

Consensus Conference

Tissue Hypoxia

How to Detect, How to Correct, How to Prevent

This report represents the results of a consensus conference that was co-sponsored by three scientific societies, the European Society of Intensive Care Medicine (ESICM), the Société de Réanimation de Langue Française (SRLF), and the American Thoracic Society (ATS). It was organized in December 1995 at Versailles, France, according to a methodology initially described by the National Institutes of Health (NIH) (1). This document will not describe this methodology in detail because it has been extensively published previously (2). Key features of this approach are that the report is written by a jury of 12 knowledgeable individuals who are not experts in the field. This format has been proposed to balance potential biases introduced by the experts, with sometimes opposing views. The report is written following a two-day conference in which experts present detailed analyses of specific questions, which are published separately (3). A comprehensive literature search is done before the meeting, and evidence based medicine techniques are applied to major randomized clinical trials (RCTs), when present. All elements are given to the jury before the conference itself. This format is particularly useful in situations where definite evidence is lacking in the literature, but there is a need for clarification for clinical purposes.

A tremendous amount of energy, research, and dedication has been devoted over the past 15 years to the understanding, detection, and treatment of the manifestations of tissue hypoxia in acutely ill patients. Despite this intense research, a number of controversies still exist with respect to methods of detection, approaches to correction, and possibilities for prevention of tissue hypoxia. The objectives of this Consensus Conference were to

evaluate the existing literature and to review the experts' presentations, with a view to answering five fundamental questions addressed to this jury. The issues addressed are clinically relevant, timely, and crucial in most of our hospitals because of the scarcity of resources and cost-control measures.

HOW DO WE DEFINE AND DETECT TISSUE HYPOXIA BY CLINICAL AND BIOCHEMICAL METHODS IN THE CRITICALLY ILL?

There are no well-accepted definitions of tissue hypoxia. Hypoxia is usually defined as a decrease in PO_2 , and, as such, one definition of tissue hypoxia could be a decrease in the partial pressure of oxygen in a given tissue. Because there are no normal values for tissue PO_2 and no clinically applicable ways to measure tissue PO_2 at the bedside, for the purposes of this consensus document we adopted the following definition: Tissue hypoxia is defined as a condition in which the cells of a tissue have abnormal oxygen utilization such that the tissue is experiencing anaerobic metabolism (4). The term *tissue hypoxia* should be distinguished from other terms used to describe low oxygen such as hypoxic, anemic, circulatory, and histotoxic hypoxia, which can lead to, but are not synonymous with, tissue hypoxia.

Tissue hypoxia can be ascertained biochemically by measurements of biochemical processes at the cellular level (e.g., decreased ATP, increased NADH, and decreased oxidized cytochrome aa_3) which can be measured in the laboratory by a number of means (e.g., nuclear magnetic resonance spectroscopy). None of these (e.g., nuclear magnetic resonance spectroscopy) and there are no "gold" standards for use in assessing tissue hypoxia. This section will review a number of clinically relevant approaches. These can be grouped into those techniques which largely measure the consequences of anaerobic metabolism (e.g., lactate) and those which indicate that the patient has a relatively low flow state that would predispose them to tissue hypoxia. Recognition of these latter conditions is important because therapeutic interventions to prevent tissue hypoxia may be possible at this time.

Clinical Assessment

Clinical assessment should be the first approach taken to assess the critically ill patient. Although there are no specific clinical signs of tissue hypoxia, a number of well-known signs (mental obtundation, decreased urine output, abnormal vital signs, etc.) often indicate specific organ dysfunction, a common late sequela of tissue hypoxia and should prompt the search for reversible causes of tissue hypoxia. Further, all physiological and biochemical assessments described below should be interpreted in light of clinical information.

pH and Lactate

One of the most common abnormalities in patients with tissue hypoxia is the development of a metabolic acidosis. Quite often the underlying cause is a lactic acidosis. There are a number of major mechanisms causing the increased lactate in the critically ill including: (1) hypoxic causes in which anaerobic production of lactate occurs globally (e.g., shock) or focal causes (e.g., bowel infarction); and (2) nonhypoxic causes (e.g., delayed clearance of

Third European Consensus Conference in Intensive Care Medicine: organized by the Société de Réanimation de Langue Française and co-sponsored by The American Thoracic Society in conjunction with the European Society of Intensive Care Medicine.

