuronium 1 mg kg$^{-1}$. The lungs were ventilated mechanically with oxygen enriched air (fractional inspired oxygen 0.6) adjusted to keep the end-tidal carbon dioxide (ETCO$_2$) around 35-40 mmHg. Anaesthesia was maintained with boluses of fentanyl up to a total dose of 25-35 µg kg$^{-1}$ and sevoflurane at a minimum concentration of 1.5 %. Only crystalloid solutions (acetated Ringer’s solution) were used before CPB was established. CPB was performed with a roller pump (Stöckert S5, Sorin group, München, Germany) providing nonpulsatile flow. The priming consisted of 1200 ml study colloids, heparin 5000 IU and mannitol 0.5 g kg$^{-1}$. Alpha-stat acid-base gas management was used, and the target range for $P_{a}O_2$ and $P_{a}CO_2$ was 200-300 mmHg and 35-45 mmHg, respectively. During CPB, phenylephrine or sodium nitroprusside were used if necessary to maintain arterial pressure between 60 and 80 mmHg. Doses of any drugs given were recorded.

Microvascular reactivity was evaluated with postocclusive reactive hyperaemia (PORH). A sphygmomanometer cuff was wrapped around the arm over the left brachial artery. Arterial occlusion was achieved by inflating a standard blood pressure cuff (EH50U, Siemens) at the upper arm to a pressure of 50 mmHg above the individual systolic pressure of each subject. The cuff was automatically inflated in less than 2 seconds to the pressure needed for the arterial occlusion. A standard cuff inflator (Tempco) was used. After 3 minutes of ischaemia, cuff pressure was rapidly released and $S_tO_2$ response was recorded until it is returned to the baseline value as demonstrated by a return of the measured signal to vicinity of its initial pre-occlusion value. Measurements from the contralateral arm were used to control for concurrent non-endothelial dependent changes in vascular tone (e.g. alterations in autonomic tone, transient environmental effects, etc).

$S_cO_2$ and $S_tO_2$ were recorded continuously. Microvascular reactivity was measured at baseline (awake), just before CPB, and at the end of the operation during skin closure.

**Study endpoints**

The main study endpoints were the effect of the priming solution on microvascular reactivity measured with NIRS. Oxygen consumption, recovery times and resaturation rate were determined.\(^{12}\)
(1) Baseline $S_tO_2$ (%)

(2) $VO_2$ nad, oxygen consumption (%/min) from baseline until nadir

(3) Minimum $S_tO_2$ (%)

(4) $t_R$ (sec) = time from release cuff to initial value

(5) $t_M$ (sec) = time from release cuff to maximum value

(6) Maximum $S_tO_2$ (%)

(7) HR (Hyphaemic response) (%) = % change from minimum to maximum value

(8) $S_tO_2$ recovery slope (rec$S_tO_2$) (%/min) = HR (%)/$t_M$ (min)

Included secondary parameters were continuous measurements of $S_tO_2$, blood gases (haemoglobin, arterial and venous oxygen tension, arteriovenous carbon dioxide tension difference, pH and lactate) at the different time moments, and continuous registration of haemodynamic parameters, urinary output and use of vasoactive medication during CPB.

**Statistics**

Prior studies demonstrated differences in rec$S_tO_2$ of 15 to 25% between healthy and diseased subjects.\(^{13,16,17}\) We therefore considered a difference of 20% in rec$S_tO_2$ between the 2 arms as clinically significant. Based on the reported mean rec$S_tO_2$ of 5.38 %/sec with a SD of 1.32 %/sec\(^{18}\), and accepting a two-tailed $\alpha$ error of 0.05 and a $\beta$ error of 0.8, 18 patients were calculated to be required in each arm. To compensate for missing data or potential dropouts, we set the group size to 20 patients per group.

General anaesthesia is known to alter microcirculation, however we did not find any studies documenting the changes in microcirculation with the anaesthetics we routinely use in our cardiac surgery patients. Therefore, in this study the anaesthesia management was standardized.

Distribution of the data was tested for normality using the Shapiro-Wilk test. Normally distributed data are presented as mean ± standard deviation. Non-parametric data are presented as median [range]. Demographic data, medical history data and laboratory values were analysed using independent samples t test and chi square test, as appropriate. NIRS data were analysed using two-way repeated measures ANOVA to assess the parameter*group interaction. Within and between group differences were assessed with the paired t-test and Mann Whitney U test, respectively. Statistical significance was accepted at $p < 0.05$. 
RESULTS

All 40 patients who were recruited completed the study. There were 20 patients in the Geloplasma® group and 20 patients in the Volulyte® group.

