Diagnostic Technologies to Assess Tissue Perfusion and Cardiorespiratory Performance

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Introduction

Fundamental to the management of critically ill patients is the on-going assessment of both cardiorespiratory status and the adequacy of tissue perfusion. However, the management of the critically ill is also context specific. What measures one makes in the operating room, where tight titration of support in the face of surgical trauma is the rule, to field and Emergency Department settings where invasive monitoring is impractical and steady state conditions rarely present, limit the generalizability of statements about specific devices and their utility. Furthermore, no monitoring device will improve outcome unless coupled to a treatment, which, itself, improves outcome. The next five years should witness a closer synchrony between monitoring techniques and goals in terms of patient-centered outcomes. Within the context, some truths have sustained clinical scrutiny and speak to consistent treatment logic that should progress more over the next five years, although they will probably not develop into mature applications.

Tissue hypoperfusion, or circulatory shock, induces a profound sympathetic response that aims to restore central arterial pressure to sustain cerebral and coronary blood flow. The body does this at the expense first of the skin, non-active muscles and renal ultrafiltration, followed closely by splanchnic vasoconstriction [1]. Fundamentally, therefore, a blood pressure within the normal range and the presence of mentation in a patient do not insure cardiovascular sufficiency. Regrettably, the opposite is true. In previously healthy trauma patients, mentation and mean arterial pressures in excess of 90 mmHg often exist within the context of profound hypoperfusion and ischemic injury to the gut mucosa and renal medulla. Such states are often referred to as compensated shock, to describe this masquerade. Furthermore, delayed resuscitation even if it restores regional blood flow, may not prevent organ injury or rapidly restore organ function. The increased morbidity and mortality from delayed or inadequate resuscitation efforts have been documented in the trauma literature [2].

Finally, monitoring and resuscitation are also context specific. Differing groups of patients reflect differing needs and can be assessed well to differing degrees. One must apply differing filters to the review of the literature and the application of technologies in assessing tissue perfusion and monitoring techniques based on a variety of criteria. However, here we shall discuss several new

and exciting developments that should become commonplace within the next five years. These advances can be broadly placed in the following categories:
1) continuous non-invasive or minimally invasive measures of tissue wellness;
2) assessments of cardiopulmonary reserve and responsiveness to therapies; and, finally
3) protocolized care to minimize medical errors, practice variation and apply best practices across broad groups of patients independent of the training of the bedside healthcare provider, sophistication of the intensive care unit (ICU) and patient population differences.

Within the framework monitoring of tissue perfusion and tissue wellness will become increasingly integrated into treatment protocols, defining not only who is ill but also the end-points of therapy.

Assessment of Tissue Wellness

A reasonable therapeutic goal is to restore blood flow to tissues so as to reverse tissue hypoperfusion, progressive ischemic cellular injury and their associated organ dysfunction. Preventing sustained tissue hypoperfusion is usually associated with a far better outcome than treatment strategies that allow tissue hypoperfusion to persist to the point of inducing organ injury or if the resuscitation is inadequate so that tissue perfusion is not fully restored to a level that will result in no perfusion deficit. However, tissue perfusion is a relative concept. Tissues need only as much blood flow as required to meet their metabolic demands. Although one can make the distinction between flow and oxygen delivery, under most conditions these two variables are coupled. Assessment of tissue wellness usually revolves around estimates of the adequacy of aerobic metabolism and the associated performance of the tissue being monitored. Measures of tissue or venous PCO_2 are often used to assess blood flow because CO_2 production is remarkably constant for all organs, except the kidney, as blood flow decreases up until the point that oxygen extraction cannot sustain oxidative phosphorylation [3]. Numerous probes have been developed and studied to assess oxygen sufficiency, regional blood flow for Doppler or CO_2 flux, and mitochondrial energy state.