Bureau of the Consensus. Secretary: J. Carlet (France), A. Artigas (Spain), D. Bihari (UK), H. Burchardi (Germany), P. Gajdos (France), M. Hemmer (Luxembourg), M. Langer (Italy), C. Richard (France), M. Wolff (France). *Organizers.* C. Richard (France), J. Carlet (France). *Scientific Advisors.* J. L. Vincent (Belgium), J. Russell (Canada). *Jury of the Consensus.* Chairman: F. Lemaire (France), L. Blanch (Spain), J. Y. Fagon (France), P. Foex (UK), G. Hedenstierna (Sweden), D. Morel (Switzerland), P. Parsons (USA), A. Pesenti (Italy), G. Ramsay (Netherlands), G. Simbruner (Germany), A. S. Slutsky (Canada).

This conference was organized with the help of the following pharmaceutical companies: Bayer, Institut Henri-Beaufour, Institut Beecham, Glaxo, Hoechst, Iris (Servier), Lederle, Pfizer, Roche, Specia.

This Conference was organized and held according to methodologic principles set forth by the Agence Nationale pour le Développement de l'Évaluation Médicale (ANDEM), which has given it its approval. However, conclusions and recommendations expressed herein are made under the responsibility of the jury and do not imply endorsement by ANDEM.

This report was developed as a result of the Third European Consensus Conference in Intensive Care Medicine, which was organized by the Société de Réanimation de Langue Française and co-sponsored by the American Thoracic Society in conjunction with the European Society of Intensive Care Medicine. This report was approved by the ATS Board of Directors in June 1996.

This paper is being co-published and copyrighted with *Intensive Care Medicine*.

Am J Respir Crit Care Med Vol 154, pp 1573-1578, 1996

lactate, accelerated aerobic glycolysis, and dysfunction of pyruvate dehydrogenase) (3). Indications for measurement of lactate include the differential diagnosis of acidemia and confirmation of clinical signs of tissue hypoperfusion. Plasma lactate has been shown to be a good prognostic indicator in critically ill patients. Plasma lactate is easy to measure and can be followed sequentially to assess prognosis or the patient's response to therapy (5).

Do_2/Vo_2

The measurement of changes in oxygen consumption (Vo_2) in response to changes in oxygen delivery (Do_2) has been suggested as a sensitive method of determining whether tissue hypoxia exists. The underlying hypothesis has been that there may be occult tissue hypoxia that can only be detected if one changes (Do_2) and then measures corresponding changes in Vo_2 . The approach requires multiple measurements at baseline and after various interventions to change (usually increase) Do_2 . This has been a controversial area in the literature for many years due to a number of difficulties with this approach. It is critical that the patient's underlying oxygen demand remains constant during the length of the procedure, but this is impossible to measure in ICU patients. There are also a number of methodologic issues related to the difficulty in accurately measuring pertinent variables mathematical coupling of data (i.e., x and y axes sharing the same measured variables) (7), and thermogenic effects of adrenergic agents used to increase cardiac output.

Obtaining an increase in Vo_2 subsequent to an increase in Do_2 , in and of itself, is insufficient to indicate tissue hypoxia, and thus, the use of changes in Vo_2 in response to changes in Do_2 is not particularly useful in the care of the critically ill patient (7, 8).

