



TISSUE HYPOXIA

How to detect, how to correct, how to prevent ?

3e Conférence de Consensus Européenne en Réanimation et Médecine d'Urgence

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Cette conférence a reçu le label de l'Agence Nationale pour le Développement de l'Evaluation Médicale (ANDEM). Ce label concerne la qualité de la méthodologie utilisée et ne préjuge en rien du contenu des conclusions et des recommandations du jury qui en assure seul la responsabilité.

A tremendous amount of energy, research and dedication have been devoted during the past 15 years to the understanding, detection and treatment of the manifestations of tissue hypoxia in acutely ill patients. The objectives of this Consensus Conference were to evaluate the existing literature and the experts' presentations at a Conference held at Versailles (December 1995), with a view to answering the fundamental question asked to this jury : among the numerous concepts and strategies developed in this field - ie : lactate measurement, gastric mucosal pH, mixed venous oxygen saturation monitoring, tracing of oxygen transport - oxygen consumption graphs, maximisation of oxygen transport etc. - which one(s) have ultimately gained enough scientific credibility to be proposed for routine use in intensive care units. These issues are timely and crucial in most of our hospitals, due to the scarcity of resources and cost-control measures.

1 - HOW TO DEFINE AND DETECT TISSUE HYPOXIA BY CLINICAL AND BIOCHEMICAL METHODS IN THE CRITICALLY ILL ?

For the purposes of this document, tissue hypoxia is defined as a decrease in oxygen utilisation associated with anaerobic metabolism. This section will review a number of clinically relevant approaches to the detection of tissue hypoxia. Since our definition includes the presence of anaerobic metabolism, we focus on techniques which directly or indirectly measure anaerobic metabolism (e.g. lactate). Because decreased oxygen transport and low flow often precedes the onset of anaerobic metabolism and because early detection of this physiological abnormality could possibly prevent tissue hypoxia, we also review techniques which indicate that the patient has a relatively low flow state.

- Clinical assessment : this should be the first approach taken to assess the critically ill patient. Although signs of tissue hypoxia are somewhat insensitive and nonspecific, several signs (abnormal skin perfusion, decreased urine output, hypotension, etc..) often indicate organ dysfunction caused by tissue hypoxia, and therefore, should prompt a search for reversible causes of tissue hypoxia. The physiologic and biochemical tests for tissue hypoxia should be used to complement clinical assessment.

- pH and lactate : a common abnormality in patients with tissue hypoxia is a metabolic acidosis often due to lactic acidosis. The major reasons to measure arterial lactate are to assess tissue hypoxia and to investigate metabolic acidosis. Plasma arterial lactate is easy to measure, is a good prognostic indicator and can be followed sequentially to assess the patient's response to therapy designed to reverse tissue hypoxia.

- Oxygen transport-oxygen consumption relationship : The measurement of changes in oxygen consumption in response to changes in oxygen transport has been suggested as a sensitive method of determining whether tissue hypoxia exists. There are a number of methodologic problems with this approach including uncertainty that the patient's underlying oxygen "demand" has remained constant, the difficulty in accurately measuring the pertinent variables, mathematical coupling of shared variables, and thermogenic effects of adrenergic agents used to increase cardiac output.

Because of these methodologic problems, the difficulty in making the appropriate measurements and the fact that many studies have not found dependency of oxygen consumption on oxygen transport (when measured by independent techniques), this approach is not particularly useful in the care of the critically ill patient.

- Mixed venous oxygen saturation and mixed venous arterial carbon dioxide gradient : decreased mixed venous oxygen saturation and pressure can be caused by decreased oxygen transport and/or increased oxygen demand. However, a normal or increased value does not rule out significant tissue hypoxia, especially in sepsis. Therefore, decreases in mixed venous oxygen saturation and pressure are more likely in cardiogenic and hypovolemic shock than septic shock. A critical level of mixed venous oxygen saturation that defines inadequate oxygen delivery is difficult to define.

- Gastric intra mucosal pH : Gastric intra-mucosal pH appears to be a good prognostic indicator of patient outcome in the intensive care unit in a selected series of patients, but it is not certain that it is much better than other predictors in unselected patients. In one randomized controlled trial, the utility of gastric intramucosal pH in guiding therapy was demonstrated. However, the technique is relatively expensive, can be difficult to use, is operator-dependent and is time consuming to measure. The gastric mucosal-arterial carbon dioxide difference is more specific than gastric intramucosal pH. Because increased gastric arterial carbon dioxide difference can be secondary to decreased gastric flow (carbon dioxide stagnation) and by anaerobic metabolism (non-specific) and because of inadequate data regarding reproducibility, response to therapy, and definition of the abnormal gradient, further studies are required before we can recommend this potentially promising technique for routine clinical use.

2 - TO WHAT EXTENT IS TISSUE HYPOXIA IMPLICATED IN ORGAN DYSFUNCTION IN THE CRITICALLY ILL ?

Although tolerance of the normal human body to hypoxaemia and anaemic hypoxia is impressively high, severe hypoperfusion or extreme hypoxaemia can lead to organ dysfunction and eventually to cell death and tissue necrosis. During hypodynamic shock, blood flow redistribution causes tissue hypoxia, the most affected organs being the gut and the kidney.

The direct role of tissue hypoxia in the pathogenesis of multiple organ dysfunction syndrome secondary to sepsis and/or the systemic inflammatory response syndrome is less well defined. Tissue hypoxia or hypoperfusion of one organ may lead to dysfunction or failure of a distant organ. For example bowel ischaemia, or at least maldistribution of blood flow between the mucosa and the muscularis, may cause translocation of bacteria and increased endotoxin levels in portal blood. This can cause a systemic inflammatory response which alters the microcirculation leading eventually to organ dysfunction, perhaps before tissue hypoxia has occurred.

