

Author's response to reviews

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

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Version: 3 **Date:** 9 April 2010

Author's response to reviews: see over

Dear Editors,

We are grateful for the excellent comments of the reviewers, which have helped to improve our manuscript significantly. We would like to address the reviewers comments point by point. You will find also all changes highlighted in the manuscript.

Reviewer 1, S.M. Cohn:

“The volume of blood removed may not have lead to significant tissue hypoperfusion, and no confirmatory measures (base deficit or lactate) were measured to confirm or dispel the notion that tissue oxygen debt had in fact occurred. Therefore, it is unclear as to whether the device failed to identify tissue ischemia (unlikely as the values decreased during vascular occlusion) or more likely, that no ischemia developed during blood donation. These facts need to be emphasized by the authors.”

Authors: “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.”

Reviewer 2, Gerrit Matthes

„The authors set out to verify a new method for monitoring minor blood loss. How was the definition of “minor” made and how came the decision regarding a volume of 500 ml blood?”

Authors: 10% of blood loss is considered to be the cut off for clinical relevant blood loss according to the current literature and may become relevant if pre- existing morbidity exists. For example, postpartum hemorrhage, defined as blood loss more than 500 ml after a vaginal delivery, is a major cause of maternal morbidity and mortality.^[17] Other authors have been able to detect 500 ml of blood loss with NIRS in various settings.^[18, 19] We have decided to investigate the 500ml 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.

“Since this protocol using a NIRS-device before and after a vascular occlusion is quite uncommon, it should be explained more extensive. Why a 3 minutes vascular occlusion?”

Authors: The use of a vascular occlusion test in combination with a NIRS device is not a novel concept and has been described by several authors before. We decided to use the same setting as in the study of Creteur et al (*Intensive Care Med* 2007, **33**:1549-1556). He explored intensively the different aspects of vascular occlusion tests monitored by a NIRS device. Therefore we decided to perform the 3 minutes vascular occlusion test.

We added to the method section: ... 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.^[14]

“The authors state that the demonstrated method is not sensitive regarding a blood loss of 500 ml. In spite of a significantly decreased systolic blood pressure after donation of blood there was no effect on the superficial thenar O₂. However, the authors mention other studies which were able to demonstrate a successful use of NIRS in monitoring a certain blood loss. How do they explain the discrepancy of results?”

Authors: Soller et al. compared two different devices in the same setting of simulated hypovolemia using progressive lower body negative pressure. (*Crit Care Med* 2008, **36**:176-182) One device has been the same that we used in our study (from Hutchinson) and the other has been an experimental one which is not commercially available. Only the experimental device was able to show hypovolemia at levels corresponding to 500ml. The author stated, that their device was able to monitor tissue-oxygenation more in depth applied to another muscle than the very superficial thenar eminence. This might be one reason for the different results. Additionally, each device uses different mathematical algorithms which are usually not published, which makes it difficult to find out the actual reason why there are differences from one device to the other in the same setting.

We added to the discussion:

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 StO₂ (Hutchinson).^[23] 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 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.

“All (conscious) volunteers had to undergo a vascular occlusion of a healthy limb for a three minute period. How did the participants tolerate this (potentially painful) procedure?”

Authors: We added to the method section:

Additionally, the vascular occlusion 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.

“Figure 1: The abbreviation VOT should be explained. Please indicate the 5 minute resting period before starting the blood donation (2nd rest period in controls).”

Authors: The abbreviation VOT does not appear any more in the figures. It is now spelled out in the whole manuscript. The 5 minute resting period before starting the blood donation has been added to figure 1 (please see new figures attached to the revised manuscript).

“Figure 2: Please briefly describe the typical aspects of the StO₂ trace within the legend”

Authors: We did add the following to the legend of figure 2:

Whole length of recorded trace showing all events: 1st vascular occlusion test, recovery period, blood donation and 2nd vascular occlusion test. Details of a vascular occlusion test are described in figure 3.

“Obviously no ethical approval was requested. This is explained by the use of a free available device. Following the protocol every participant had to suffer at least a vascular occlusion of a healthy limb. This, in fact, appears to be an intervention making an ethical approval necessary.”

Authors: The noninvasive vascular occlusion of maximal 3 minutes is not related with any ischemic, e.g. nerve-damage, if this is the concern. Fortunately, the circulatory system of a nerve is specially designed to protect it from reduced blood supply, say from a blocked artery. Nerves normally receive much more blood than they need to function. This large safety zone means that even if circulation is impaired or blocked, the nerve will probably get enough blood to work well. In critical situations, a nerve can even work for some time by absorbing oxygen and glucose from surrounding muscles. Experiments have shown that our skin feels numb about 13-15 minutes after the blood flow is arrested, and that all sensation, except for pain, is gone after about 18 minutes. Muscular weakness begins at about 25 minutes, and paralysis sets in after 30 minutes. If the circulation is cut off for more than about 40 minutes, the effects can be much more serious.

Additionally, the vascular occlusion 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.

As mentioned above, we added to the method section:

Additionally, the vascular occlusion 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.

Reviewer 3, S. Mougiakakou

The authors should explain better the 19 minutes of the blood donation.

Authors: 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 phlebotomy and the actual blood donation, which lasted 11 minutes (range 9 – 13).

In Fig. 1 the resting period of 5 minutes prior the first application of the probe should be added, along with the time of the second vascular occlusion test (VOT).

Authors: We added the 5 minutes rest period to figure 1. (please see the new figures attached to the revised manuscript).

In Figs. 2-4 the authors should add legend and scaling to the horizontal axes.

Authors: We added legend and scaling to the x-axis. (please see the new figures attached to the revised manuscript).

The authors should decide if they want to keep four or two decimals both in tables and in the main text of the manuscript.

Authors: We changed the decimals of p-values in the result section to two decimals.

The authors should explain in the manuscript the used abbreviations e.g. VOT.

Authors: The abbreviation VOT does not appear any more in the figures. It is now spelled out in the whole manuscript.

The authors should move their statement on ethical approval from Data processing section to the protocol section.

Authors: We moved the statement on ethical approval from the Data processing section to the protocol section.

The title should reflect better either the results or the aim of the study.

We changed the title to:

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

We hope that we could answer all the comments and questions by the reviewer.

Yours sincerely,

Victor Jeger, MS

Aristomenis K Exadaktylos, MD