SvO_2

A decrease in mixed venous oxygen saturation (SvO_2) can be caused by a decrease in Do_2 and/or an increase in oxygen demand. However a normal or increased value does not rule out tissue hypoxia, especially in sepsis. Therefore, decreases in SvO_2 are more likely in cardiogenic or hypovolemic shock. SvO_2 can be measured intermittently by withdrawing blood from a pulmonary artery catheter, or it can be measured continuously by a fiberoptic pulmonary artery catheter. SvO_2 is a flow-weighted average of venous effluent from all perfused vascular beds. A critical value of SvO_2 that defines inadequate Do_2 is difficult to determine. Specific recommendations for the use of SvO_2 could not be made due to a lack of data in the literature.

ΔPco_2

ΔPco_2 can change due to changes in Vco_2 , is prone to errors because $Paco_2$ is not very different from venous carbon dioxide pressure ($Pvco_2$), and its interpretation depends on the absolute $Paco_2$. Hence, ΔPco_2 is not recommended for routine clinical use.

pHi

This technique, also called gastric tonometry, measures gastric mucosal pHi (pHi) by allowing the equilibration of CO_2 pressures between a fluid filled balloon and the interstitial fluid of the mucosa. Gastric CO_2 can increase (or pHi can decrease) due to changes in blood flow to the stomach and/or due to the increase in tissue CO_2 that occurs during cellular hypoxia. The rationale for measuring pHi is that the mucosal layers or the stomach are highly vulnerable to decreases in perfusion/oxygenation. Although measurement of pHi is specific to the stomach, it is often used to assess global adequacy of perfusion. pHi appears to be a good prognostic indicator of patient outcome in the ICU in a selected series of patients, but it is not certain that it is much better than other predictors in unselected patients. In one inter-

vention study, the utility of pHi was shown in guiding therapy (9). However, the technique is expensive, difficult to use, is highly operator dependent and is time consuming. Further studies are required before we can recommend this potentially promising technique for routine clinical use. Hopefully, new technological advances will improve the ease of use of this technique (10).

In conclusion, there is no gold standard for the detection of tissue hypoxia. There are no specific clinical signs and no clear-cut thresholds for any single laboratory test. Nonetheless, measurements of pH and lactate is a good prognostic indicator, is easy to measure and can be sequentially followed. Assessment of Do_2/Vo_2 and ΔPco_2 is not helpful, and measurements of pHi (or equivalent) shows promise, but there are insufficient data to recommend its clinical use.

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

The tolerance of the normal human body to hypoxaemia and anaemic hypoxia is impressively high thanks to a complex strategy of compensatory mechanisms, including an increase in blood flow and local oxygen extraction, induction of heat shock and glucose-regulated proteins (11, 12). There is no doubt that when an organ or a tissue suffers severe hypoperfusion or extreme hypoxia, organ dysfunction ensues. It is likely that specialized functions are given up first, and then general cell energetics are affected, leading eventually to cell death and tissue necrosis. During hypodynamic circulatory shock, conditions of tissue hypoxia/hypoperfusion are created. Blood flow redistribution such as decreased gut and renal blood flow is part of the physiological response to low flow states, the most affected organs being the gut and the kidney.

The direct role of tissue hypoxia in the pathogenesis of multiple organ dysfunction syndrome (MODS) secondary to sepsis and/or systemic inflammatory response syndrome (SIRS) is less well defined. Hypoperfusion or tissue hypoxia of one organ (e.g., gut) may lead indirectly to dysfunction or failure of distant organs through the release of mediators and various toxins. Relevant examples are ischaemia/reperfusion syndromes, or the role played by the gut in generating MODS. Bowel ischaemia, or at least maldistribution of blood between the mucosa and the muscularis (13), may cause translocation of bacteria and increased endotoxin release into portal blood (14), which can lead to a systemic inflammatory response involving leukocyte activation, mediator release, and interaction with endothelial cells. This forms the basis for alteration of the circulation at the microscopic level including capillary damage and eventually organ dysfunction.

