

Measurement of skeletal muscle tissue oxygenation in the critically ill

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ABSTRACT

Shock is a state of acutely reduced tissue oxygenation. In cardiogenic shock oxygen delivery (DO₂) is reduced, but oxygen extraction is preserved. In septic shock DO₂ is preserved, but oxygen extraction is decreased because of microvascular changes and disturbed metabolism. Global assessment of DO₂ and oxygen consumption does not tell us enough about adequacy of regional perfusion. The aim of this study was to assess the value of near infrared spectroscopy (NIRS) in detecting skeletal muscle tissue oxygenation (StO₂) in critically ill patients.

*Patients in cardiogenic shock (n=17), septic shock (n=14), without shock but with localized infection (n=14) and healthy volunteers (n=15) were included. Thenar StO₂ was measured with NIRS before (baseline StO₂, %), between (downward StO₂ slope, %/min) and after 90 seconds of upper arm stagnant ischemia (hyperemic StO₂, %). Muscle oxygen extraction (mOER) was calculated as follows: mOER (%) = (1-baselineStO₂/hyperemic StO₂)*100. Repeatability was assessed using the Bland Altman method (95 % of values within limits of agreement), comparing 55 pairs of measurements performed in 5-minute intervals.*

Repeatability of measurements was clinically acceptable. Compared to septic shock patients, cardiogenic shock patients had lower baseline StO₂ (68.9 ± 10.0 % vs. 84.3 ± 10.4 %; p < 0.05) and hyperemic StO₂ (80.8 ± 7.8 % vs. 91.8 ± 8.3 %; p < 0.05), and a higher downward StO₂ slope (-17.4 ± 31.7 %/min vs. -9.1 ± 2.6 %/min; p < 0.05). mOER was higher in healthy volunteers (11.9 ± 3.8 %) and volunteers with cardiogenic shock (14.8 ± 7.3 %) compared to septic shock patients (8.1 ± 7.8 %) and those with localized infection (7.6 ± 5.4 %) (p < 0.05).

Repeatability of baseline StO₂ and hyperemic StO₂ is clinically acceptable. Results support the hypothesis that skeletal muscle oxygen extraction capability is preserved and extraction is increased in cardiogenic shock compared to septic shock.

Key words: repeatability, NIRS, tissue oxygenation, cardiogenic shock

Introduction

Tissue hypoxia in shock correlates with a higher mortality in the critically ill. (1) Assessment of global oxygen delivery (DO₂) and consumption (VO₂) can be made with right heart catheterization using Fick's principle, based on cardiac output, hemoglobin saturation and total value of arterial and central venous blood oxygen contents. Delivery of blood through the capillaries and cellular capability to uptake and utilize oxygen define hemoglobin saturation. Where these two are intact, we see an

increase in VO₂ to compensate for lower blood flow. Examples are cardiogenic, hypovolemic and obstructive shock. In these states, oxygen consumption is limited only by delivery of oxygen, the relationship being linear when delivery drops below consumption capability. A different set of dynamics is seen in distributive shock, where oxygen delivery is usually maintained or even increased, while oxygen consumption is disturbed because of microvascular and metabolic changes. (2) It is not entirely clear whether microvascular shunts or mitochondrial shutdown is predominant but both are probably important. (3,4)

Unfortunately, measurements of global oxygen delivery and consumption, as well as of other global hemodynamic parameters, are uninformative of local tissue blood flow since it can be inadequate despite normal global parameters. (5) Additionally, these measurements are invasive which limits their usefulness since inadequate perfusion should be recognized early in shock development. (6) A good method for tissue perfusion assessment should, therefore, have to be local and noninvasive so it could be used early. In circulatory failure, blood flow redistributes from less important peripheral organs (skin, muscles,

bowels) to vital organs (brains, heart, kidney), hence peripheral tissues can be used for early assessment of tissue perfusion.

