Towards better monitoring of oxygen imbalance in critically ill patients

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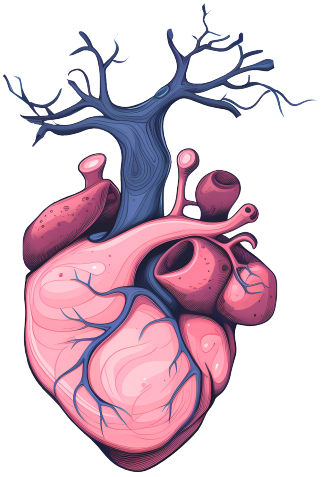

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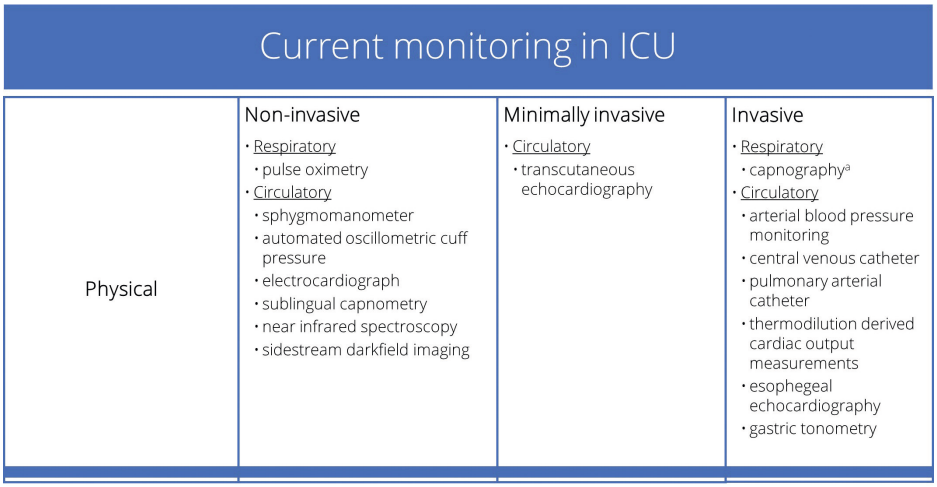
Introduction

MONITORING CRITICALLY ILL PATIENTS IN THE INTENSIVE CARE UNIT

The worldwide establishment of intensive care units (ICU) was a consequence of the polio pandemic in the 20th century and primarily focused on supporting respiratory functions.(1, 2) Since the polio pandemic, intensive care medicine has made tremendous advances to support critically ill patients.(2) To be able to support critically ill patients, close monitoring is one of the cornerstones in the ICU.(3) The primary goal of monitoring is to quantify the severity of critical illness in a timely, accurate manner. Monitoring is performed using physical examination, non-invasive (pulse oximetry, sphygmomanometer), minimally invasive (cardiac function by transcutaneous echocardiography) and invasive (arterial blood pressure, central venous catheter, cardiac output by thermodilution or with the pulmonary arterial catheter) monitoring tools (figure 1).(4-7) None of these monitoring tools can be used as a standalone for the overall assessment of the critically ill patient and not all critically ill patients need invasive monitoring tools. Together these monitoring tools aim to measure cardiac function, cardiac output and tissue oxygenation for the assessment of the severity of critical illness.(7)

Figure 1. Overview of current monitoring techniques used in the intensive care units.(4-6)

