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Monitoring of Free Flaps with Combined Tissue Spectrophotometry and Laser Doppler Flowmetry in an Animal Experimental Model

Mette Marie Berggren-Olsen, MD[1,2] Andreas Rauff-Mortensen, MD[3,4] René Holst, PhD[2,5]
Kim Christian Houlind, MD, PhD[1,2] Hanne Birke-Sørensen, MD, PhD[6]

[1] Department of Vascular Surgery, Kolding Hospital, Kolding, Denmark
[2] Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark
[3] Department of Anaesthesiology and Intensive Care Medicine, Aarhus University Hospital, Aarhus, Denmark
[4] Research Centre for Emergency Medicine, Aarhus University Hospital, Aarhus, Denmark
[5] Oslo Centre for Biostatistic and Epidemiology, University of Oslo, Oslo, Norway
[6] Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

Address for correspondence Mette Marie Berggren-Olsen, MD, Department of Vascular Surgery, Kolding Hospital, DK-6000 Kolding, Denmark (e-mail: Mette.marie.berggren.olsen@rsyd.dk).

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Abstract

Background When mobilizing free flaps, postoperative monitoring of perfusion is crucial to detect ischemia. Continuous monitoring may be feasible by applying a combination of tissue spectrophotometry and laser Doppler flowmetry (oxygen-2-see [O2C]).

Material and Methods On 10 pigs, two symmetrical myocutaneous flaps were mobilized on each side of the abdomen based on the deep inferior epigastric vessels. Flaps were randomized to clamp either the artery or the vein and measurements using O2C were performed before, during, and after the intervention yielding information on blood flow, saturation (sat), and relative tissue hemoglobin (rHgb) concentration.

Results Baseline values were similar in all groups. Introduction of ischemia caused a rapid decline in arterial ischemic flaps which all reached threshold levels in 3 minutes, whereas that was only the case for three of six venous ischemic flaps. Venous clamping resulted in a decline in sat, while the response to arterial clamping was an initial decline followed by an increase in sat. In all arterial ischemic flaps, rHgb concentration either decreased or remained at baseline levels but increased in all venous ischemic flaps. The median time to a 30% rise was 1 minute at an 8-mm depth. The rate of decreasing flow along with the rHgb measurements made it possible to distinguish the arterial ischemia (AI) from the venous ischemia (VI) within the first few minutes.

Conclusion In this animal experimental model, O2C measurements of blood flow reliably detected ischemia. By adding information about rHgb, it was possible to distinguish between AI and VI.

Keywords
- free flap
- monitoring
- O2C

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Free tissue transfer has made extensive resection and reconstruction possible. Although the rate of success is high, reoperation is required in 5 to 25% of tissue transfers due to vascular compromise.[1–4] Early detection of vascular compromise enables early re-exploration, which is essential, as the salvage rate decreases with duration of ischemia.[5–7] Traditionally, free tissue transfers are monitored clinically by evaluation of color, capillary response, and bleeding after needle prick. An often-used regime includes evaluation every hour during the first 24 postoperative hours,[8] but other methods of monitoring have shown that vascular compromise may be detected earlier.[9]

Flap monitoring should ideally be harmless to patient and flap, reliable and accurate, easy to use and interpret, and give continuous information about the condition of the flap.[9,10] The oxygen-2-see (O2C, LEA Medizintechnik GmbH, Gießen, Germany) is a combined laser Doppler and tissue spectrophotometer that continuously monitors blood flow, oxygen sat, flow velocity, and the amount of hemoglobin in the tissue at depths of 2 and 8 mm. It can be used to monitor all tissue transfers with an accessible cutaneous part. Chubb et al[11] reported of 166 cases of using the O2C for monitoring free tissue transfers, but the method has not been evaluated in a standardized setup.

The aim of this animal study was to investigate the ability of the O2C to detect arterial ischemia (AI) and venous ischemia (VI) in pedicled flaps and to distinguish between the two types of ischemia.

Materials and Methods

The experiment was approved by the Danish Ministry of Justice, the Animal Experimentation Inspectorate (2012-15-2934-00145), and conducted in accordance with the Danish Animal Welfare Act.