Demographic data and preoperative laboratory values were not statistically different between the two groups (table 1). Preoperative values were obtained while patients were awake.

Table 1. Demographics and preoperative values

<table>
<thead>
<tr>
<th></th>
<th>Group Geloplasma®</th>
<th>Group Volulyte®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.4 ± 8.7</td>
<td>67.7 ± 9.7</td>
<td>0.44</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.4 ± 15.1</td>
<td>79.8 ± 15.6</td>
<td>0.28</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.7 ± 10</td>
<td>169.2 ± 6.8</td>
<td>0.84</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>14.1 ± 1.2</td>
<td>14.7 ± 1.6</td>
<td>0.17</td>
</tr>
<tr>
<td>S_aO_2 (%)</td>
<td>96.2 ± 1.1</td>
<td>95.9 ± 1.3</td>
<td>0.43</td>
</tr>
<tr>
<td>S_vO_2 (%)</td>
<td>64.7 ± 21.1</td>
<td>53.1 ± 21.7</td>
<td>0.11</td>
</tr>
<tr>
<td>P_aO_2 (mmHg)</td>
<td>81.3 ± 8.9</td>
<td>77.8 ± 10.5</td>
<td>0.26</td>
</tr>
<tr>
<td>P_vO_2 (mmHg)</td>
<td>36 ± 12.6</td>
<td>28.9 ± 9.9</td>
<td>0.66</td>
</tr>
<tr>
<td>P_aCO_2 (mmHg)</td>
<td>7.1 ± 6</td>
<td>10.9 ± 5.9</td>
<td>0.59</td>
</tr>
<tr>
<td>pH</td>
<td>7.4 ± 0</td>
<td>7.4 ± 0</td>
<td>0.33</td>
</tr>
<tr>
<td>Lactate</td>
<td>10.7 ± 3.5</td>
<td>11.9 ± 2.1</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. Hb: Haemoglobin; S_aO_2: Arterial oxygen saturation; S_vO_2: Venous oxygen saturation; P_aO_2: Arterial oxygen tension; P_vO_2: Venous Oxygen Tension; P_aCO_2: arteriovenous carbon dioxide tension difference

Medical history and preoperative medication use are presented in table 2. The use of diuretics was significantly higher in the Volulyte® group (7 patients) than in the Geloplasma® group (1 patient).
Table 2. Medical history and preoperative medication use

<table>
<thead>
<tr>
<th></th>
<th>Group Geloplasma®</th>
<th>Group Volulyte®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (n)</td>
<td>5</td>
<td>4</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous myocardial infarction (n)</td>
<td>3</td>
<td>4</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>13</td>
<td>14</td>
<td>1.00</td>
</tr>
<tr>
<td>Neurologic antecedents (n)</td>
<td>1</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Antithrombotic agents (n)</td>
<td>19</td>
<td>20</td>
<td>1.00</td>
</tr>
<tr>
<td>Lipid lowering agents (n)</td>
<td>18</td>
<td>16</td>
<td>0.66</td>
</tr>
<tr>
<td>Ace inhibitors (n)</td>
<td>7</td>
<td>8</td>
<td>1.00</td>
</tr>
<tr>
<td>Beta-blockers (n)</td>
<td>16</td>
<td>14</td>
<td>0.72</td>
</tr>
<tr>
<td>Ca-channel blockers (n)</td>
<td>6</td>
<td>4</td>
<td>0.72</td>
</tr>
<tr>
<td>Diuretics (n)</td>
<td>1</td>
<td>7</td>
<td>0.04</td>
</tr>
<tr>
<td>Gender (M/F) (n)</td>
<td>15/5</td>
<td>18/2</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Data are expressed as number of patients.

Preoperative NIRO data (obtained while patients were awake) were not statistically different between the two groups (table 3).