Evidence that tissue hypoxia is a major primary event in sepsis and SIRS is inconclusive (6). Sepsis causes a hypermetabolic state with increased Vo_2 , and this is usually met by a hyperdynamic cardiovascular response. Inadequacy of this response has been advocated as the possible cause of tissue hypoxia. Minimally elevated blood lactate levels cannot be taken as proof of tissue hypoxia in sepsis, because alternative mechanisms can increase lactate levels, (e.g., increased aerobic hypermetabolism or blockade of pyruvate dehydrogenase by endotoxin) (15). In hypotensive, hyperdynamic septic dogs, infusion of dichloroacetate, a substance known to reverse the endotoxin-induced inhibition of pyruvate dehydrogenase, has been shown to lower plasma lactate levels without affecting the Do_2/Vo_2 relationship, indicating that increased lactate levels in endotoxaemia is due at least partly to this metabolic effect and not secondary to cellular hypoxia (16). These experimental results have recently been confirmed in a multicenter clinical trial in which the use of dichloroacetate successfully lowered blood lactate levels but did not change mortality (17). Maldistribution of microcirculatory blood flow may be ascribed to various mechanisms including altered vascular re-

activity, microaggregation of neutrophils, platelets, and fibrin. Endothelial cell injury resulting in increased microvascular permeability and tissue oedema further impedes oxygenation and nutrition of cells (18).

In summary, the role of tissue hypoxia is therefore a complex one. First, hypoxia of one organ may cause dysfunction or failure of a distant one. Second, sepsis and SIRS 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, but the ability to monitor the adequacy of tissue Do_2 and Vo_2 is still limited by technological limitations in humans.

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

The blood tests that are used to detect hypoxia (lactate, pH, Do_2/Vo_2 , SvO_2 , ΔPCO_2) are normally obtained from systemic venous, arterial, or pulmonary arterial sources. The resulting values are flow-weighted averages and must be considered as global measurements. In the face of regional hypoxia, such tests cannot identify the presence or the site of hypoxia. Indeed, the sensitivity of global indices of hypoxia to detect regional hypoxia is limited by the diluting effect brought about by the contribution of blood from normoxic tissues. This also means that regional hypoxia may not always result in measurable changes in global indices (19).

As the conventional global measurements of tissue hypoxia are not specific for a certain region and may not be sensitive enough to detect regional hypoxia, there is a need to consider regional indices.

pHi

The reduction of pHi reflects increases in tissue CO_2 resulting, *inter alia*, from decreases in blood flow and tissue hypoxia. As the gastro-intestinal mucosa is highly vulnerable to decreases in perfusion or oxygenation, changes in pHi are considered early markers of hypoxia in the mesenteric territory, a condition associated with high mortality (9). It is one of the few indices of regional hypoxia currently available for clinical use.

Regional Blood Flow

Because of the extensive redistribution of regional blood flow in hypovolaemic and septic shock, measurement of regional blood flow would be of value to the clinician. Yet, methods to directly measure regional blood flows are complex and relatively difficult to use in clinical practice because they rely on the insertion of multiple catheters, often positioned under fluoroscopy. Methods based on the Fick principle allow the measurement of blood flow and metabolism in the brain, kidneys, splanchnic bed and other organs (19).

Polarographic Oxygen Electrodes

These can be inserted into tissues or placed on the surface of tissues and organs. Though generally not available in clinical practice, polarographic electrodes are tools for the investigation of regional Po_2 . Hypoxia, defined as inadequate oxygen utilization resulting in reduced production of ATP, may, however, occur in the presence of normal Po_2 (cytotoxic hypoxia) (13).

Infrared and Near Infrared Spectrometry

Using the same principles as in pulse oximetry, it is possible to monitor the oxidation-reduction state of haemoglobin, myoglobin or cytochrome *aa_3* *in vivo*, at least for research purposes (20).

Luminescent Oxygen Probes

The absorption spectrum of NADH allows its fluorescence to be measured as an indicator of the intramitochondrial redox state. The technique is still under development.