Anesthesia and Preparation

Ten female Danish landrace pigs weighing a mean of 39 kg (range: 38–41 kg) were anesthetized with intravascular S-ketamine (10 mg/kg). The pigs were placed in a supine position and were endotracheal intubated and connected to a ventilator (Datex-Ohmeda, S/5 Advance, GE Healthcare). Anesthesia was maintained by an infusion of propofol and fentanyl. An infusion of acetated Ringer's solution (Fresenius Kabi AB, Uppsala, Sweden) (10 mL/kg/h) was given to maintain an hourly urinary output of 30 to 100 mL. The infusion rate was adjusted accordingly every hour by an increase or decrease in the infusion rate by 200 mL/h. Core temperature was maintained between 38 and 39°C using forced air warming (Bearhugger).

Surgery

On each pig, two symmetrical myocutaneous flaps were mobilized—one on each side of the abdomen—based on the deep inferior epigastric vessels (►**Fig. 1a**). The vessels were skeletonized and only one artery and one vein were preserved (►**Fig. 1b**). All surfaces of the flaps except the skin were covered

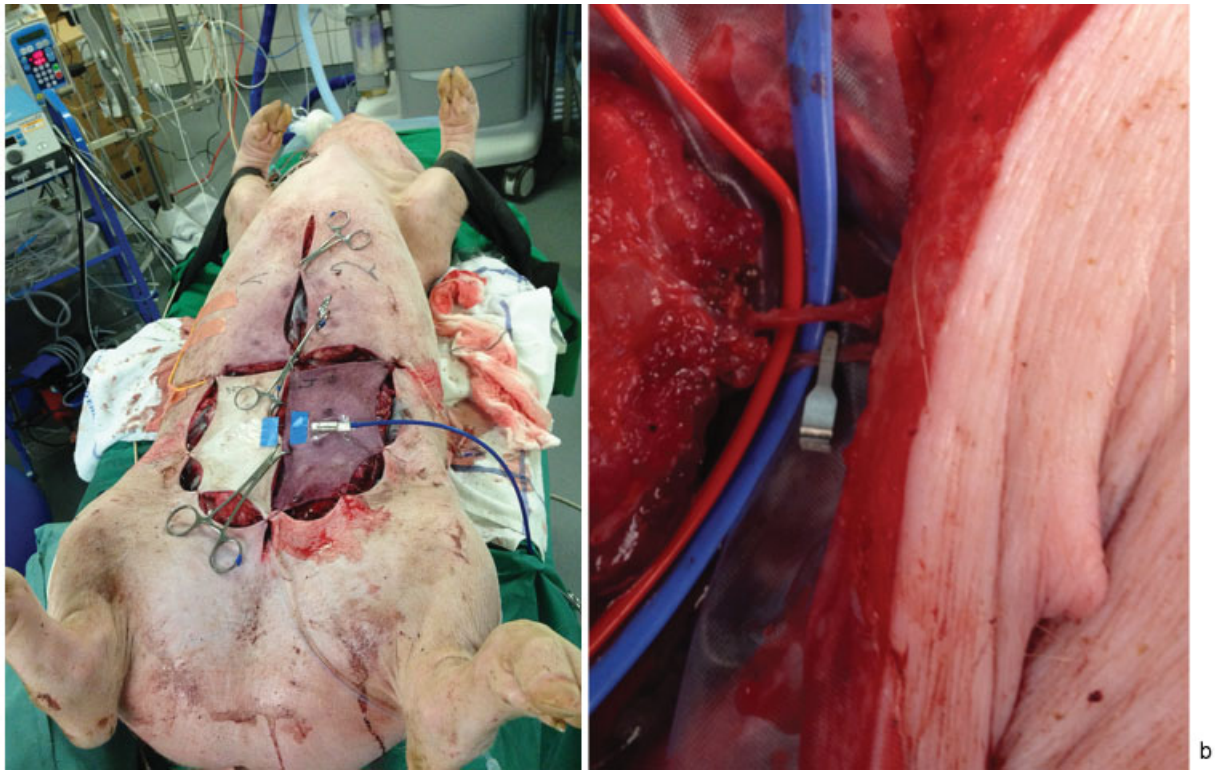

Fig. 1 (a) The setup. Picture of the pig in supine position with ischemic flaps and the probe attached to the VI flap. (b) Vascular pedicle with clamp. Vessel clamps were used to introduce ischemia. VI, venous ischemia.

with plastic to avoid diffusion to and from surrounding tissue, and the flaps were fixed in their original position using skin sutures.