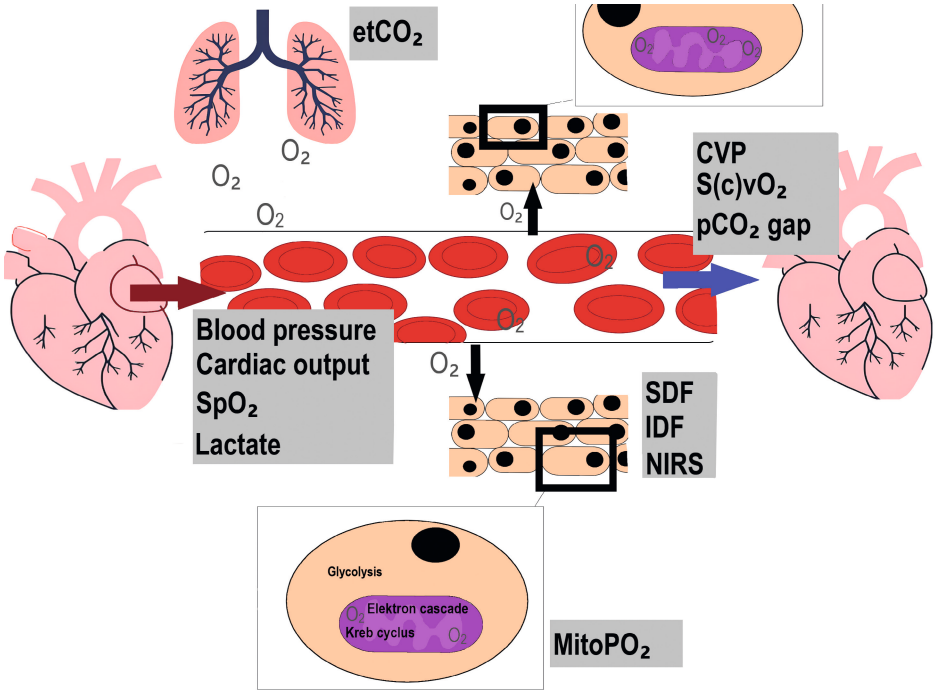


[a] Capnography in intubated patients

Cardiac function can be assessed with echocardiography, while the cardiac output can be assessed using less invasive or invasive monitoring tools. However, today no reliable bedside monitoring tool is available for the direct assessment of tissue oxygenation.(8)

Tissue oxygenation and perfusion are therefore assessed using surrogate markers like mean arterial blood pressure (MAP), cardiac output (CO), lactate levels, carbon dioxide veno-arterial gradient (pCO_2 gap), and venous oxygen saturation or central venous oxygen saturation (SvO_2 or $ScvO_2$).(6) Other monitoring tools used in experimental studies to assess tissue oxygenation and microcirculation include near infrared spectroscopy (NIRS) and sidestream darkfield (SDF) or incident darkfield (IDF) imaging (figure 2). Another marker of tissue oxygenation is hemoglobin (Hb) concentration, since oxygen is mostly transported bound to Hb to the tissues. Since Hb is one of the factors contributing to tissue oxygenation, we have to be aware of iatrogenic and other factors contributing to anemia in critically ill patients.(9-11)

Figure 2. Oxygen is transported by the hemoglobin molecule through the circulation to eventually deliver it to the mitochondria in tissues, in which the oxygen is used in the cellular respiration. Currently used monitoring techniques in the ICU, measure the tissue oxygenation and perfusion in the macrocirculatory and microcirculatory level.



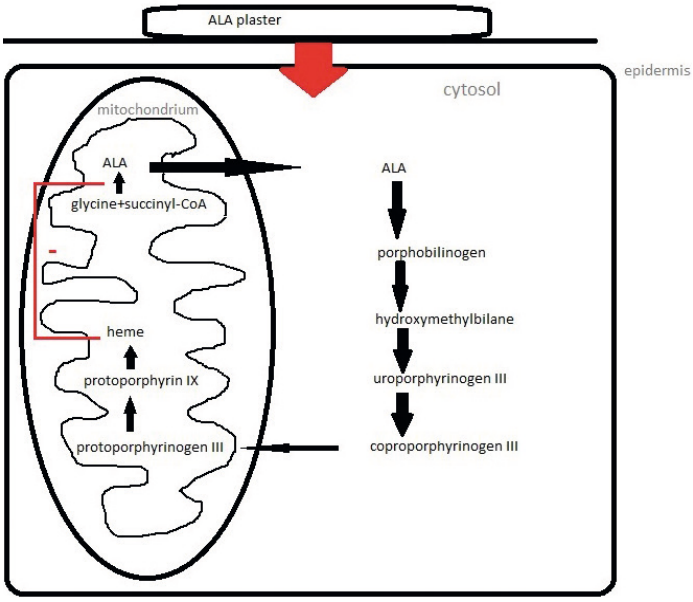
CVP central venous pressure; *etCO*$_2$ End-tidal carbon dioxide pressure; *IDF* incident darkfield; *mitoPO*$_2$ mitochondrial oxygen tension; *NIRS* near-infrared spectroscopy; *pCO*$_2$ *gap* veno-arterial carbon dioxide difference; SvO_2 venous oxygen saturation *ScvO*$_2$ central venous oxygen saturation; *SDF* side-stream dark field imaging; *SpO*$_2$ oxygen saturation measured with pulse oximetry

The surrogate markers of tissue oxygenation are mostly assessing either macrocirculation or the microcirculation, but none of these markers are assessing the mitochondrial level where more than 90% of the oxygen is consumed. Furthermore, changes in tissue perfusion and oxygenation are not directly identified by any of these surrogate markers. Lactate level, for example, is measured in arterial blood samples, implying not a continuous bedside measurement. Regular lactate level measurements are used to assess the trend of lactate levels over time. In addition, the increase in lactate level in response to hypoxia can occur within minutes, while the normalization of the lactate level can take more than 24 hours.(12-14) One should also keep in mind that an increased lactate level in critically ill patients may be both a consequence of tissue hypoxia and the result of non-hypoxic causes.(12, 15)