Table 3. Preoperative NIRO values

<table>
<thead>
<tr>
<th></th>
<th>Group Geloplasma®</th>
<th>Group Volulyte®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_tO_2$ at start of PORH (%)</td>
<td>70 [56,80]</td>
<td>68 [48,80]</td>
<td>0.55</td>
</tr>
<tr>
<td>Minimum $S_tO_2$ (%)</td>
<td>46 [6,63]</td>
<td>45 [14,67]</td>
<td>0.94</td>
</tr>
<tr>
<td>$VO_2$nad (%/min)</td>
<td>13 [4,30]</td>
<td>11 [4,25]</td>
<td>0.63</td>
</tr>
<tr>
<td>$t_R$ (sec)</td>
<td>11 [5,50]</td>
<td>12 [7,29]</td>
<td>0.60</td>
</tr>
<tr>
<td>$t_M$ (sec)</td>
<td>27 [16,59]</td>
<td>26 [17,62]</td>
<td>1.00</td>
</tr>
<tr>
<td>Maximum $S_tO_2$ (%)</td>
<td>79 [50,89]</td>
<td>78 [64,88]</td>
<td>0.94</td>
</tr>
<tr>
<td>HR (%)</td>
<td>78 [21,1055]</td>
<td>74 [16,455]</td>
<td>0.70</td>
</tr>
<tr>
<td>Rec$S_tO_2$ (%/min)</td>
<td>173 [57,3013]</td>
<td>207 [24,1138]</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Data are expressed as median [minimum, maximum]. $S_tO_2$: tissue oxygen saturation; PORH: postocclusive reactive hyperaemia; $VO_2$nad: oxygen consumption (%/min) from baseline until nadir; $t_R$: time from release cuff to initial value; $t_M$: time from release cuff to maximum value; HR: Hyperaemic response; rec$S_tO_2$: $S_tO_2$ recovery slope.
Table 4 presents the PORH parameters before and after CPB. Before CPB, PORH values were not different between the 2 groups. After CPB a significant difference in recovery rate and recovery times between the 2 groups was observed. Recovery times were significantly shorter in the Volulyte® group (tm 36 sec [24,104] vs 44 sec [22,81] in the Geloplasma® group, p=0.02). Rate of recovery increased in the Volulyte® group with 31 %/min, while it decreased in the Geloplasma® group (-34 %/min), p=0.02 between the 2 groups.

The other PORH parameters did not differ significantly between the 2 groups (table 4).

Table 4. NIRS parameters before and after cardiopulmonary bypass

<table>
<thead>
<tr>
<th></th>
<th>Group Geloplasma®</th>
<th>Group Volulyte®</th>
<th>p-value</th>
<th>p-value</th>
<th>par*group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>preCPB</td>
<td>postCPB</td>
<td>preCPB</td>
<td>postCPB</td>
<td>interaction</td>
<td>between groups</td>
</tr>
<tr>
<td>S\textsubscript{O}\textsubscript{2} at start of PORH (%)</td>
<td>67 [57,75]</td>
<td>70 [62,80]</td>
<td>0.01</td>
<td>64 [51,80]</td>
<td>67 [44,81]</td>
<td>0.61 0.86</td>
</tr>
<tr>
<td>Minimum S\textsubscript{O}\textsubscript{2} (%)</td>
<td>40 [17,66]</td>
<td>45 [20,64]</td>
<td>0.44</td>
<td>40 [27,71]</td>
<td>40 [15,68]</td>
<td>0.52 0.78</td>
</tr>
<tr>
<td>VO\textsubscript{2}nad (%/min)</td>
<td>12 [4,24]</td>
<td>13 [4,22]</td>
<td>0.70</td>
<td>13 [4,19]</td>
<td>14 [4,22]</td>
<td>0.40 0.78</td>
</tr>
<tr>
<td>t\textsubscript{R} (sec)</td>
<td>13 [6,36]</td>
<td>17 [7,52]</td>
<td>0.03</td>
<td>15 [8,50]</td>
<td>16 [7,36]</td>
<td>0.002 0.008</td>
</tr>
<tr>
<td>t\textsubscript{M} (sec)</td>
<td>35 [17,79]</td>
<td>44 [22,81]</td>
<td>0.05</td>
<td>40 [19,97]</td>
<td>36 [24,104]</td>
<td>0.09 0.02</td>
</tr>
<tr>
<td>Maximum S\textsubscript{O}\textsubscript{2} (%)</td>
<td>79 [71,89]</td>
<td>79 [71,88]</td>
<td>0.11</td>
<td>79 [59,85]</td>
<td>79 [59,86]</td>
<td>0.88 0.99</td>
</tr>
<tr>
<td>HR (%)</td>
<td>93 [20,431]</td>
<td>86 [19,266]</td>
<td>0.56</td>
<td>97 [20,192]</td>
<td>103 [17,283]</td>
<td>0.21 0.53</td>
</tr>
<tr>
<td>RecS\textsubscript{O}\textsubscript{2} (%/min)</td>
<td>161 [35,1035]</td>
<td>127 [18,348]</td>
<td>0.14</td>
<td>119 [20,427]</td>
<td>150 [15,553]</td>
<td>0.34 0.07</td>
</tr>
</tbody>
</table>