Time Schedule

After a baseline monitoring of 5 minutes, the two flaps of each pig were randomly allocated to one of two possible interventions: AI or VI and introduction of ischemia at 0 or 15 minutes after invention. The initiation of ischemia was obtained by clamping either the artery or the vein of the vascular pedicle. Two flaps were allocated as controls. Continuous measurements by O2C were made 5 minutes after the introduction of ischemia and subsequently for 2 minutes with 15 minutes interval. The pigs were euthanized after the experiment.

Oxygen-2-See

The O2C (LEA Medizintechnik GmBH, Gießen, Germany) combines laser Doppler flowmetry and tissue spectrophotometry. The $1 \times 2.4\ cm^2$ probe emits continuous wave laser light at 830 nm, 30 mW, and white light at 500–800 nm, 20 W through a fiber optic cable. Both white light and laser light are backscattered by the tissue and collected by the same probe.

Oxygenated and deoxygenated hemoglobin reflect and absorb light differently. For light at wavelengths in the range of 500 to 800 nm, fully oxygenated hemoglobin has two absorption peaks, at 542 and 577 nm, whereas deoxygenated hemoglobin has only one absorption peak, at 556 nm. By comparing the spectra of the reflected light to the spectra of hemoglobin with a known oxygen saturation (sat) level, the amount of oxyhemoglobin as a part of the total amount of hemoglobin in the tissue can be calculated; this is termed sat. From the intensity of the backscattered light, the relative amount of hemoglobin (rHgb) is calculated and is given in arbitrary units (AU).

The movement of erythrocytes causes a Doppler shift in the frequency of the laser light, which is registered by the probe as flow velocity because the shift in frequency is proportional to the velocity of the movement. By including the information on rHgb, the measurement of velocity enables the calculation of the third output "blood flow," which in this article will be mentioned as "flow" and is also given in AU.

Light entering vessels with a diameter > 100 µm is fully absorbed, which means information is primarily gathered from backscattering from venules, the microcirculation.[11,12]

Outcomes

Detection of ischemia was defined as a decrease in flow to values below 10 AU. Detection of VI was defined as ischemia in combination with a 30% rise in rHgb.

Statistical Analysis

The statistical modeling and analysis intended to assess the potential for distinguishing arterial from venous ischemia by the use of O2C. As such, the statistical models needed to capture all essential aspects of the mean value structures for the three outcome variables: flow, sat, and rHgb. For reliable discrimination, the model also had to provide precise estimates of standard errors. This was achieved by a proper covariance structure that reflected the sampling path by which data were generated.

For ease of computation, only measurements at eight time points were used in the analysis: -2, 1 to 5, 30, and 60 minutes after clamping. The first measurement, representing the state immediately before clamping, was used as a baseline variable for predicting the outcomes at time points after clamping.

Data were analyzed using mixed effects models.[13] For each of the three outcomes, the start models allowed for the effects of ischemia, depth, time, and the initial state. These effects were allowed to depend on each other: the effect of depth could vary between the two types of ischemia, the time trends could vary between the types of ischemia and between the depths, and so forth.

Exploratory plots indicated an exponential progress over time for all outcomes, and thereby suggested that time was being used on a logarithmic scale. Box–Cox analyses were used for finding suitable normalizing transformations of the outcome variables.

The correlation induced by multiple measurements taken on the same flap within the same pig was handled by applying a corresponding random effects structure in the mixed effects models. This approach ensured correct standard errors of the parameter estimates and allowed for the estimation of the proportion of random variation at the measurement level, between flaps within pigs and between pigs. All models were checked by q–q plots and the Shapiro–Wilks' test for normality of the residuals. Analysis was conducted using Stata (IC, version 14) and R (version 3.2.2).

Results

A total of 8 flaps were allocated to VI, 10 flaps to AI, and 2 flaps to nonischemic controls. One VI flap was excluded due to a malfunctioning clamp and a second was excluded due to thrombosis during dissection, leaving six flaps undergoing VI. All cases of ischemia were detected by O2C.