Normal values of macrocirculatory surrogate markers do not guarantee normal tissue oxygenation in critically ill patients, since in that case hemodynamic coherence is assumed.(16, 17) Hemodynamic coherence is defined as correction of systemic oxygenation and perfusion parameters resulting in correction of regional and microcirculatory perfusion and oxygenation. The underlying assumptions of hemodynamic coherence are that the oxygen delivery is matched to the oxygen demand of various tissues and that the compensatory mechanism to regulate this process are intact.(16) However, in critically ill patients these regulatory mechanisms can be disrupted leading to loss of hemodynamic coherence.(16) Monitoring microcirculatory perfusion and oxygenation is therefore essential in critically ill patients. Normal $ScvO_2$ and pCO_2 gap values do not guarantee a normal microcirculatory flow. SDF and IDF imaging techniques are limited in use due to their technical limitations.(6, 18) No specific or sensitive monitoring tool is thus available to measure microcirculatory perfusion and oxygenation.

Until recently no bedside monitoring tool was available to measure mitochondrial oxygenation. Techniques were developed to measure oxygen concentration in the microcirculation, but were mostly limited to research purposes.(19-23) The research group of Mik et al. recently have developed a medical device based on these techniques to measure oxygen concentration in the mitochondria.(19, 24)

Figure 3. Protoporphyrin IX is a precursor of heme and is produced in the mitochondria. Exogenous administration of 5-aminolevulinic acid (ALA) can bypass the negative feedback in ALA production.(25)

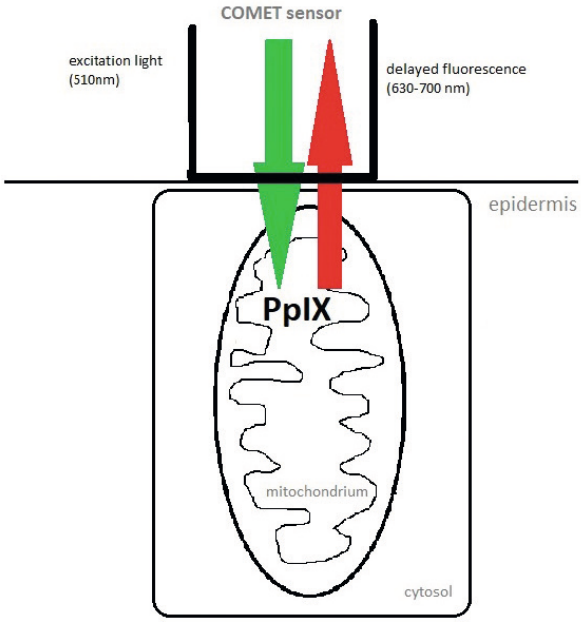


MITOCHONDRIAL OXYGEN TENSION MONITORING

The protoporphyrin IX-triple state lifetime technique (PpIX-TSLT) is the underlying technique to measure mitochondrial oxygen tension (mitoPO$_2$). Protoporphyrin IX(PpIX) is used as a dye to measure mitoPO$_2$. It is synthesized in the mitochondria as a precursor of heme (figure 3). The rate of conversion of PpIX to heme is a rate limiting step that can be overcome by administration of 5-aminolevulinic acid (ALA), a precursor of PpIX. One of the characteristics of PpIX is that it is photo excitable, leading to population of its triplet state. Relaxation into its ground state occurs spontaneously, but can be accelerated by collision of its triplet state with oxygen molecules (called quenching). During this process photons are released, leading to a phosphorescence and delayed fluorescence signals. Using the Stern-Volmer relationship, the oxygen concentration is calculated, in which a higher oxygen tension yields in more quenching and thereby a shorter duration for PpIX to reach its ground state. In vivo research in animals has shown stable quenching constants in various organs, indicating that this technique is applicable in all organs.(26-28) The location of measurement, in the mitochondria, was validated in an in-vitro study.(19) The possibility to measure mitoPO$_2$ in the skin with this technique after at least 4 hours topical ALA administration was confirmed in both animal

and human studies.(29, 30) It has been postulated that the skin as an organ reflects the tissue oxygenation in an easy and fast way, like a canary in mines,(24) since the skin is one of the first organs affected by the vasoconstriction of the vessels as a result of sympathetic reaction to shock.(31, 32) An in vivo study has shown the correlation of cutaneous mitoPO$_2$ with liver, kidney and gastrointestinal tract mitoPO$_2$ in rats infused with lipopolysaccharide.(33) The cutaneous mitoPO$_2$ has been implied as an earlier indicator of disturbance in systemic oxygen consumption in a pig model compared to lactate, mean arterial pressure, and tissue oxygenation with NIRS techniques.(34) Based on these results, the monitor for cellular oxygen metabolism (COMET) was developed to make mitoPO$_2$ measurements possible in humans (Photonics Healthcare, Utrecht, the Netherlands) (figure 4).