We use various methods in clinical practice with the most important still being clinical examination of a patient's finger skin temperature, color, sweating and capillary refill. It is difficult to interpret these signs in the setting of distributive shock, with evidence that tissue hypoperfusion exists, despite normal clinical signs. (7,8,9) Another method is measurement of the difference between core and peripheral temperatures. This method has poor value in the setting of low room temperature and in distributive shock. (10)

Near infrared spectroscopy

Near infrared spectroscopy (NIRS) is measuring tissue oxygenation in muscles (StO₂). (11,12) NIRS is a noninvasive, continuous, bedside method used for tissue oxygenation monitoring. A probe with a near infrared light source is placed on the skin where it transilluminates tissues and detects reflected light. Near infrared light (wave length 700-1000 nm) penetrates into tissue relatively well. The amount of light reflected back to the probe depends on oxygen saturation of chromophores (hemoglobin, myoglobin, cytochrome c oxidase), since saturation defines their absorption spectra. This can be seen with blood where bright red denotes arterial blood and dark blue venous blood. For now, precise quantitative analysis of hemoglobin concentration is not possible for we can only obtain relative relationships of oxygenated and deoxygenated forms of substances. This is done with the Beer-Lambert method, modified for longer paths of rays in tissues. The path of rays depends on the type of tissue, wavelength of light used and intraoptode distance (distance between emitter and detector of light) and is basically telling us the volume of tissue that is being measured. NIRS is indiscriminate towards blood vessel compartments and gives out average values of tissue saturation. Estimations suggest that relationships between

arterial, venous and capillary systems are 10:20:70%. (13) Besides continuous measurements of hemoglobin and myoglobin saturation, technology for measuring the absorption of oxydated cytochrome c only, is being developed which could be used for monitoring cellular breathing. (14)

To assess tissue consumption of oxygen in the muscles of the arm with NIRS, an area of stagnant ischemia is produced by constricting the arm with an inflatable cuff (to 260 mmHg), thus restricting blood flow to the hand. NIRS was used before, during and after inducing ischemia in healthy individuals. (15) During ischemia, an almost linear drop in tissue hemoglobin and myoglobin saturation was observed until it reached a plateau after 3 to 4 minutes, with no further changes. After deflating the cuff, a rapid increase in saturation was observed, reaching values higher than in the initial steady state, which returned to the initial values after around 5 minutes. The drop in saturation during ischemia has been attributed to consumption of oxygen by cells for metabolism with the plateau explained as a shut down of oxygen metabolism rather than complete desaturation of hemoglobin. Increase in saturation after ischemia results from reperfusion and reactive hyperemia. In healthy individuals, this method was proven effective in measuring oxygen consumption in muscles. (16)

The aim of our study was to assess the value of near infrared spectroscopy (NIRS) in detecting skeletal muscle tissue oxygenation (StO₂) in the critically ill.

Materials and methods

Patients

The National Ethics Committee of Slovenia approved the study; informed consent was obtained from all patients or their relatives. The study was performed from November 2005 to May 2006. Patients admitted to ICU with localized infection, septic shock or cardiogenic shock, were included. The group of healthy volunteers was also included as controls.

Definitions

The criteria used for the diagnosis of localized infection and septic shock were defined by the ACCP/SCCM consensus conference (1992). (17) Seriousness of disease was evaluated using SOFA (Sequential organ failure assessment score) (18), lactate (LacTest, Roch Diagnostics, Germany) and based upon the usage of vasopressors, inotropes and need for ventilatory support.

Treatment

All patients received standard treatment of localized infection, severe sepsis and septic or cardiogenic shock including: source control, IV fluids, catecholamine infusion, organ failure replacement and/or support therapy, intensive control of blood glucose and corticosteroid substitution therapy according to current Surviving Sepsis Campaign Guidelines. (19) Mechanically ventilated patients were sedated with midazolam and/or propofol infusion and no paralytic agents were used.