Flow

Baseline value for flow at an 8-mm depth was higher than at 2 mm (23.92 AU [95% confidence interval, CI: 14.35–33.50] vs. 73.05 AU [95% CI: 48.43–97.67]; $p = 0.001$). There was no significant difference in baseline flow between AI and VI or controls. In one flap in the AI group and two flaps in the VI group, flow was below 10 AU at a baseline depth of 2 mm. Conversely, in all flaps, flow was higher than 10 AU at a depth of 8 mm.

As shown in ►**Fig. 2**, the introduction of AI caused an abrupt decline in flow in all cases. In all cases of AI, flow reached the critical value of 10 AU within the first 3 minutes at both 2- and 8-mm depths, and remained at these very low levels during the 60-minute observation period, except for one flap in which flow did not drop below 10 AU at an 8-mm depth despite a significant drop in flow at the 2-mm depth. In VI flaps, the decline was slower: in only 3 of 6 flaps did flow fall below 10 AU in 5 minutes at both the 2- and 8-mm depths.

The confidence bands for AI and VI were disjointed between 1 and 3 minutes after clamping, but thereafter the bands were convergent (►**Fig. 3**). The effects of ischemia

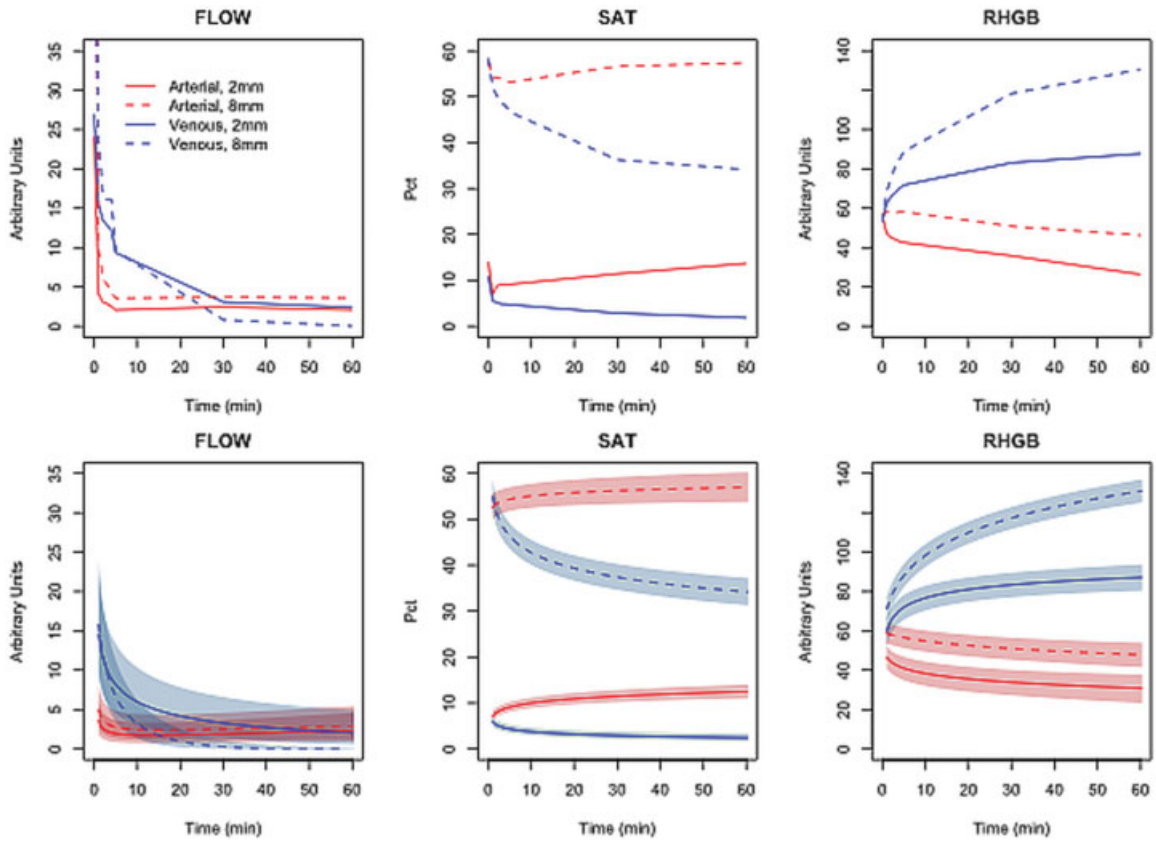

Fig. 2 Results of the measurements in arterial ischemic and venous ischemic flaps during the 1 hour observation period. Top row: mean values of flow, sat, and rHgb at baseline and during observation period. Bottom row: predicted and fitted values with confidence bands. rHgb, relative hemoglobin; sat, saturation.

on flow were different at the two depths and depended on baseline values but were independent of time (►**Table 1**). The median time for flow to decay to 10 AU was 1 minute for AI flaps at both 2- and 8-mm depths and 5 minutes for VI flaps at both 2- and 8-mm depths (►**Fig. 4**).