Oxygen Sufficiency

Of all the measures of regional perfusion, oxygen measures are the least accurate because they rely on too many unproven assumptions. On a global level, one can measure mixed venous oxygen saturation (SvO_2). Assuming arterial oxygen saturation (SaO_2) is > 92% then SvO_2 will be a function of the oxygen carrying capacity, the mean weighted flow to all organs and metabolic demand. Over a short time interval, hemoglobin and hemoglobin oxygen binding affinity usually do not change, and if metabolic demand is controlled, then one can use SvO_2 as a measure of global oxygen delivery (DO_2) sufficiency. Under normal conditions

SvO_2 stays around 72%. However, if it becomes ≤ 70% then circulatory stress is occurring and, if SvO_2 becomes < 65%, some areas of tissue ischemia probably exist [4]. However, an SvO_2 > 72% does not insure that all tissues have adequate blood flow because shunt flow may artificially increase end-capillary PO_2 in hyperperfused regions masking tissue ischemia. In fact, this is often the argument given for why organ dysfunction is seen in septic patients when their SvO_2 is > 72%, cardiac output elevated, but hyperlactatemia is present. Although other reasonable explanations for these findings can be given, including mitochondria block, decreased lactate clearance and failure of lactate dehydrogenase to convert lactate to pyruvate [5], clear documentation of microcirculatory derangements in septic patients has also been described [6]. Decreases in SvO_2 have also been used to identify those ventilatory-dependent subjects who will fail to wean from mechanical ventilatory support, as weaning successes did not display a decrease in SvO_2 during their spontaneous breathing trials [7].

Recently, interest in using central venous SO_2 ($ScvO_2$) as an alternative to SvO_2 has been proposed, because $ScvO_2$ can be measured from a central venous catheter, is similar though not identical to SvO_2 and eliminates the need for pulmonary arterial catheterization to measure SvO_2 [8, 9]. A resuscitation protocol based on $ScvO_2$ as a surrogate of SvO_2 resulted in better outcome from septic shock in patients treated in an emergency department than similar patients treated without the aid of $ScvO_2$ or SvO_2 guided therapy [10]. Thus, measures of compensated shock, even if measured using degraded measures, such as $ScvO_2$, may still improve outcome if coupled to an aggressive treatment protocol. Although this approach has been endorsed by the SCCM and ESICM Surviving Sepsis campaign for the treatment of patients with septic shock [11], the published protocol [10] did not treat acutely ill in-patients within an ICU, but subjects presenting to an emergency department whose entire protocolized treatment was done there. Furthermore, care once in the ICU was not controlled and this emergency department protocol used very large red blood cell transfusions independent of fluid resuscitation, which could have independently altered outcome. Furthermore, using threshold values of $ScvO_2$ to drive these protocols is problematic, since the relation between $ScvO_2$ and SvO_2 may vary markedly in shock states and during therapy [12]. However, this study clearly documented that using measures of oxygen extraction stress as a marker of compensated shock identified patients whose outcome improved if resuscitation persisted further to resolve this presumed deficiency.

Although regional measures of tissue PO_2 are possible, including splanchnic oxygen consumption [13], in-dwelling oxygen-sensitive electrode catheters placed into tissues [14] and non-invasive measures of tissue PO_2 [15], the clinical utility of these devices has not been shown and their use has been limited to a few research centers. When muscle PO_2 levels are measured during experimental hemorrhagic shock and resuscitation, the trends appear to reflect ischemia and its recovery. Thus, measures of oxygen sufficiency exist and on a global level have proven useful to drive therapy in one clinical trial. Still, the sensitivity of global measures of oxygen sufficiency is poor, whereas regional measures of tissue PO_2 have not been used to drive treatment protocols. Finally, in subjects with prolonged cardiovascular insufficiency, as may occur in patients with se-

vere sepsis and septic shock, the potential exists that mitochondrial dysfunction may develop owing to impaired mitochondrial protein synthesis needed to drive oxidative phosphorylation [16]. Under these conditions, otherwise adequate tissue PO_2 levels (i.e., > 10 mmHg) may still be associated with impaired energy metabolism. However, under these circumstances of metabolic block, both oxygen consumption and CO_2 production will be limited. To date, no studies have reported decreased CO_2 production as part of high output circulatory shock.

