500 ml of blood loss does not decrease non-invasive tissue oxygen saturation (StO₂) as measured by near infrared spectroscopy - A hypothesis generating pilot study in healthy adult women

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Abstract
Background: The goal when resuscitating trauma patients is to achieve adequate tissue perfusion. One parameter of tissue perfusion is tissue oxygen saturation (StO₂), as measured by near infrared spectroscopy. Using a commercially available device, we investigated whether clinically relevant blood loss of 500 ml in healthy volunteers can be detected by changes in StO₂ after a standardized ischemic event.

Methods: We performed occlusion of the brachial artery for 3 minutes in 20 healthy female blood donors before and after blood donation. StO₂ and total oxygenated tissue hemoglobin (O₂Hb) were measured continuously at the thenar eminence. 10 healthy volunteers were assessed in the same way, to examine whether repeated vascular occlusion without blood donation exhibits time dependent effects.

Results: Blood donation caused a substantial decrease in systolic blood pressure, but did not affect resting StO₂ and O₂Hb values. No changes were measured in the blood donor group in the reaction to the vascular occlusion test, but in the control group there was an increase in the O₂Hb rate of recovery during the reperfusion phase.

Conclusion: StO₂ measured at the thenar eminence seems to be insensitive to blood loss of 500 ml in this setting. Probably blood loss greater than this might lead to detectable changes guiding the treating physician. The exact cut off for detectable changes and the time effect on repeated vascular occlusion tests should be explored further. Until now no such data exist.

Introduction
The goal of resuscitation is to achieve adequate tissue perfusion. The patient’s history, ongoing bleeding and clinical signs of hypovolemia are the first trigger for volume substitution. Tissue perfusion is conventionally monitored using arterial base deficit and serum lactate, but these laboratory parameters are not always immediately available at the point-of-care. Additionally, relevant blood loss may not be detected by conventional hemodynamic monitoring [1].

Therefore, in the trauma setting, there is growing interest in non-invasive techniques measuring tissue perfusion. Near infrared spectroscopy (NIRS) has become a widely used method for tissue hemoglobin oxygen saturation (StO₂) measurement in muscle and has been validated in animals [2-4] and in humans [5-11].

NIRS uses light with a wavelength of 650-950 nm and easily crosses biological tissues. Near infrared light is mainly absorbed by hemoglobin and only monitors vessels with a diameter <1 mm, because the blood levels in
larger vessels are too high to reflect enough light [12]. In
this setting, NIRS measurements primarily indicate the
venous oxyhemoglobin concentration, as only 20% of
blood volume is arterial and the NIRS device does not
differentiate between systole and diastole [13].

NIRS can be used to observe the microcirculatory reac-
tivity of peripheral tissue after a standardized ischemic
event. It has been shown that StO₂ recovery after tran-
sient occlusion of the brachial artery differs in hemody-
namically unstable trauma patients in comparison to
healthy volunteers [14]. The StO₂ response after a vascu-
lar occlusion test is an example of functional hemody-
namic monitoring, in which the response of the specific
system to a pre-determined stress is the monitored vari-
able. After induction of an artificial ischemic stress, local
metabolic demand and reperfusion reserve can be assessed
from the changes in parameters [14].

The aim of this study was to investigate the impact of a
controlled and clinically relevant blood loss (500 ml) on
resting StO₂ values, as well as microcirculatory reactivity
triggered by a vascular occlusion test in healthy blood
donors. 500 ml of blood donation correspond to a loss of
10% of the whole blood volume. 10% of blood loss is con-
sidered to be the cut off for clinical relevant blood loss
according to the current literature and may become rele-
vant if pre-existing morbidity exists. For example, post-
partum hemorrhage, defined as blood loss more than 500
ml after a vaginal delivery, is a major cause of maternal
morbidity and mortality [15]. Other authors have been
able to detect 500 ml of blood loss with NIRS in various
settings [16,17].

We have decided to investigate the 500 ml blood loss
because of the controlled and safe study setting and
because higher blood volume losses are anyway related
with detectable changes in physiological parameters (e.g.
blood pressure, pulse rate). For the clinician, " borderline"
patients without obvious signs of blood loss present the
greater challenge.

We hypothesized that NIRS after a vascular occlusion
test would be able to detect this amount of blood loss,
because of the industries promise of "earliest" detection
of volume depletion.

**Methods**

**Volunteers**

We investigated 20 healthy female blood donors and 10
healthy female medical students as control subjects. The
study was restricted to women, as they have lower body
mass index (BMI) than men and are therefore more prone
to show slight symptoms of hypovolemia after blood
donation.