Saturation

In all VI flaps, sat responded by a decline continuing for 60 minutes at both 2- and 8-mm depths, whereas in all AI flaps, the response was an initial decline only for 1 minute at a 2-mm depth and 5 minutes at an 8-mm depth, after which the values showed a tendency to increase (►**Fig. 2**).

Saturation depended on both ischemia and depth, with different effects at different depths, for measurements of AI or VI flaps. The time effect was modified both by type of ischemia and by the initial level of sat before clamping (►**Table 2**).

Relative Hemoglobin

rHgb responded differently to the two types of ischemia. In all AI flaps, rHgb decreased or remained at the baseline level, whereas it increased in all VI flaps. There was no difference in baseline values between depths or types of ischemia. The rHgb measurements were affected by both ischemia and by depth. The baseline values affected both the overall level and the trend at time points after introducing ischemia. The trend was also affected by the combination of ischemia and depth (►**Table 3**).

The median time to a 30% rise in rHgb in VI flaps was 5 minutes (range: 1–30 minutes) at a 2-mm depth and 1 minute (range: 1–30 minutes) at an 8-mm depth (►**Fig. 5**).

Random Variation

A proper assessment of the potential for differentiating AI from VI also involves evaluating the random noise and its sources. The sampling design in this study involved three sources of random variation: measurement errors at the individual measurement level within the flaps, between-flap variations within pigs, and between-pig variations.

Twenty-seven percent of the random variation in flow could be attributed to between-pig variation, whereas ~7% could be attributed to between-flap within pigs. The remaining 66% of the random variation in flow originated from measurement errors at the individual measurement level within flaps.

In contrast to flow, sat and rHgb measurements showed similar patterns. A negligible amount of random variation resulted from between-pig variations, whereas ~55% of random variation resulted from between-flap variations and ~40% resulted from measurement error.

Discussion

Vascular compromise leading to tissue loss is a major risk when performing tissue transplants.[1,2,10] As early intervention is