Data are expressed as median [minimum, maximum]. CPB: cardiopulmonary bypass; S\textsubscript{O}\textsubscript{2}: tissue oxygen saturation; PORH: postocclusive reactive hyperaemia; VO\textsubscript{2}nad: oxygen consumption (%/min) from baseline until nadir; t\textsubscript{R}: time from release cuff to initial value; t\textsubscript{M}: time from release cuff to maximum value; HR: Hyperaemic response; recS\textsubscript{O}\textsubscript{2}: S\textsubscript{O}\textsubscript{2} recovery slope; par*group interaction: parameter*group interaction
DISCUSSION

In the present study we compared the effects of Volulyte® and Geloplasma® on microvascular reactivity during extreme haemodilution. After CPB, recovery times were significantly shorter and rate of recovery was significantly faster in the Volulyte® group, indicating that Volulyte® provides better microcirculatory perfusion than Geloplasma® in case of extreme haemodilution.

Geloplasma® is the current standard priming solution in our department. It contains 30 grams per liter of modified liquid gelatin. Gelatines have the advantage of their unlimited daily dose recommendation.

Volulyte® contains 6% hydroxyethyl starch (HES 130/0.4) in a balanced electrolyte solution. HES 130/0.4 is a third generation starch, which is characterized by the molar substitution by hydroxyethyl groups (0.4), the mean molecular weight (130,000 Da), the concentration (6%), and the substitution ratio (C2/C6 ratio) of approximately 9:1. Hydroxyethyl starch 130/0.4 is a derivative of thin boiling waxy maize starch, which mainly consists of a glucose polymer (amylopectin).

It has been suggested that the latest generation synthetic colloid solutions might provide better microcirculatory perfusion due to improved rheology of the blood and by attenuating responses to injury of the glycocalyx.1-3 The data of the present study suggest better microcirculatory perfusion with Volulyte® compared to Geloplasma®.

Shahbazi et al. evaluated the effects of tissue and organ perfusion during and after coronary artery bypass graft surgery with either colloid (Voluven®) or crystalloid (Lactated ringer’s) as the priming solution. Tissue and organ perfusion markers included lactate, troponin I, liver and renal function tests. In this study no significant difference between Voluven® and lactated ringer’s was observed.19

In contrast to the study of Shahbazi, and in concordance with our observation, other studies report an improvement in tissue oxygenation when using HES 130/0.4. A study in healthy volunteers undergoing acute normovolemic haemodilution showed a more pronounced and earlier increase of skeletal muscle tissue oxygenation using HES 130/0.4 compared to HES 70/0.5 or 200/0.5.1

Pinar et al performed a study in 40 patients undergoing minor lower extremity surgery. The patients were randomized into two groups and received either normal saline or HES 130/0.4. They demonstrated that ischaemia reperfusion injury was absent in the HES 130/0.4 group, while there was significant ischaemia reperfusion injury in the normal saline group.20
The effects of HES 130/0.4 and HES 200/0.5 on microcirculation perfusion and tissue oxygenation in 30 patients undergoing liver surgery has been examined by measuring the gastric mucosal pH. Compared with HES 200/0.5, the use of HES 130/0.4 could significantly improve internal organ perfusion and tissue oxygenation in patients undergoing liver surgery with a relatively large amount of blood loss.\textsuperscript{21}

Goal directed colloid fluid therapy using HES 130/0.4 was compared with goal-directed crystalloid fluid therapy on healthy and perianastomotic colon tissue in a pig model of colon anastomosis surgery. Goal-directed colloid fluid therapy significantly increased microcirculatory blood flow and tissue oxygen tension in healthy and injured colon compared to goal-directed crystalloid fluid therapy.\textsuperscript{22}