Blood donors had a median age of 30.5 y (range 19 - 62).
Their BMI was 21 kg/m² median (range 18 - 23.5). The
median blood volume is estimated as 70 ml/kg body
weight or 4060 ml (range 3500 - 4550). The median capil-
larary hemoglobin was 139 g/l (range 127 - 157). This was
measured once immediately after arrival at the blood
donation service.

In the control group, the median age was 23 y (range 22
- 25). The median BMI was 21 kg/m² (range 19 - 23). The
median blood volume was 4165 ml (range 3500 - 4480).

**Protocol**

Blood donors and control subjects were in a zero degree
supine position during the whole test. In both groups,
there was a resting period of 5 minutes before applying
the probe and performing the vascular occlusion test
measurement. We measured blood pressure manually
before every vascular occlusion test, using the same
sphygmomanometer cuff as when occluding the artery.
Blood donation started after a recovery period of 5 min-
utes. The second vascular occlusion test in the blood
donor group started immediately after the end of blood
donation.

In the control group, measurements were performed in
exactly the same way as in the blood donor group. In
order to detect a possible time effect from the vascular
occlusion tests, a 19-minute rest period was maintained
between the two vascular occlusion tests of the control
group. (Fig. 1) These 19 minutes are a median (range 14
- 22 minutes) measured in the blood donor group between
the end of the first and the start of the second vascular
occlusion test. This period included the recovery from
the first vascular occlusion, the preparation for phlebo-
tomy and the actual blood donation, which lasted 11 min-
utes (range 9 - 13).

As this was an observational study aimed at controlling
the quality of a freely available device, and because no
additional data were collected from the volunteers, no
formal ethical approval was necessary, according to our
local ethical committee. Additionally, the vascular occlu-
sion using a cuff pressure of 50 mmHg above systolic
blood pressure, correlates to cuff pressures reached in
non invasive (Riva Rocci) blood pressure measurement.
Because no data on ethical considerations related to such
kind of setting have been available, AKE and VJ have
acted as volunteers. The discomfort has been within the
usual limits of blood pressure measurement and was later
very well tolerated by the volunteers and did not cause
any discomfort.

**Measurements**

We measured StO₂ at the thenar eminence (opposite to
the blood donating arm) with a commercially available
tissue spectrometer (InSpectra Model 650, Hutchinson
Technology, Hutchinson, Minn. US), which is promoted
as being able to detect blood loss in an emergency setting.
The method has been previously validated [19]. The probe spacing was 15 mm.

The device measures and records $\text{StO}_2$ and tissue hemoglobin index (THI) every two seconds. THI is a quantitative estimation of tissue hemoglobin concentration [20]. From these values, oxygenated hemoglobin ($O_2\text{Hb}$) was obtained by multiplying $\text{StO}_2$ and THI, because $\text{StO}_2 = \frac{O_2\text{Hb}}{O_2\text{Hb} + \text{HHb}}$ [19]. Accordingly, the amount of deoxygenated hemoglobin (HHb) equals the residual hemoglobin: $\text{THI} - O_2\text{Hb} = \text{HHb}$. We defined baseline variables before starting a vascular occlusion test as the median over 2 minutes for $\text{StO}_2$, $O_2\text{Hb}$, and HHb.

A vascular occlusion test was performed by inflating the sphygmomanometer cuff for 3 minutes with a pressure of 50 mmHg over systolic BP as described in detail by Creteur et al. [12]. The rate of decrease was calculated from the linear part of the decrease (first 25%) after cuff inflation [14]. The rate of recovery of $\text{StO}_2$ and $O_2\text{Hb}$ was defined over a mean of 14 seconds (8 data points) following the nadir $\text{StO}_2$ and $O_2\text{Hb}$ value at the end of ischemia. Delta $\text{StO}_2$ and delta $O_2\text{Hb}$ are defined as the difference between the maximal value after reperfusion and the baseline [12]. (Fig. 2, Fig. 3)

**Data processing**

Prism 5 (GraphPad Software, Inc., San Diego, CA, USA) was used to calculate the statistics. Non-parametric tests were used (Wilcoxon rank sum test for within-group differences, Mann-Whitney U-test for between-group differences). Data is presented as medians and interquartile ranges. P-values have been interpreted in an exploratory fashion.

**Results**

There was a markedly decrease in systolic blood pressure in both groups before and after blood donation. Systolic
blood pressure decreased from 118 mmHg median (interquartile range: 118 - 123) to 110 mmHg (106 - 115) (p < 0.001) in the donor group and from 112 mmHg (103 - 118) to 106 mmHg (100 - 111) (p = 0.02) in the control group. Systolic blood pressure decreased markedly more in the donor group than in the control group (p = 0.02). (Fig. 4)

For variables measured with NIRS, the differences from the first to the second vascular occlusion test did not differ between the two groups. The only exception was the differences in \( O_2 \text{Hb} \) 2 min median, which was slightly larger in the control group -0.4 (-1.0 - -0.3) than in the blood donor group -0.1 (-0.4 - 0.3) (p = 0.03). Therefore the two groups are considered to be similar and comparable.