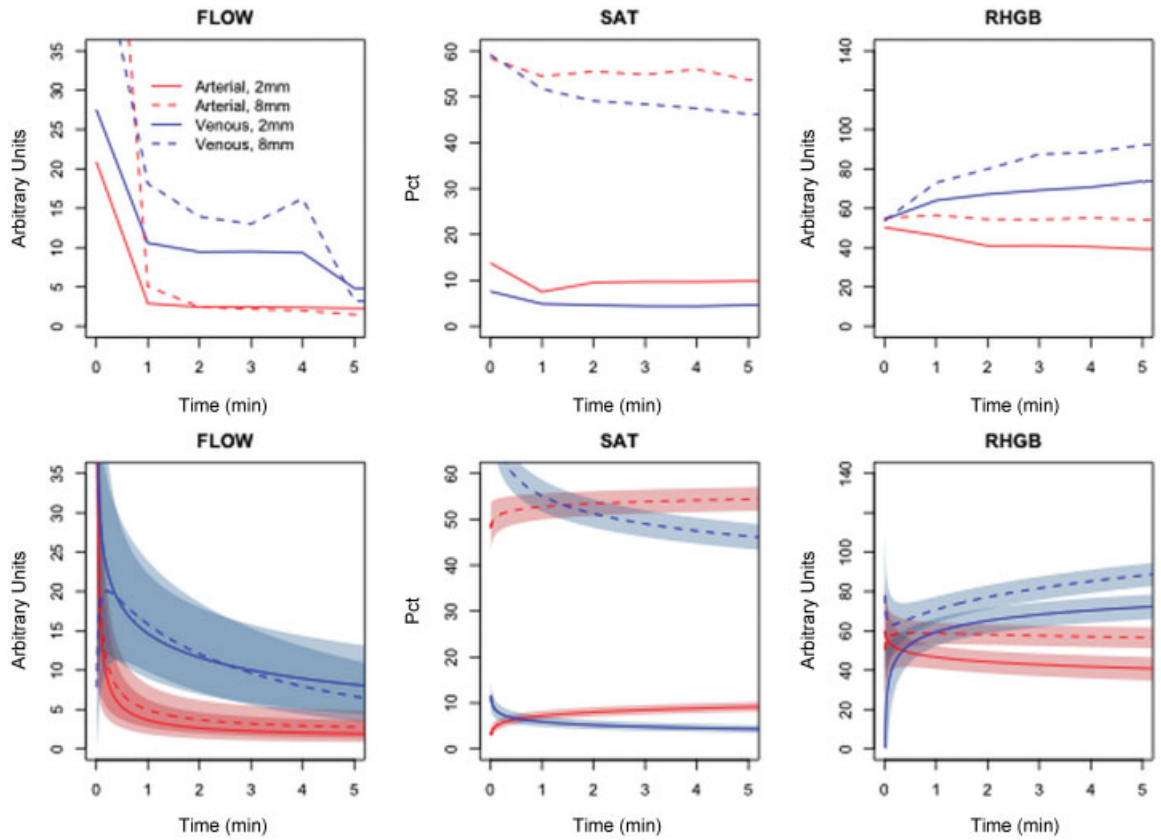

Fig. 3 Results of the measurements in arterial ischemic and venous ischemic flaps during the first 5 minutes of the observation Period. Top row: mean values of flow, sat, and rHgb at baseline and during the first 5 minutes. Bottom row: predicted and fitted values with confidence bands. rHgb, relative hemoglobin; sat, saturation.

necessary in the case of vascular compromise to prevent flap loss, monitoring is crucial.[5,10,11]

In this standardized setup, the O2C detected all cases of ischemia with no false negatives. Two flaps were allocated to nonischemic controls; in neither of these cases did the O2C measurements show signs of ischemia. The baseline values of flow in three flaps were below 10 AU at a 2-mm depth, but in all flaps, flow values were higher than 10 AU at an 8-mm depth. In both AI and VI flaps, flow decreased to levels below 10 AU, whereas AI flaps reached a minimum value of flow in the first 2 minutes of ischemia and VI flaps reached their minimum after 60 minutes of ischemia. This is consistent with the findings of Yuen and Feng, who found that, in the case of VI, flow declined gradually, none of the flaps reached critical value in 8 minutes, and only three of seven flaps reached critical values in 15 minutes.[14]

Table 1 Flow: results of the mixed effects model for flow

Variable	Estimate	SE	Pr > z	95% CI-Lo	95% CI-Hi
Bv	0.0918	0.0416	0.027	0.0103	0.1733
Log (time)	− 0.2834	0.0822	0.001	− 0.4445	− 0.1222
Depth Isch log (time)^2					
8 mm arterial	− 0.0043	0.0108	0.694	− 0.0254	0.0169
8 mm venous	− 0.0820	0.0122	0	− 0.1059	− 0.0582
Log (time)^2	0.0552	0.0196	0.005	0.0168	0.0936
Venous	0.9154	0.2519	0	0.4638	1.4512
Venous log (time)^2	− 0.0621	0.0121	0	− 0.0858	− 0.0383
Intercept	1.3087	0.2271	0	0.8635	1.7539

Abbreviations: Arterial, arterial ischemia; Bv, baseline values; CI-Hi, confidence interval—higher limit; CI-Lo, confidence interval—lower limit; Isch, type of ischemia; SE, standard error; Venous, venous ischemia.