Measurement of tissue oxygenation

StO₂ of the thenar muscles was measured continuously with NIRS for 48 hours after admission. We used the tissue spectrometer InSpectra™ (Hutchinson Technology Inc., BioMeasurement Division, Hutchinson, Min, USA). A 25 mm probe was placed on the skin of the thenar, where the highest StO₂ value was shown. StO₂ was recorded continuously for 3 minutes before, during and after arterial occlusion with an inflatable cuff. The cuff was inflated to 260 mmHg for 90 seconds. In healthy volunteers and conscious patients measurements were conducted after 15 minutes of bed rest, avoiding any muscular contractions. Results were recorded in the form of a curve using InSpectra software and analyzed with InSpectra Analysis Program V2.0 (Hutchinson Technology Inc., USA) that works under MatLab 7.0 (MathWorks Inc., USA). Baseline StO₂ (%) was measured before inflating the cuff, hyperemic StO₂ (%) after deflation and curve change was calculated, downward StO₂ slope (%/min) during cuff inflation and upward StO₂ slope

(%/min) after pressure was released. Muscular extraction rate (mOER, %) in basal conditions was calculated as: $mOER = (1 - \text{baseline } StO_2 / \text{hyperemic } StO_2) * 100$. The arterial occlusion test was performed in 5-minute intervals to study repeatability.

Data analysis

Data was expressed as absolute values or mean values \pm standard deviation (SD). One-way ANOVA with Tukey or Tamhane test for post hoc multiple comparisons and Chi-Square test was applied to analyze data (SPSS 12.0

for Windows™, SPSS Inc., USA). A p value of <0.05 was considered statistically significant. Repeatability bias of differences and 95 % limits of agreement were calculated. (20) Bias was considered acceptable within 5 % of mean value of paired measurements. In Bland-Altman graphs, 5 % of values out of limits of agreement were considered clinically acceptable for repeatability to be valid.

Results

Data on patients and healthy volunteers are shown in table 1.

There was no difference in gender,

age and length of treatment in ICU between groups ($p > 0.05$). Patients with cardiogenic and septic shock had a higher SOFA score ($p = 0.001$) and lower survival ($p = 0.029$) than patients with limited infection.

Table 2 shows that vital signs (blood pressure, heart rate, urine output, and hemoglobin saturation) did not differ significantly among patients with infections and those in shock ($p > 0.05$).

CRP- C-reactive protein, L- leucocytes, Hb- hemoglobin, arterial blood gas analysis: pH, pCO_2 , pO_2 , BE, SAO_2 . C-reactive protein (CRP) was raised

Table 1. Demographics data on patients with cardiogenic shock, septic shock, limited infection and the control group of healthy volunteers.

| | Cardiogenic shock (n = 17) | Septic shock (n = 14) | Limited infection (n = 14) | Healthy volunteers (n = 15) | Total (n = 60) | F/ χ^2 | p |
|-----------------------------------|----------------------------|-----------------------|----------------------------|-----------------------------|----------------|-------------|-------|
| Gender (men/women) | 7/10 (41 %) | 10/4 (71 %) | 8/6 (57 %) | 7/8 (47 %) | 32/28 (53 %) | 3.201 | 0.362 |
| Age (years) | 71 \pm 15 | 64 \pm 15 | 68 \pm 10 | 42 \pm 18 | 68 \pm 13 | 0.843 | 0.438 |
| SOFA (score) | 8 \pm 2 | 9 \pm 4 | 5 \pm 3 | / | 8 \pm 3 | 8.471 | 0.001 |
| Length of treatment in ICU (days) | 14 \pm 9 | 8 \pm 6 | 9 \pm 8 | / | 10 \pm 8 | 2.115 | 0.135 |
| Survival (survived/died) | 9/8 (53 %) | 7/7 (50 %) | 13/1 (93 %) | / | 28/17 (62 %) | 7.068 | 0.029 |