\( O_2 \text{Hb} \) 2 min median did not change substantially in the blood donor group before and after blood donation, but decreased in the control group after the rest period: \( O_2 \text{Hb} \) 2 min median decreased from 82.0% (79.5 - 85.0) to 80.5% (76.8 - 83.8) (p = 0.02), \( O_2 \text{Hb} \) 2 min median decreased from 10.9 (9.6 - 12.4) to 10.2 (9.4 - 11.8) (p = 0.03). HHb 2 min median did not change in the blood donor group, but increased in the control group markedly from 2.35 (2.08 - 2.56) to 2.45 (2.20 - 2.92) (p = 0.01) (Table 1).

Variables measured during the vascular occlusion test did not change in the blood donor group: The rate of decrease, rate of recovery and delta for \( O_2 \text{Hb} \) did not show any substantial difference before and after blood donation. In the control group, \( O_2 \text{Hb} \) variables did not change markedly - in contrast to the \( O_2 \text{Hb} \) values.

\( O_2 \text{Hb} \) rate of decrease was less steep after the rest period (before: -0.039 (-0.051 - -0.026); after: -0.031 (-0.046 - -0.020); p < 0.01), whereas \( O_2 \text{Hb} \) rate of recovery (before: 0.49 (0.39 - 0.63); after: 0.54 (0.39 - 0.69); p = 0.05) and \( O_2 \text{Hb} \) delta (before: 3.88 (2.43 - 4.20); after: 4.0 (3.32 - 5.72); p = 0.01) increased after the rest period (Table 2).

**Discussion**

The principal finding of this study is, that although systolic blood pressure decreased substantially, blood loss had no effect on superficial thenar \( \text{StO}_2 \) before and after blood donation measured by NIRS. However other experimental NIRS devices have been successfully used to monitor blood loss after blood donation. Torella et al. showed that even 2% blood volume loss reduced peripheral hemoglobin oxygen saturation (\( \text{PsO}_2 \), calf) significantly [16]. Soller et al. simulated hypovolemia using progressive lower body negative pressure and showed that hypovolemia corresponding to 400 - 500 ml of blood loss resulted in a decrease in forearm muscle oxygen saturation [17]. The same group could also show, in the same setting, that deep muscle oxygen saturation is more sensitive in detecting hypovolemia (experimental NIRS device) than superficial thenar \( \text{StO}_2 \) (Hutchinson) [21].

Soller et al. discussed, that the location of the NIRS sensor as well as the tissue depth might be responsible for variations in results, although the technique used by the two devices is in principle the same. We did use exactly...
Table 1: NIRS variables and systolic blood pressure before each vascular occlusion test.

<table>
<thead>
<tr>
<th>Blood donors</th>
<th>Before blood donation</th>
<th>After blood donation</th>
<th>two-tailed p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median</td>
<td>IQR</td>
<td>median</td>
</tr>
<tr>
<td>StO₂</td>
<td>79.0</td>
<td>74.5 - 83.5</td>
<td>78.5</td>
</tr>
<tr>
<td>O₂Hb</td>
<td>10.7</td>
<td>9.3 - 11.9</td>
<td>10.8</td>
</tr>
<tr>
<td>deoxy Hb</td>
<td>2.62</td>
<td>2.39 - 3.24</td>
<td>2.70</td>
</tr>
<tr>
<td>SBP</td>
<td>118</td>
<td>118 - 123</td>
<td>110</td>
</tr>
<tr>
<td>Control</td>
<td>Before rest period</td>
<td>After rest period (19 minutes)</td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>IQR</td>
<td>median</td>
<td>IQR</td>
</tr>
<tr>
<td>StO₂</td>
<td>82.0</td>
<td>79.5 - 85.0</td>
<td>80.5</td>
</tr>
<tr>
<td>O₂Hb</td>
<td>10.9</td>
<td>9.6 - 12.4</td>
<td>10.2</td>
</tr>
<tr>
<td>deoxy Hb</td>
<td>2.35</td>
<td>2.08 - 2.56</td>
<td>2.45</td>
</tr>
<tr>
<td>SBP</td>
<td>112</td>
<td>103 - 118</td>
<td>106</td>
</tr>
</tbody>
</table>

IQR: interquartile range, *: p < 0.05

Table 2: NIRS variables during the vascular occlusion tests.