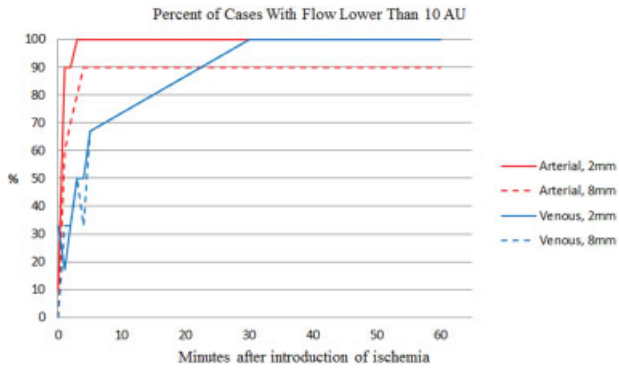

Fig. 4 The introduction of AI caused an abrupt decline in flow in all cases. In 9 of 10 cases of AI, flow reached the critical value of 10 AU within the first 3 minutes at both 2- and 8-mm depths. In VI flaps, the decline was slower: only three of six flaps did flow fall below 10 AU in 5 minutes at both the 2- and 8-mm depths. AI, arterial ischemia; AU, arbitrary unit; VI, venous ischemia.

In AI flaps, flow decreased rapidly after the introduction of ischemia, and after 4 minutes, all 10 flaps had reached the critical value of 10 AU at a 2-mm depth and 9 of the 10 flaps reached the critical value at an 8-mm depth. After 4 minutes, only three of six VI flaps had reached 10 AU at the 2-mm depth and two of six had reached 10 AU at the 8-mm depth. After 30 minutes, all six flaps with VI had decreased to 10 AU at both depths (►**Figs. 2** and **3**). This is similar to the findings of Yuen and Feng,[15] who found that arterial compromise was characterized by an abrupt fall in flow and sat, whereas venous compromise led to a more slowly decreasing value of flow over several hours.

In a similar setup, Hjortdal et al found that tissue pO_2 decreased significantly in both AI and VI flaps when blood flow was reduced and subsequently cutoff for 1 hour.[16] Furthermore, pO_2 was significantly lower in cases with AI than in the setting of VI. In our study, we also found decreasing levels of sat in flaps undergoing VI, but in AI flaps, we saw a slight decrease during the first 5 minutes of ischemia, while sat increased with prolonged ischemia.

Table 2 Sat: results of the mixed effects model for sat

Variable	Estimate	SE	Pr > z	95% CI-Lo	95% CI-Hi
Bv log (time)	− 0.0348	0.0071	0	− 0.0486	− 0.0209
8 mm	4.5767	0.0781	0	4.4236	4.7297
Venous	− 0.2595	0.1140	0.023	− 0.4829	− 0.0361
8 mm venous	0.4217	0.0973	0	0.2311	0.6124
log (time)	0.3355	0.0448	0	0.2478	0.4233
Venous log (time)	− 0.4530	0.0357	0	− 0.5229	− 0.3830
Intercept	2.6848	0.1004	0	2.4880	2.8816

Abbreviations: Bv, baseline values; CI-Hi, confidence interval—higher limit; CI-Lo, confidence interval—lower limit; sat, saturation; SE, standard error; Venous, venous ischemia.

Table 3 rHgb: results of the mixed effects model for rHgb

Variable	Estimate	SE	Pr > z	95% CI-Lo	95% CI-Hi
Bv	0.8006	0.0961	0	0.6123	0.9890
Bv log (time)^2	− 0.0393	0.0066	0	− 0.0522	− 0.0265
8 mm	51.5737	4.4195	0	42.9116	60.2359
Isch log (time)					
Arterial	0.9309	6.3782	0.884	− 11.5702	13.4320
Venous	36.6401	8.2342	0	20.5013	52.7789
Venous	64.9413	15.7248	0	34.1212	95.7614
Depth Isch log (time)^2					
2 mm arterial	3.1371	1.9220	0.103	− 0.6299	6.9042
2 mm venous	5.8083	2.2291	0.009	1.4393	10.1773
8 mm arterial	4.3009	1.9284	0.026	0.5212	8.0805
8 mm venous	16.6901	2.2208	0	12.3373	21.0428
Intercept	− 3.6128	20.6619	0.861	− 44.1094	36.8839

Abbreviations: Arterial, arterial ischemia; Bv, baseline value; CI-Hi, confidence interval—higher limit; CI-Lo, confidence interval—lower limit; Isch, type of ischemia; rHgb, relative hemoglobin; SE, standard error; Venous, venous ischemia.