Table 2. Differences in vital signs among the three groups of patients (cardiogenic shock, septic shock and limited infection).

| | Cardiogenic shock (n=17) | Septic shock (n=14) | Limited infection (n=14) | Total (n = 45) | F/ χ^2 | p |
|------------------------------------|--------------------------|---------------------|--------------------------|----------------|-------------|-------|
| Body Temperature (°C) | 37.3 \pm 0.9 | 38.2 \pm 1.0 | 37.1 \pm 1.2 | 37.5 \pm 1.1 | 2.895 | 0.073 |
| Systolic blood pressure (mmHg) | 111 \pm 14 | 123 \pm 31 | 130 \pm 33 | 120 \pm 26 | 1.728 | 0.195 |
| Diastolic blood pressure (mmHg) | 68 \pm 12 | 69 \pm 13 | 72 \pm 19 | 70 \pm 15 | 0.246 | 0.783 |
| Heart rate (beats/minute) | 107 \pm 25 | 111 \pm 25 | 91 \pm 16 | 103 \pm 24 | 2.008 | 0.153 |
| Urine output (mL/hour) | 78 \pm 44 | 36 \pm 44 | 63 \pm 30 | 60 \pm 38 | 1.341 | 0.295 |
| Arterial hemoglobin saturation (%) | 98 \pm 1 | 98 \pm 1 | 97 \pm 2 | 98 \pm 1 | 1.212 | 0.322 |

in all groups (average CRP 195 mg/L). It was lowest in patients with cardiogenic shock (average CRP 123 mg/L) and highest in patients with septic shock (average CRP 261 mg/L), but differences were not statistically significant ($p=0.099$). Patients with septic shock had higher values of leucocytes in comparison to patients with cardiogenic shock ($20 \pm 9 * 10^9$ cells/L vs. $11 \pm 2 * 10^9$ cell/L, p

< 0.05). Creatinine values were also higher in patients with cardiogenic and septic shock compared to patients with localized infection, although not statistically significant ($p=0.079$) (table 3).

FiO_2 – fraction of oxygen in inspired air.

Patients with septic shock required a higher percentage of inspired oxygen than patients with localized infection (p

< 0.05). Most patients with cardiogenic (82 %) and septic shock (100 %) were treated with vasoactive support. Most patients with cardiogenic shock also received inotropes (94 %) (table 4).

Values of baseline StO_2 and follow-on StO_2 were lower in patients with cardiogenic shock in comparison to patients with septic shock and patients with localized infection (68.9 ± 10.0 % vs. 84.3 ± 10.4 % vs. 85.2 ± 9.7

Table 3. Differences in laboratory data among the three groups of patients (cardiogenic shock, septic shock and limited infection).

| | Cardiogenic shock (n=17) | Septic shock (n=14) | Limited infection (n=14) | Total (n = 45) | F/ χ^2 | p |
|---------------------------|--------------------------|---------------------|--------------------------|----------------|-------------|-------|
| CRP (mg/L) | 123±53 | 243±154 | 142±108 | 186±135 | 2.524 | 0.099 |
| L (* 10^9 cell count/L) | 11±2 | 20±9 | 17±9 | 17±8 | 1.540 | 0.246 |
| Hb (g/L) | 115±15 | 125±20 | 123±13 | 123±16 | 0.532 | 0.597 |
| Creatinine (μ mol/L) | 199±165 | 227±186 | 74±27 | 156±148 | 2.933 | 0.079 |
| pH | 7.36±0.09 | 7.29±0.19 | 7.38±0.83 | 7.34±1.36 | 1.261 | 0.306 |
| pCO ₂ (kPa) | 5.7±1.4 | 6.4±1.6 | 6.0±1.2 | 6.1±1.3 | 0.265 | 0.770 |
| pO ₂ (kPa) | 11.6±2.4 | 20.3±6.6 | 17.3±10.0 | 17.3±8.3 | 1.524 | 0.242 |
| BE (mmol/L) | -4.4±6.1 | -3.5±9.9 | 1.4±5.1 | -0.7±7.5 | 1.301 | 0.297 |
| SaO ₂ (%) | 97±3 | 98±3 | 97±4 | 98±3 | 0.732 | 0.494 |
| Lactate (mmol/L) | 4.3±3.2 | 3.5±2.6 | 1.0±0.5 | 3.4±2.8 | 2.516 | 0.100 |