NIRS was used to obtain our data. NIRS is an easily applicable, non-invasive technique that measures tissue oxygenation continuously. The technique is based on relative transparency of human tissue for near-infrared light and on the existence of chromophores in the biological tissues whose light-absorbing properties vary with oxygenation. Several NIRS devices are commercially available. In the present study, the NIRO-200NX was used. NIRO employs the technique of Spatially Resolved Spectroscopy (SRS, multiple closely spaced detectors to measure light attenuation as a function of source-detector separation) to measure $S_tO_2$ and changes in haemoglobin (Hb). Independently of the SRS method, NIRO measures changes in concentration of oxyHb, deoxyHb and Hb using the Modified Beer-Lambert method.

NIRS was originally manufactured for brain monitoring.\textsuperscript{11} In recent years, its use has been expanded to evaluation of oxygenation of other tissues, and its feasibility to assess microvascular reactivity has been proposed.\textsuperscript{23,24,25}

Microvascular reactivity can be assessed with NIRS by measuring the endothelium-mediated changes in vascular tone after inducing postocclusive reactive hyperemia (PORH). Several indices have been proposed to evaluate microvascular reactivity during the PORH test. Kragelj and his group suggested that the most useful parameters to distinguish between healthy and impaired peripheral vasculature were the time parameters ($t_R$ and $t_M$), the rate of reactive hyperaemia ($\text{RecS}_tO_2$), and the maximal change of reactive hyperaemia.\textsuperscript{26,27}

Although NIRS has been introduced as a way to quantify endothelium-mediated changes in vascular tone, it has to be emphasized that it does not directly measure microcirculatory blood
flow. It is the dynamic change in NIRS parameters in response to a period of ischaemic stress (PORH) that provides a means to assess the integrity and functionality of the vascular endothelium. The down slope reflects the oxygen consumption rate, which depends on both the local metabolic demand and the capability of the microcirculation to provide oxygen to the tissue. The recovery slope and the hyperaemic response reflects the capability of the microcirculation to adapt to an ischaemic challenge by recruitment of the microvascular network.

The use of NIRS has some limitations. First, NIRS determines tissue oxygenation by monitoring the absorption of light at different wavelengths by oxyhaemoglobin and deoxyhaemoglobin. Therefore, external light sources can cause significant artefacts. Second, measurements are influenced by the tissue thickness. It is possible that subcutaneous fat exceeding 2 to 3 cm at the sensor site may interfere with the device’s ability to obtain a reading. The measurements are also influenced by the tissue composition. The interindividual variability in the exact composition of tissue causes a wide variation in normal baseline values. Therefore it is more appropriate to use NIRS as a trend monitor rather than as an absolute value.

Third, NIRS technology does not directly measure microcirculatory blood flow. However, several authors have reported that the increase in muscle tissue oxygenation following transient arterial occlusion is accompanied by an increase in local total tissue haemoglobin concentration, which could suggest recruitment in perfused capillaries, and increased oxygen delivery.

Finally, there is no gold standard to which NIRS data can be directly compared.
CONCLUSION

Microscopic maldistribution of blood flow occurs during acute haemodilution. In other studies it has been suggested that the latest generation colloids might improve the rheology of the blood and therefore provide better tissue oxygenation.\textsuperscript{1-3} Therefore, we performed a prospective, randomized, blinded study in which we evaluated the effect on microvascular reactivity of HES 6\% 130/0.4 (Volulyte\textsuperscript{®}) as a priming solution of CPB and compared it with the standard priming solution in our department, gelatine (Geloplasma\textsuperscript{®}).