NMR Spectroscopy and Positron Emission Tomography

These are research tools with which cellular metabolism can be investigated. Both methods have sufficient spatial resolution to allow characterization of regional metabolism even in a moving organ such as the heart. Practical reasons limit their usefulness in the intensive care setting (21, 22).

In conclusion, the answer to the question, to what extent do global measurements reflect regional abnormalities of tissue oxygenation, is that such tests cannot identify the site of hypoxia. However, they may detect the presence of a regional abnormality if the region is large enough to result in measurable global changes. The way forward requires the development of new technologies for the bed-side measurement of regional blood flow and metabolism.

HOW TO CORRECT TISSUE HYPOXIA?

Detection of tissue hypoxia depends on adequate monitoring as outlined above. The jury noted that there are very few randomized control-trials addressing the question posed to this section. Accordingly, most of the recommendations of this section follow common knowledge and good clinical practice; however, they are not based on outcomes or clinically applicable measurements. As early as possible, the following approaches should be used to correct tissue hypoxia: (1) optimization of delivery of oxygen to the tissues, and (2) reduction in oxygen demand.

Optimization of Do_2

Fluid resuscitation. Early resuscitation by expanding the circulating volume is crucial for patients in hypovolaemic and distributive shock and delays are associated with the development of refractory tissue hypoxia. The adequacy of fluid resuscitation is more important than the type of fluid given. Analysis comparing crystalloids and colloids has not demonstrated any significant advantage in favour of one or the other. However the colloid used in most studies was albumin. Gelatin and starch solutions have not been adequately compared with crystalloids. Blood transfusions should be considered when hematocrit is below 30% (hemoglobin < 10 g/dl). However blood transfusions may impair microcirculation and tissue oxygenation due to poor deformability of cells, particularly if old stored blood is used (23). If signs of inadequate perfusion persist despite adjusted volume loading, vasoactive drugs are recommended.

Vasoactive drugs. The response to vasoactive agents can never be assumed but must always be measured. Catecholamines may have adverse effects and may increase the tissue oxygen demand (in particular epinephrine) but at the same time increase microcirculatory blood flow and thereby improve tissue oxygenation. Optimization of Do_2 is a major therapeutic goal but consideration should also be given to achieving adequate MAP. Given the typical septic profile of low peripheral vascular resistance, dopamine is an appropriate first choice. If moderate doses of dopamine do not produce an adequate response, dobutamine should be considered. In situations of very low peripheral vascular resistance with low MAP, norepinephrine could be added. Despite some experimental and clinical evidence, the role of vasodilators is uncertain. Other potential therapies remain experimental. Improving clinical signs, increasing urine output, a fall in lactate levels and correction of metabolic acidosis are signs of improving tissue perfusion.

Reduction in Oxygen Demand

Sedation and analgesia. The goal is to use the lowest dose of sedation and analgesia commensurate with the abolition of pain, stress and anxiety. Sedation reduces total energy expenditure in critically ill patients, decreases central sympathetic activity, decreases spontaneous muscular activity and reduces work of breathing. Nevertheless, excess sedation may produce adverse effects, e.g., negative inotropic effect. Increased sympathetic activity should be reduced, but not abolished, as some sympathetic activity is necessary to preserve microcirculatory control. Therefore, the level of sedation and its effects should be individually monitored. Excessive sedation should be avoided but so should shivering and excessive (otherwise unexplained) agitation. Muscle relaxants may occasionally be required. Excessive temperature elevation should be treated. Cooling the febrile patient decreases oxygen consumption unless shivering occurs (24).

Mechanical ventilation. The usual indication for mechanical ventilation is to improve gas exchange. Another reason for applying appropriate and adequate ventilatory support is to decrease the work of breathing and the energy demand of the respiratory muscles. In critically ill patients, the oxygen cost of breathing can be very high. In shock states placing the respiratory muscles at rest has a strong theoretical, experimental and clinical basis, allowing a reduction of respiratory oxygen demand and an improvement of the oxygenation of other hypoperfused organs. Therefore, in patients with evidence of persistent tissue hypoxia, mechanical ventilation should be considered even if arterial P_{O_2} and P_{CO_2} are acceptable.