Regional Blood Flow

Regional blood flow is heterogeneous both among organs and within organs, and regional blood flow distribution may vary over time in response to changes in sympathetic tone and treatments [17]. However, under most circumstances, regional blood flow is proportional to regional metabolic demand. Since regional metabolic demand reflects oxidative phosphorylation, CO_2 production is also proportional to regional blood flow. Thus, tissue PCO_2 remains remarkably constant across tissues as metabolic rate varies as long as blood flow can co-vary with metabolic rate. Since total PCO_2 is also dependent on tissue CO_2 stores, measures of a specific threshold value for tissue PCO_2 are less informative than are measures of the differences between tissue PCO_2 and arterial PCO_2. This so-called regional PCO_2 gap can be used to measure regional blood flow in the gut, if measured by gastric tonometry [18], the mouth, if measured by sublingual PCO_2 [19] in muscle and subcutaneous tissues, if measured by indwelling PCO_2 electrodes [20], and in the bladder musoca using surface electrodes [21]. Gutierrez et al. used an elevated gastric PCO_2 gap equivalent to identify compensated shock in critically ill subjects following an initial resuscitation [22]. Others have shown that gastric tonometry can identify occult circulatory failure during weaning [23]. Subjects who fail to wean from mechanical ventilatory support also develop an elevated gastric PCO_2 gap, consistent with gastric vasoconstriction during the stress of weaning [7]. Interestingly, when PCO_2 measures are coupled with pH measures, one has the unique opportunity to access the emergency of regional tissue metabolic acidosis, as the point wherein tissue pH decreases more rapidly than can be explained by the associated increase in PCO_2 based on the Henderson-Hasselbalch equation. Potentially coupled pH-PCO_2 measures will be used in the future to identify critical DO_2 states and the onset of metabolic acidosis. Thus, measures of regional blood flow exist and may be more robust than measures of oxygen sufficiency. However, their primary limitation at the present is the difficulty in acquiring reliable measures of PCO_2 and its change over time.

Regional gastric mucosal blood flow can also be measured by local laser Doppler techniques; although this technique is useful for research purposes, it has not been used to document results of resuscitation or drive resuscitation protocols in humans. Presumably, this lack of study is due to the invasive nature of the technique and its instability over time. Finally echo-imaging techniques allow for the assessment of renal cortical blood flow and myocardial blood flow. Similarly, trans-cranial Doppler measures are used to assess cerebral blood flow. Along this same line, echo-derived estimates have been reported for numerous

regional vascular beds. However, although such echo-derived measures of regional blood flow can be used to describe large vessel blood flow, their ability to assess actual tissue blood flow or effective blood flow is limited.

Cellular Energy Status

Cellular energy production through metabolism of three-carbon units within the tricarboxylic acid cycle to produce CO_2 and reduced cytochromes needed to feed mitochondrial oxidative phosphorylation for the production of ATP and consumption of oxygen reflects the basic means by which cells, organ and whole animals survive and adapt to the environment. Although anaerobic metabolism of glucose to pyruvate and then lactate can generate some ATP, this strategy is grossly inefficient and unable to sustain cellular metabolism at any but the most quiescent level. Accordingly, numerous techniques have been studied that aim to assess mitochondrial redox state. With increased hypoxic stress, oxidative phosphorylation is impaired with increased intracellular reduced cytochrome a/a3 and NADH levels. Since adequate oxygen flux from capillaries to mitochondria represents the final pathway of oxygen transport to the cells, measures of reduced cytochrome a/a3 and NADH levels represent a direct evaluation of the effectiveness of resuscitation to sustain cellular function [24]. Although circulatory shock states have been demonstrated to induce impaired intracellular oxidative phosphorylation, and resuscitation has been shown to improve these measures, they have not been used in clinical trials. The reasons for this are multiple, not the least of which is the reality that such measures are, by necessity, highly localized and marked regional differences in tissue oxygen sufficiency often exists in both health and disease. Potentially, measuring these parameters non-invasively over a spectrum of tissues and sites within tissues may give a clearer picture of tissue wellness. The second major weakness of these approaches is the lack of a calibrated threshold below which injury occurs and above which tissue energy production is adequate. In essence, absolute levels of any oxidative phosphorylation factor or co-factor are less important than the rate of ATP turnover. Levels of these agents are analogous to the number of wheels on a car, not the rate at which the car is moving. Furthermore, increased reduced cytochrome and co-factor levels, using this same analogy, reflect the state of inflation of those tyres, not their potential rate of turn given an adequate substrate.