Table 4. Supportive treatment given to patients with cardiogenic shock, septic shock and limited infection.

| | Cardiogenic shock (n=17) | Septic shock (n=14) | Limited infection (n=14) | Total (n = 45) | F/ χ^2 | p |
|--|--------------------------|---------------------|--------------------------|----------------|-------------|-------|
| FiO_2 (%) | 50±18 | 75±20 | 46±12 | 57±22 | 7.639 | 0.003 |
| Artificial ventilation (yes/no) | 16/1 (94 %) | 12/2 (86 %) | 9/5 (64 %) | 37/8 (82 %) | 1.857 | 0.395 |
| Patients with vasoactive support (noradrenalin, dopamine) (yes/no) | 14/3 (82 %) | 14/0 (100 %) | 5/9 (36 %) | 33/12 (73 %) | 13.319 | 0.001 |
| Patients with inotropes (dobutamine, levosimendan) (yes/no) | 16/1 (94 %) | 7/7 (50%) | 3/11 (21 %) | 27/19 (60 %) | 13.648 | 0.001 |

%, $p < 0.05$). mOER was higher in healthy volunteers and patients with cardiogenic shock compared to patients with localized infection ($11.9 \pm 3.8\%$ vs. $14.8 \pm 7.3\%$ vs. $7.6 \pm 5.4\%$, $p < 0.05$). The downward StO_2 slope was steeper in patients with cardiogenic shock compared to septic shock ($-17.2 \pm 6.3\%$ vs. $-9.1 \pm 2.6\%$, $p < 0.05$) (table 5).

NIRS repeatability analysis was done in 55 measurements on 45 patients (table 6). Figures 1 to 4 represent bias of repeated measurements with 95% limits of agreement. Biases of baseline StO_2 and hyperemic StO_2 are acceptable, while biases of downward StO_2 slope and upward StO_2 are beyond the 5% of acceptable limits. 95% of values are within limits of agreement for baseline StO_2 , hyperemic StO_2 and downward StO_2 slope. One measurement is out

of agreed limits for all four variables and eliminating it from analysis improves the result for the downward StO_2 slope and upward StO_2 slope so they also meet the criteria of repeatability.

Discussion

The current study confirmed repeatability of skeletal muscle tissue oxygenation measurements with NIRS in critically ill patients with cardiogenic shock, septic shock and localized infection. We found lower values of baseline StO_2 , hyperemic StO_2 , higher mOER and a steeper downward StO_2 slope in patients with cardiogenic shock in comparison to patients with septic shock.

Repeatability

Purpose of repeatability evaluation is to prove NIRS is clinically applicable.

As can be seen in figures 1 to 4, measurements of baseline StO_2 and hyperemic StO_2 are within acceptable criteria according to Bland and Altman. One measurement has been out of agreed limits in all four variables and eliminating it from analysis had improved the result for the downward StO_2 slope and upward StO_2 slope so they also met the criteria of repeatability.