In conclusion, to correct tissue hypoxia, therapy should minimize oxygen demand (sedation and mechanical ventilation and cooling of the febrile patients), provide adequate volume replacement (fluid loading), defend and maintain blood pressure with vasopressors (norepinephrine and dopamine), and maintain adequate cardiac output with the use of moderate doses of inotropic drugs (dobutamine). Finally, and for the majority of the patients, the aforementioned therapeutic plan requires detailed hemodynamic assessment and monitoring.

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

Numerous factors including the patient's age, chronic health status, and severity of acute illness as well as type, timing, and process of therapy contribute to the success or failure of any therapeutic intervention. In critically ill patients the contribution of pre-existing patient illness may be the predominant factor in determining outcome, thus diminishing the potential of any acute therapeutic intervention to increased survival.

In analyzing whether increasing Do_2 improves survival in critically ill patients it is helpful to address three related questions:

- Is there a relationship between Do_2 and mortality?
- Is survival improved in patients who can readily achieve supranormal Do_2 compared with those patients who cannot?
- Are there specific groups of critically ill patients in whom increasing Do_2 decreases mortality?

The answer to the first question is yes. Several studies have demonstrated that critically ill patients with normal or supranormal Do_2 are more likely to survive than those patients with less than normal Do_2 . In addition, those patients are less likely to develop MODS. These findings were the impetus for a number of subsequent studies with investigated the role of supranormal Do_2 in improving mortality.

In relation to the second question, in a post hoc analysis of a number of randomized controlled trials aimed at improving Do_2 , it appears that mortality is decreased in subsets of patients who achieve and, perhaps, maintain, supranormal Do_2 . These results have been used as evidence that efforts to maximize Do_2 should be undertaken in all critically ill patients, but there is another potential explanation for the results. Although the association found is strong and statistically significant, a causal effect was not demonstrated. It is likely that patients who are capable of achieving supranormal Do_2 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. Furthermore, using intent to treat analysis of these randomized controlled trials shows no decrease of mortality of patients randomized to supranormal Do_2 . The risks in overinterpreting post hoc subgroup analysis are well known, and this type of analysis should be used for hypothesis generation, not hypothesis testing. Thus, the answer to the second question is yes but the explanation for the association remains controversial.

At least nine studies that qualify as randomized controlled clinical trials have specifically investigated the third question. As shown in Table 1, these studies differ in many ways including sample size, patient selection, timing of patient enrollment, therapeutic modalities, and goals. Three studies examined perioperative surgical patients; mortality was decreased in two (25, 26) and unchanged in one (24). In two studies of patients who sustained severe trauma (28, 29), mortality was significantly decreased in patients who were managed by protocols directed at maximizing Do_2 in one study but not the other. However, in two studies of patients with sepsis and/or ARDS (30, 31) there was no statistically significant improvement in mortality in the protocol patients. These results suggested that critically ill patients were not a homogeneous group and the response to maximizing Do_2 varied with the patient population studied. Two studies have addressed this issue by studying heterogeneous populations of critically ill patients (32, 33) and found no benefit to improving Do_2 to supranormal levels when all patients were analyzed. Furthermore, in one of those studies the aggressive attempts to improve Do_2 appeared to be harmful as mortality was increased (32), perhaps because the goal was an increase in Vo_2 . In the most recent of the two studies, there was a sufficient number of patients to allow for the analysis of subsets and, again, no improvement in mortality was found for any of the possible subgroups including surgical status, major diagnosis, achievement of hemodynamic goals and intensive care unit characteristics (33).