Assessment of Cardiorespiratory Reserve and Responsiveness to Therapy

Hypoxemia

Hypoxemia, defined as an $SaO_2 < 92\%$, usually corresponds to an arterial PO_2 of approximately 65 mmHg. As arterial PO_2 decreases below this value SaO_2 rapidly decreases owing to the shape of the hemoglobin oxygen dissociation curve. Although chronic hypoxemia can be tolerated remarkably well, acute arterial desaturation usually causes end-organ dysfunction. Although one may accurately

measure SaO_2 during arterial blood gas analysis, this approach has been largely superseded by the indirect measure of SaO_2 using pulse oximetry to derive pulse oximetry saturation (SpO_2). Pulse oximeters determine SO_2 by measuring the light absorption of arterial blood at two specific wavelengths, 660 nm (red) and 940 nm (infrared). While pulse oximetry is accurate in reflecting one-point measurements of SaO_2, it does not reliably predict changes in SaO_2 [25]. Moreover, the accuracy of pulse oximeters deteriorates when SaO_2 falls to 80% or less. Still, since the lungs and the body do not store sufficient oxygen reserves to meet metabolic demands, changes in arterial oxygenation may be seen in changes in SpO_2. Importantly, titration of positive-end expiratory pressure (PEEP) and inspired oxygen fraction (FiO_2) in patients with acute lung injury (ALI) is usually done to achieve a $SpO_2 < 90\%$ [26].

Subjects with acute exacerbations of chronic obstructive lung disease often have arterial desaturation. The etiology of this desaturation is often complex and includes ventilation/perfusion (V/Q) mismatching, increased metabolic demand and intrapulmonary shunting [27]. Importantly, exercise, by increasing both cardiac output and pulmonary arterial pressure tends to minimize V/Q mismatch while not affecting shunt. Since exercise also increases oxygen consumption, SvO_2 usually decreases as well. Since V/Q mismatch is amenable to small increases in FiO_2 and is not influenced greatly by low SvO_2 values, patients with predominately V/Q mismatch will improve their SpO_2 with sitting up, whereas those patients with primarily fixed intrapulmonary shunts will demonstrate a decrease in SpO_2. The advantage of this simple test is that the treatments for V/Q mismatch and shunt are different, thus allowing a simple non-invasive measure to both make a diagnosis and define therapy. Such provocative uses of non-invasive SpO_2 monitoring represent the new frontier of this technique, which has gone underutilized for too long.

Preload-responsiveness

Over the past few years it has become increasingly evident that static measure of left ventricular (LV) volumes or indirect estimates of LV preload, such as pulmonary artery occlusion pressure (PAOP) and right atrial pressure, do not reflect actual LV end-diastolic volume or predict the subsequent change in LV stroke volume in response to volume loading [28]. However, other provocative monitoring techniques have been documented to be very sensitive and robust parameters of preload-responsiveness.

Volume challenge: The traditional method of assessing preload-responsiveness in a hemodynamically unstable patient is to rapidly give a relatively small intravascular bolus of volume and observe the subsequent hemodynamic response in terms of blood pressure, pulse, cardiac output and related measures [11]. Volume challenges, if given in too large a volume, carry the risk of inducing acute volume overload with its associated right ventricular (RV) failure (acute cor pulmonale) or LV overload (pulmonary edema). Importantly, several surrogate methods of

creating reversible or transient volume challenges include passive leg raising and using ventilatory maneuvers.