Figure 4. The delayed fluorescence signal from the excited protoporphyrin IX (PpIX) is measured with the COMET device, using the Stern-Volmer equation.



The results of studies with the COMET device have shown that mitoPO$_2$ values range from 40-60 mmHg in healthy volunteers,(24, 35, 36) that the values can change up to 20mmHg with repeated measurements at the same measurement time in healthy individuals,(36) and that it can be safely applied in humans.(35, 37, 38) Described adverse effects were local, and resolved within one month.(35) Minimalizing the exposure to light during and first day after measurements seemed to reduce the occurrence of these adverse events, since adverse effects were the consequence of phototoxicity due to

topical ALA application. Not only was it advised to cover the skin exposed to ALA during the measurements to protect from phototoxicity, but to protect from photobleaching as well.(37) The delayed fluorescence signal measurement with the COMET device is a sensitive measurement which can be influenced by noise (e.g. background delayed fluorescence signal not related to PpIX or oxygen).(39) Therefore, an adequate signal amplitude is needed to minimize the noise-associated measurement error of mitoPO_2. The signal quality of the mitoPO_2 measurement is depicted during the measurement, in which the signal quality represents the signal-to-noise ratio.(40) A signal quality of at least 10-20% is shown to minimize the noise-associated measurement error of mitoPO_2 below 2%.(40) The signal quality is increased by longer duration of topical ALA application.(41)

MONITORING LACTATE IN THE ICU

Lactate concentration is a regularly used surrogate marker of cellular dysfunction in critically ill patients. It is recommended as a monitoring tool in critically ill patients with sepsis, (42) but also in other critically ill patients with circulatory shock.(43-46) Lactate is a product of glycolysis and can be increased in anaerobic conditions due to limited microvascular oxygen supply. However, hyperlactatemia (lactate >2 mmol/L) could also be a consequence of diminished lactate clearance, i.e. liver failure, or due to metabolic changes, i.e. mitochondrial dysfunction, or due to toxins, i.e. metformin or β-agonists.(47) One should therefore interpret the lactate values carefully in critically ill patients and assess the reason of hyperlactatemia. High lactate concentrations at admission to the ICU, both in patients with sepsis as in general critically ill patients, have been associated with increased mortality and morbidity. Also, the duration of hyperlactatemia has been associated with organ dysfunction and a poor prognosis.(47-49) In critically ill patients with sepsis, a decrease of lactate concentration of more than 10% compared to admission lactate concentration has been associated with improved survival. This association was confirmed in other subgroups of critically ill patients.(47, 50-53) The time in which this decrease should be reached, for an improved survival, ranges from 6 to 24 hours.(47, 51) Despite lactate concentration being an important predictor of mortality and morbidity in critically ill patients, it is not yet used as a predictor in the Acute Physiology and Chronic Health Evaluation (APACHE) prediction models to predict in-hospital mortality of critically ill patients.(54-56)

MEASUREMENT ERROR IN MONITORING

As with all diagnostic tools, monitoring of mitoPO$_2$ and tissue oxygenation and perfusion in critically ill patients should yield values that are as close as possible to the true, unobserved, value with minimal bias and uncertainty around it.(57) Not only is the measurement accuracy important, but also the measurement repeatability and reproducibility. Measurement error will be present in different gradations in the different monitoring devices, in which the accepted amount of measurement error depends on the measured variable, since the narrower the normal range of this variable, the less measurement error is desired. All these characteristics of a monitoring tool should be kept in mind while interpreting the value of the measure.(57) Little is known about the amount of measurement error in the new monitoring device COMET. Unfortunately, no uniform golden standard for assessment of tissue oxygenation or mitochondrial oxygenation measurement at the bedside are available making the assessment of the diagnostic performances more difficult.

As mentioned in the above, monitoring tissue oxygenation and perfusion is achieved using complementary techniques, with their own limitations and complexities. Despite lactate concentration being an important predictor of mortality and morbidity, it is not part of the APACHE prediction models in the critically ill patients. Therefore, we examined in chapter 1 the added predictive value of lactate concentration in the APACHE IV model in septic patients, which we validated in a different population in chapter 2.

The COMET device appears a promising additional monitoring device for assessing tissue oxygenation and perfusion, but little is known about the reliability of mitoPO$_2$ measurements over time in critically ill patients. This was studied in our pilot study, as depicted in chapter 3. Due to the increased variability of mitoPO$_2$ between and within critically ill patients over time, we studied the reliability of mitoPO$_2$ measurements over time in healthy volunteers in chapter 4. Moreover, we describe diagnostic blood sampling as a cause of anemia in chapter 5. In chapter 6 we studied the effect of red blood cell transfusion on mitoPO$_2$ and other measures of tissue oxygenation and perfusion in critically ill patients over time.

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