A number of concerns have been raised for each of these nine studies. These include the methods used for randomization, the inability of many of the protocol patients to achieve the Do_2 goals, and the retrospective analysis of subgroups (Table 1). Despite the differences and criticisms, the overall results strongly suggest that outcome is not significantly improved for unselected patients in the intensive care unit. Although the specific studies of perioperative patients suggest that mortality may be decreased, these studies were small and, in at least one, volume replacement was not equal between protocol and control groups. Further studies are required in perioperative patients to assess the effect on mortality of maximizing Do_2 .

Thus, we conclude that continued aggressive attempts to increase Do_2 to supranormal values in all critically ill patients are unwarranted. However, timely resuscitation and achievement of normal hemodynamics is essential (34).

In conclusion, research needs to continue in the field of tissue hypoxia. Future research directions include: noninvasive measurement of tissue oxygenation and assessment of these techniques in critically ill patients, development of clinically useful techniques for measurement of regional blood flow, oxygena-

TABLE 1
RANDOMIZED CLINICAL TRIALS TESTING THE HYPOTHESIS THAT INCREASING OXYGEN DELIVERY HAS AN IMPACT ON MORTALITY

Authors	Sample Size	Treatment Timing Location	Patient Selection					Patient Severity		% Protocol Patients that Achieved Therapeutical Goals	Results		Statistical Significance p Value	Raised Concerns
			Sepsis	Trauma	Surg.	Med.	Severity Scoring Systems	Overall Mortality %	Control Group		Treatment Group			
												Hospital Mortality %		
Shoemaker 1988 <i>Chest*</i>	88	Pre-op.	0	1	87	0	NA†	20	NA†	22/33	4	0.02	1, 2	
Berlauk 1991 <i>Ann Surg</i>	89	Pre-op.	0	0	89	0	NA†	3.4	0	15	9.5	0.08	3, 4	
Tuchs Schmidt 1992 <i>Chest</i>	51	ICU	51	0	0	0	APACHE II	61	73	72	50	0.14	3	
Fleming 1992 <i>Arch Surg</i>	67	ICU	0	67	0	0	ISS	34	88	44	24	0.08	1, 3	
Boyd 1993 <i>JAMA</i>	107	Mostly Pre-op.	5	0	102	0	APACHE II	14	83	22	6	0.015	2, 5	
Yu 1993 <i>Crit Care Med</i>	67	ICU	52	0	57	10	APACHE II	34	60	34	34	NS††	3	
Hayes 1994 <i>N Engl J Med</i>	100	ICU	47	2	42	28	APACHE II	44	30	34	54	0.04**	4	
Gattinoni 1995 <i>N Engl J Med</i>	762	ICU	116	116	269	261	OSF	50	45/67‡	48	49/52‡	0.64§	4	
Bishop 1995 <i>J Trauma</i>	115	ICU	0	115	0	0	RTS	28	70	37	18	0.02	2	
							ISS							

Definition of abbreviations: ISS = Injury Severity Score; OSF = Organ System Failure; SAPS = Simplified Acute Physiologic Score; RTS = Revised Trauma Score; 1: randomization; 2: non comparability between groups; 3: retrospective subgroup analysis; 4: level of achievement of target goals; 5: used dopexamine.

* Only the second series was analyzed.

† Not available.

‡ Numbers refer to two arms.

§ Comparing the three groups.

|| Septic shock.

** Mortality was higher in the treatment group.

†† Not significant.

tion and metabolism, evaluation of modulation of vascular tone and effects on tissue oxygenation (nitric oxide and inhibitors), and manipulation of oxygen consumption. In addition, well-designed randomized controlled trials of increasing Do₂ in selected subgroups of patients (such as the high surgical patient) are necessary. As our understanding of the pathogenetic mechanisms of tissue hypoxia increases, so will our ability to measure and monitor the adverse effects. Each new development will need to be critically assessed for the potential applicability in patient care. As in other fields of medicine, widespread use in clinical care should occur only after outcome studies demonstrate each technique's utility.

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