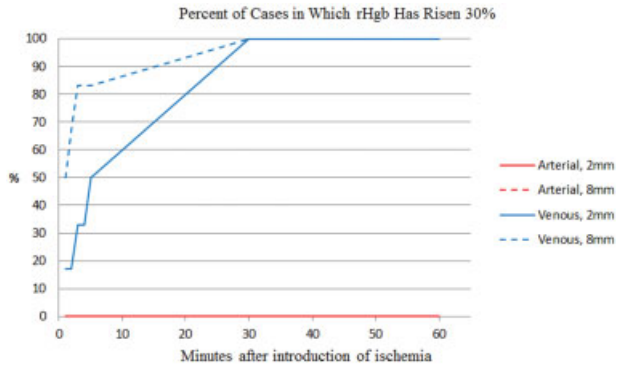

Fig. 5 In all AI flaps, rHgb decreased or remained at the baseline level, whereas it increased in all VI flaps. The median time to a 30% rise in rHgb in VI flaps was 5 minutes (range: 1–30 minutes) at a 2-mm depth and 1 minute (range: 1–30 minute) at an 8-mm depth. AI, arterial ischemia; rHgb, relative hemoglobin; VI, venous ischemia.

During VI, sat decreased as expected. The measurements of sat by spectrophotometry requires the presence of hemoglobin in the tissue which could explain the inconsistency in findings. As oxygenated hemoglobin absorbs more light than deoxygenated hemoglobin,[11] the sat readings in AI flaps could become artificially elevated, due to the low amount of hemoglobin in the tissue. This means that a high sat measured by O2C does not necessarily mean that the flap is well perfused.

The response in rHgb to ischemia was characterized by opposite trends in the two types of ischemia. In all VI flaps, rHgb increased and in all cases of AI, rHgb decreased or remained at the baseline level. This pattern was seen at both 2- and 8-mm depths, as illustrated in ►**Figs. 2** and **3**. This is consistent with the findings of Hölzle et al, who presented a study with 166 free flaps, including 24 flaps that developed vascular compromise.[12] The O2C was used for monitoring and revealed all cases of ischemia with no false positives or negatives using clinical observation as the "gold standard." With a threshold value of a 30% rise in rHgb as a basis for the decision regarding re-exploring, they were able to distinguish between flaps with venous compromise that needed re-exploration and flaps with clinical signs of venous problems, which recovered without further operation. In our study, rHgb reached this threshold during the first 5 minutes in 50% of flaps undergoing VI when measured at a 2-mm depth, and in 83% of flaps when measured at an 8-mm depth (►**Fig. 5**).

Near-infrared spectroscopy (NIRS) has shown to improve flap salvage rate in clinical studies.[17,18] It continuously monitors tissue oxygenation in the flap, and is able to detect ischemia before clinical signs appear, but this method has not the benefit of the rHgb measurement, which means it does not provide information on the type of ischemia, AI or VI.

Spatial frequency domain imaging measures deoxyhemoglobin, oxyhemoglobin, and tissue oxygen sat using two NIRS cameras.[19] This allows for the discrimination between AI and VI as concentrations of both oxyhemoglobin and deoxyhemoglobin decreases in AI and increases in VI during the first few minutes of ischemia,[20] but this system is based on cameras not fixed to the flap and cannot be used for postoperative monitoring when the patient moves.

The O2C continuously measures flow, sat, and rHgb for an unlimited time, but as we only had one probe and two flaps in each pig, we had to shift the probe between the two flaps, which meant that we lost some information.

In case of vascular compromise, early intervention is crucial to flap salvage.[1,6,7] Continuous monitoring contributes to the early recognition of the need for re-exploration. The combination of flow, sat, and rHgb offers the opportunity to recognize vascular problems at an early stage. The combination of rapidly decreasing flow and sat indicates arterial compromise, whereas an increase in rHgb and a slow decline in flow and sat indicates compromise in venous outflow. In our experience, measurements at an 8-mm depth are more reliable than at a 2-mm depth. Even though variance was larger than the 8-mm depth, it seemed less sensitive to changes in ambient light, movement, etc., but data did not allow us to further pursue that line of inquiry.

Conclusion

The aim of this study was to investigate whether the O2C can be a reliable tool for monitoring free flaps. We found the values obtained by the O2C to be reliable and easy to interpret. In this standardized setup, it was possible by using the O2C to both detect and distinguish AI and VI. Nevertheless, further studies must be performed to evaluate the potential and the limitations of O2C in clinical settings.

Acknowledgments

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