Sepsis and the systemic inflammatory response syndrome are associated with increased oxygen consumption which is usually met by a hyperdynamic cardiovascular response. Inadequacy of this response has been suggested to cause tissue hypoxia. Minimally elevated blood lactate levels cannot however be taken as proof of tissue hypoxia in sepsis, since alternative mechanisms can be at play, such as increased aerobic metabolism or inhibition of pyruvate dehydrogenase by endotoxins. Direct endothelial cell injury by inflammatory mediators, microcirculatory plugging by circulating cells, and increased microvascular permeability combine to impair microcirculatory perfusion and tissue oedema, further altering oxygenation and nutrition of cells.

The role of tissue hypoxia in the critically ill is therefore a complex one. First, hypoxia of one organ may cause dysfunction or failure of a distant one. Second, sepsis and the systemic inflammatory response syndrome cause organ dysfunction that is only partially explained by tissue hypoxia per se. Third, maldistribution of microperfusion and alteration of the microvasculature by the systemic inflammatory response appears to play a major role in organ dysfunction.

3 - TO WHAT EXTENT DO GLOBAL MEASUREMENTS REFLECT REGIONAL ABNORMALITIES OF TISSUE OXYGENATION ?

The blood tests that are used to detect tissue hypoxia (lactate, pH, oxygen transport/oxygen consumption, mixed venous oxygen saturation, venous arterial carbon dioxide gradient) are normally obtained from systemic venous, arterial or pulmonary arterial sources and hence must be considered as global measurements. The resulting values are flow-weighted averages. This has two consequences: 1) because of the diluting effect brought about by the contribution of blood from normoxic tissues, regional hypoxia may not always result in measurable changes in global indices and 2) abnormalities in these tests cannot identify the site of hypoxia. Despite the lack of specificity, an unexplained high lactate should prompt a search for the source of the abnormality (e.g., ischemic bowel).

As the conventional global measurements of tissue hypoxia are not specific for particular organs, and may not be sensitive enough to detect regional hypoxia, there is a need to consider regional indices. Approaches that may enable a regional analysis in the future include: the use of polarographic oxygen and luminescent probes, infrared and near infrared spectrometry, nuclear magnetic resonance spectroscopy and positron emission tomography.

4 - HOW TO CORRECT TISSUE HYPOXIA?

Approaches to correct tissue hypoxia are optimisation of delivery of oxygen to the tissues and reduction in oxygen demand. For most patients with tissue hypoxia the following therapeutic plan requires hemodynamic assessment and monitoring, usually with a pulmonary artery catheter.

Optimization of oxygen delivery

Early resuscitation by expanding the circulating volume is crucial for patients in hypovolaemic and distributive shock since delays can be associated with the development of refractory tissue hypoxia. The adequacy of fluid resuscitation is more important than the type of fluid given. Blood transfusions should be considered when hematocrit is below thirty percents (hemoglobin < 10 g/dl). If signs of inadequate perfusion persist despite volume loading, vasoactive drugs are recommended. Given the typical septic profile of low peripheral vascular resistance dopamine is an appropriate first choice. If the response is inadequate or a high lactate persists, dobutamine should be considered. In situations of very low peripheral vascular resistance with low mean arterial pressure, norepinephrine may be useful.

Reduction in oxygen demand

Sedation should be used at the lowest dose commensurate with the abolition of pain, stress and anxiety. Increased sympathetic activity should be reduced but not abolished as some sympathetic activity is necessary to preserve microcirculatory control. Muscle relaxants may occasionally be required. In patients with evidence of persistent tissue hypoxia, mechanical ventilation should be considered even if arterial oxygen pressure and carbon dioxide pressure are acceptable, since placing the respiratory muscles at rest decreases respiratory muscle oxygen consumption and thus may improve the oxygenation of other hypoperfused organs.

5 - WHAT EVIDENCE IS THERE THAT INCREASING OXYGEN TRANSPORT IN THE CRITICALLY ILL IMPROVES SURVIVAL?

Several studies have demonstrated that critically ill patients with normal or supranormal oxygen transport are more likely to survive than patients with less than normal oxygen transport. In addition, these patients are less likely to develop multiple organ dysfunction syndrome. These findings formed the basis for a number of studies which investigated whether increasing oxygen transport to supranormal values could decrease mortality.

Post hoc analysis of randomized controlled trials of improving oxygen transport suggests that mortality is lower in subsets of patients who achieve and, perhaps, maintain, supranormal oxygen transport. However, it is likely that patients who are capable of achieving supranormal oxygen transport are more likely to survive and it is their ability to respond to the manipulations rather than the result of the manipulations that accounts for the improvement in survival.

To date there are at least nine studies, that qualify as randomized controlled clinical trials that specifically investigate whether increasing oxygen transport in the critically ill improves survival; these studies differ in many ways including sample size, patient selection, timing of patient enrollment, and therapeutic modalities and goals. Concerns relating to the methods used for randomisation, the inability of many of the protocol patients to achieve the oxygen transport goals, and the retrospective analysis of subgroups have been raised for each of these nine studies. Despite the differences and criticisms, the overall results strongly suggest that outcome is not significantly improved when applied non-selectively to all high risk patients in the intensive care unit. Although the specific studies of perioperative patients suggest that outcome may be improved, these studies are small and, in at least one, volume replacement was not equal in the protocol and control groups. Therefore, the utility of maximizing oxygen delivery to supranormal values in perioperative patients deserves further study.

Thus, continued aggressive attempts to increase oxygen transport to supranormal values in all patients are unwarranted. However, timely resuscitation and achievement of normal hemodynamics is essential.

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