We have found NIRS method to be precise and repeatable, but since we have not compared NIRS results with more standardized methods of measurement, we cannot claim that measured results are true values of tissue oxygenation. To avoid measurement error, a correct measurement procedure is important. A probe with the appropriate intraoptode distance should be used and the same position on the muscle should be used for probe

Table 5. Near infrared spectroscopy (NIRS) measurements in patients with cardiogenic shock, septic shock, limited infection, and in healthy volunteers.

| | Cardiogenic shock (n=17) | Septic shock (n=14) | Limited infection (n=14) | Healthy volunteers (n=15) | F/ χ^2 | p |
|--------------------------------|--------------------------|---------------------|--------------------------|---------------------------|-------------|--------|
| Baseline StO_2 (%) | 68.9±10.0 | 84.3±10.4 | 85.2±9.7 | 84.1±3.8 | 12,530 | <0.001 |
| Hyperemic StO_2 (%) | 80.8±7.8 | 91.8±8.3 | 92.2±8.3 | 95.5±1.7 | 13.102 | <0.001 |
| mOER | 14.8±7.3 | 8.1±7.8 | 7.6±5.4 | 11.9±3.8 | 4.518 | 0.007 |
| Downward StO_2 slope (%/min) | -17.2±6.3 | -9.1±2.6 | -13.3±4.5 | -37.0±7.6 | 70.156 | <0.001 |
| Upward StO_2 slope (%/min) | 75.4±31.7 | 59.1±35.9 | 73.9±61.9 | 284.8±107.0 | 39.399 | <0.001 |

Table 6. Repeatability of 55 near infrared spectroscopy (NIRS) measurements in patients with infection, shock and in healthy volunteers.

| | Bias of differences | 95% Limits of agreement | Mean of paired measurements | Number of outliers (%) |
|--------------------------------|---------------------|-------------------------|-----------------------------|------------------------|
| Baseline StO_2 (%) | 0.74 ± 0.41 | ± 5.96 | 82.30 ± 1.46 | 2 (3.6 %) |
| Hyperemic StO_2 (%) | -0.40 ± 0.56 | ± 8.06 | 88.88 ± 1.18 | 2 (3.6 %) |
| Downward StO_2 slope (%/min) | -1.04 ± 0.66 | ± 9.52 | -12.03 ± 0.79 | 1 (1.8 %) |
| Upward StO_2 slope (%/min) | -0.80 ± 1.90 | ± 27.14 | 49.43 ± 4.29 | 3 (5.5 %) |

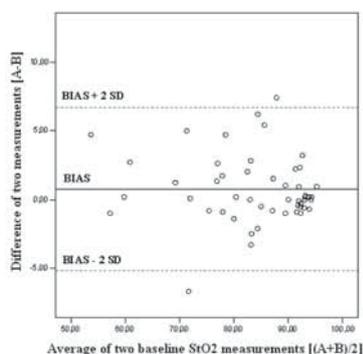
placement. The optimal position on the muscle is where StO_2 is highest (largest volume of transilluminated tissue) to avoid underestimation of StO_2 . It is also important to avoid muscle activity during measurements since contractions change results considerably. Skeletal muscle tissue oxygenation in cardiogenic and septic shock Tissue oxygenation in vivo depends on concentration of hemoglobin, number of open capillaries and vessel circumference (vasodilatation or vasoconstriction). (1) Peripheral tissue increases oxygen extraction (mOER) in cardiogenic shock where tissue flow is decreased.

(21) Lower tissue blood flow was found in patients who later died than in patients who survived. (22) We had similar findings in our study, with a few exceptions, that could be explained by an unusually strong inflammatory response reducing tissue extraction via the same mechanism as in sepsis. In septic shock mOER is reduced because of changes in microcirculation and mitochondria while tissue blood flow is increased with some areas hyperperfused and some hypoperfused. Tissue oxygenation is thus near normal or even increased. These findings have been confirmed in numerous studies on animals (23,24) and humans. (25)

Other studies found that in severe inflammation, lasting over 12-16 hours, cellular breathing and ATP production is slowed down. (26) Current opinion is that multi-organ failure is an attempt to preserve affected cells switching to a hibernation-like state. (27) Muscular oxygen extraction rate for patients with localized infection is similar to that in patients with septic shock. This unexpected result could be attributed to baseline StO_2 higher than 90 % in 8 out of 14 patients. This shows a weakness in our definition of mOER, as higher baseline StO_2 affects calculations. Our definition of mOER, as a relationship between baseline StO_2 and hyperemic StO_2 , is only a robust estimate of VO_2 versus DO_2 ratio. Further studies are needed to confirm our results using additional methods for local tissue metabolism assessment.