<table>
<thead>
<tr>
<th>Blood donors</th>
<th>Before blood donation</th>
<th>After blood donation</th>
<th>two-tailed p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median</td>
<td>IQR</td>
<td>median</td>
</tr>
<tr>
<td>StO₂ rate of decrease(%/sec)</td>
<td>-0.19</td>
<td>-0.21 - -0.16</td>
<td>-0.19</td>
</tr>
<tr>
<td>StO₂ rate of recovery (%/sec)</td>
<td>3.04</td>
<td>2.57 - 3.45</td>
<td>3.29</td>
</tr>
<tr>
<td>StO₂ delta (%)</td>
<td>14.0</td>
<td>12.0 - 15.8</td>
<td>13.5</td>
</tr>
<tr>
<td>O₂Hb rate of decrease (/sec)</td>
<td>-0.033</td>
<td>-0.043 - -0.026</td>
<td>-0.027</td>
</tr>
<tr>
<td>O₂Hb rate of recovery (/sec)</td>
<td>0.59</td>
<td>0.50 - 0.72</td>
<td>0.63</td>
</tr>
<tr>
<td>O₂Hb delta</td>
<td>4.33</td>
<td>3.47 - 4.97</td>
<td>4.76</td>
</tr>
<tr>
<td>Control</td>
<td>Before rest period</td>
<td>After rest period (19 minutes)</td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>IQR</td>
<td>median</td>
<td>IQR</td>
</tr>
<tr>
<td>StO₂ rate of decrease (%/sec)</td>
<td>-0.17</td>
<td>-0.19 - -0.15</td>
<td>-0.15</td>
</tr>
<tr>
<td>StO₂ rate of recovery (%/sec)</td>
<td>2.64</td>
<td>2.00 - 2.88</td>
<td>2.43</td>
</tr>
<tr>
<td>StO₂ delta (%)</td>
<td>12.5</td>
<td>11.3 - 13.3</td>
<td>13.5</td>
</tr>
<tr>
<td>O₂Hb rate of decrease (/sec)</td>
<td>-0.039</td>
<td>-0.051 - -0.026</td>
<td>-0.031</td>
</tr>
<tr>
<td>O₂Hb rate of recovery (/sec)</td>
<td>0.49</td>
<td>0.39 - 0.63</td>
<td>0.54</td>
</tr>
<tr>
<td>O₂Hb delta</td>
<td>3.88</td>
<td>2.43 - 4.20</td>
<td>4.00</td>
</tr>
</tbody>
</table>

IQR: interquartile range, *: p < 0.05
the same superficial thenar StO2 probe from Hutchinson as Soller in her study, which may explain why we did not detect any changes in NIRS parameters following blood loss.

A second finding of this study is that there might be an intrinsic effect of repeated vascular occlusion tests on O2Hb. This hypothesis is based on the increase in delta O2Hb and O2Hb rate of recovery and a decrease in oxygen consumption (O2Hb rate of decrease), which was measured in the control group but not in the blood donor group. This could be explained if there is a time effect of repeated vascular occlusion tests, designated as ischemic preconditioning [22]. This improves the ischemic tolerance of various tissues, including skeletal muscle, after one or more brief periods of ischemia, each followed by a short reperfusion phase. The underlying mechanisms are still not clear. One reason may be the reduction in the resting rate of oxygen consumption [23]. Although blood loss does not result in different StO2 or O2Hb variables after the vascular occlusion test, it seems to mask the effect of ischemic preconditioning in the blood donor group.

Limitations
One limitation with our paper is the assumption that withdrawal of 500 ml of blood in a healthy volunteer represents a clinically relevant blood loss. Anyhow 10% of circulating blood volume can not be neglected.

In addition we did not supply data on base excess and/or lactate, the two parameters which are conventionally used to estimate tissue oxygenation. This would have helped to indicate whether a 500 ml blood loss was indeed relevant, but was not feasible in the giving setting of volunteer blood donation. Therefore, it is unclear as to whether the device failed to identify tissue ischemia completely, which is unlikely as the values decreased during vascular occlusion, or more likely, that no ischemia developed during blood donation.

Conclusion
StO2 measured at the thenar eminence seems to be insensitive to blood loss of 500 ml in this setting. Probably blood loss greater than this might lead to detectable changes guiding the treating physician. The exact cut off for detectable changes and the time effect on repeated vascular occlusion tests should be explored further. Until now no such data exist. Finally, our findings suggest that StO2 measured by NIRS is not able to detect acute blood loss of 500 ml and therefore, it might not be useful to apply this device in the acute assessment of a bleeding trauma patient. However, the device could help to identify hemodynamic worsening during the ICU stay but at the moment not enough evidence exists to support this hypothesis.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
VJ, SF and AE conducted the study. All authors contributed to the design of the study, the analysis of the data and the writing of the manuscript. All authors have seen the original study data, reviewed the analysis of the data, and approved the final manuscript. VJ is the author responsible for archiving the study files.

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