To evaluate microvascular reactivity we used PORH. The measurements were obtained before and after CPB using NIRS technology. We found that after CPB, recovery times were significantly shorter and rate of recovery was significantly faster in the Volulyte\textsuperscript{®} group. This indicates that Volulyte\textsuperscript{®} provides better microcirculatory perfusion than Geloplasma\textsuperscript{®} in case of extreme haemodilution.
REFERENCES

1. Standl T, Burmeister MA, Schroeder F, Currlin E, Schulte am Esch J, Freitag M. Hydroxyethyl Starch (HES) 130/0.4 provides larger and faster increases in tissue oxygen tension in comparison with prehemodilution values than HES 70/0.5 or HES 200/0.5 in volunteers undergoing acute normovolemic hemodilution. ANESTHESIA AND ANALGESIA 2003; 96:936–43


3. Simon TP, Schuerholz T, Haugvik SP, Forberger C, Burmeister MA, Marx G. High molecular hydroxyethyl starch solutions are not more effective than a low molecular hydroxyethyl starch solution in a porcine model of septic shock. MINERVA ANESTHESIOL 2013; 79:44-52


10. Neff TA, Fischler L, Mark M, Stocker R, Reinhart WH. The influence of two different hydroxyethyl starch solutions (6% HES 130/0.4 and 200/0.5) on blood viscosity. ANESTHESIA AND ANALGESIA 2005; 100:1773-1780


20. Pinar H, Pinar A, Mavioglu O, Yener N. Effect of hydroxyethyl starch 130/0.4 on ischemia-reperfusion determinants in minor lower extremity surgery with tourniquet application. JOURNAL OF CLINICAL ANESTHESIOLOGY. Online 2015. Opgehaald op 1 februari 2015, van http://dx.doi.org/10.1016/j.jclinane.2014.07.001


SUMMARY

De invloed van een zetmeeloplossing (Volulyte®) in vergelijking met een vloeistof op basis van gelatines (Geloplasma®) als kunsthartvloeistof op de microvasculaire reactiviteit.

Inleiding

Bij plotse verdunning van het bloed wordt de microcirkulatie verstoord waardoor de vitaliteit van de weefsels bedreigd wordt. Herstel van de rheologie van het bloed is een belangrijke factor in het behouden van de weefselperfusie en de zuurstofvoorziening in de weefsels onafhankelijk van het herstel van de zuurstofdragen de capaciteit. De laatste generatie colloïden zouden de weefselperfusie verbeteren door een verbetering van de rheologie en het verzwakken van de reactie op schade aan de glycocalyx. In deze studie wilden we het effect onderzoeken van Volulyte® op de weefseloxygenatie en microvasculaire reactiviteit tijdens extreme bloedverdunning. Daarom werd Volulyte® gebruikt als vloeistof in de hart-longmachine. Hierbij werd het effect van Volulyte® vergeleken met de standaard kunsthartvloeistof op onze afdeling namelijk Geloplasma®. Onze werkhypothese was dat Volulyte® zorgt voor een betere perfusie van de microcirculatie dan Geloplasma®.

Methode

Er werden 40 patiënten die gepland waren voor hartchirurgie geïncludeerd en gerandomiseerd waarbij er ofwel Volulyte® gebruikt werd ofwel Geloplasma®. De studie was geblindeerd door de perfusionist. Enkel cristalloïde oplossingen werden gebruikt voor de start van de hart-longmachine. Om de microvasculaire reactiviteit te testen werd gebruik gemaakt van post occlusieve hyperemie (PORH). PORH verwijst naar de toename in doorbloeding na tijdelijke arteriële occlusie. De snelheid en de graad van herstel hangt af van de capaciteit om meer arterioles en capillairen te rekruteren en is zo een maat voor de integriteit van de microcirculatie. Dit werd uitgevoerd door een opblaasbare cuff rond de bovenarm op te blazen die na drie minuten gelost werd waarbij de zuurstofvoorziening in de weefsels gemeten werd. Deze meting gebeurde met bijna-infrarood spectrometrie voor inductie, voor kunsthart en op het einde van de operatie. De tijd tot herstel van de weefseloxygenatie en de snelheid van herstel werden bepaald.
Resultaten

Na de hart-longmachine was de tijd tot herstel van weefseloxygenatie significant korter in de Volulyte® groep in vergelijking met de Geloplasma® groep. De snelheid van herstel nam toe in de Volulyte® groep terwijl het verminderde in de Geloplasma® groep.

Discussie

Studies toonden aan dat de nieuwste generatie colloïden de weefselperfusie kan verbeteren ten gevolge van een verbeterde rheologie en het beperken van schade aan de glycocalyx. Onze resultaten suggereren in overeenstemming hiermee een beter microvasculaire reactiviteit.

Conclusie

Onze resultaten suggereren een betere perfusie van de microcirculatie bij het gebruik van Volulyte® als kunsthartvloeistof in vergelijking met Geloplasma®.