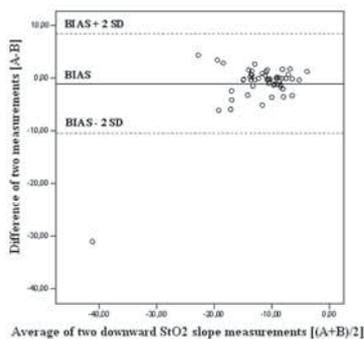
Analyzing the StO_2 curve change (downward StO_2 slope) can give us a good estimation of VO_2 . The baseline curve (before cuff inflation) represents the difference between oxygen delivery and consumption and is constant for the respective tissue. After cuff inflation, when oxygen delivery is shut down, the StO_2 curve slopes down because of continued oxygen consumption. The linear drop, as shown in figure 1, is true for shorter total arterial constrictions, while the drop for longer cuff inflation is exponential and reaches a plateau after 3 minutes, when consumption is also shut down. The slope of the curve in lower values of StO_2 (majority of hemoglobin is desaturated) is probably also affected by myoglobin. Myoglobin and hemoglobin absorptions cannot be differentiated with NIRS. In higher values of pO_2 , myoglobin is saturated and constant and does not affect relative StO_2 measurements. The role of myoglobin in lower pO_2 and StO_2 values is unknown. (28,29) It is therefore reasonable to measure the StO_2 slope right after cuff inflation when VO_2 is not slowed down because of ischemia and myoglobin does not affect the measurements.

After cuff deflation a short period of hyperemia prevails with vasodilatation



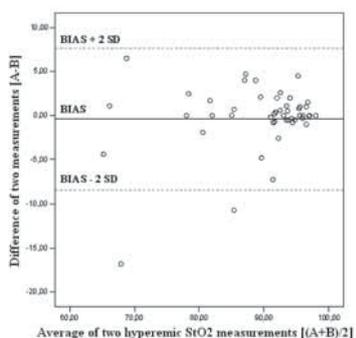
A – first measurement,
B – repeated measurement.

Figure 1. Bland Altman graph of muscle oxygen saturation for baseline StO_2 .



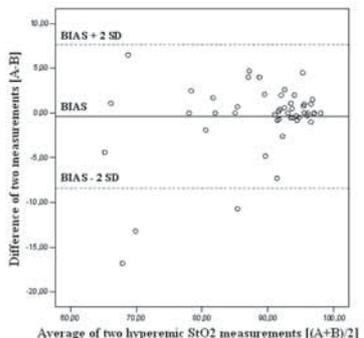
A – first measurement, B – repeated measurement.

Figure 3. Bland Altman graph of muscle oxygen saturation for downward StO_2 slope.



A – first measurement,
B – repeated measurement.

Figure 2. Bland Altman graph of muscle oxygen saturation for hyperemic StO_2 .



A – first measurement,
B – repeated measurement.

Figure 4. Bland Altman graph of muscle oxygen saturation for upward StO_2 slope.

and vessel recruitment. It is not known which mechanism is predominant.

Conclusions

Repeatability of tissue oxygenation measurements using the NIRS method was confirmed. We found lower values

of baseline StO_2 , hyperemic StO_2 , higher $mOER$ and a steeper downward StO_2 slope in patients with cardiogenic shock in comparison to patients with septic shock. This confirms that oxygen extraction is intact and even increased in patients with cardiogenic shock.

Key messages

- NIRS measurements are repeatable.
- Muscular oxygen extraction is intact and even increased in patients with cardiogenic shock.
- Muscular oxygen extraction is decreased in patients with septic shock.

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