Passive leg raising: Passive leg raising transiently increases venous return [29]. In one study, subjects who demonstrate a sustained increase in mean cardiac output or arterial pressure 30 seconds after the legs were raised were found to be preload responsive [30]. The advantage of this approach is that it can be used in patients who are breathing spontaneously, on mechanical ventilation or partial ventilatory assist, and it can be used even in the setting of atrial fibrillation. One limitation of this technique is that the volume mobilized by leg raising is also dependent on total blood volume and could be small in severely hypovolemic patients.

Central venous pressure (CVP) and inferior vena caval (IVC) diameter changes during spontaneous ventilation: Since the primary determinant of preload-responsiveness is RV performance, tests that specifically assess RV performance are inherently attractive. During spontaneous inspiration, the pressure gradient for venous return increases and intrathoracic pressure becomes more negative. CVP will decrease in preload-responsive patients [31] because the right ventricle can accommodate the increased inflow without over-distending. Similarly, IVC diameter measured in its intrahepatic position will collapse if CVP is < 10 mm Hg [32]. Unfortunately, the changes in CVP are quite small and may be within the error of measurement of most ICUs. Similarly, measures of IVC diameter require an expert bedside echocardiographer to visualize the intra-hepatic IVC.

Changes in LV output during positive-pressure ventilation: During positive-pressure ventilation, changes in LV output reflect combined RV-LV performance. Positive-pressure inspiration transiently decreases venous return, causing LV filling to vary in a cyclic fashion as well. If the RV–LV system is preload-responsive, then these small cyclic changes must also alter LV stroke volume. Since the greater the increase in tidal volume, the greater the transient decrease in venous return and subsequently greater decrease in LV output [33], one can program a ventilator to deliver a series of increasing tidal volumes and assess the degree of stroke volume decrease as a measure of preload-responsiveness [34]. During fixed tidal volume positive-pressure ventilation cyclic variations in systolic pressure [35], pulse pressure [36], LV stroke volume [37] or aortic flow [38] quantify preload-responsiveness. Several monitoring devices are available to measure these pressure and flow variations, although none have been studied prospectively as a guide to treatment. Importantly, since measures of systolic pressure, pulse pressure, aortic flow, and descending aortic flow and flow velocity all have different relations to the dynamic change in LV end-diastolic volume to stroke volume relation for the same subject, the threshold values for each parameter predicting preload-responsiveness must be different between parameters and may demonstrate different degrees of robustness in their clinical utility [39].

Dobutamine challenge: Assuming that some preload-reserve is present but limited by impaired cardiac contractility, then one may increase inotropic state as a

challenge and observe its effect of regional oxygenation. Using this test, Creteur et al. [40] demonstrated that occult splanchnic ischemia could be unmasked in approximately 30% of critically ill patients who were otherwise considered stable.

Use of Protocolis Driven by Physiological End-Points to Standardize Resuscitation

The application of evidence-based guidelines to clinical practice has gained increased acceptance in recent years. Using a rigorous and open method of grading the scientific evidence and then placing it within the framework on known physiology and local practice patterns can produce remarkable treatment algorithms that, though not perfect, even at their inception, are still better than the nearly random behavior of the present practice of medicine. There are obvious potential advantages of introducing decision-making that is rational and based on evidence. Clinical care can be simplified by the use of treatment algorithms that may facilitate cooperation between different healthcare professionals. This approach may also reduce costs for healthcare purchasers [41]. Unfortunately, standardization of care by the use of guidelines and protocols may not necessarily be a success. There are no certainties in clinical care and individual patients may have needs that fall outside standard guidelines. The rigid application of protocols cannot replace clinical judgment. Furthermore, practice guidelines imposed from outside and without clear rational or perceived benefit may not be accepted by the practicing physicians. However, by merging bedside monitoring technologies with clinical information technology that can assess tissue wellness to run decision-support systems, real-time support and monitoring can be accomplished, and in a cost-effective fashion.

For example, fluid optimization as an endpoint of resuscitation has been shown to reduce length of hospital stay and important complications in patients undergoing a variety of major surgical procedures [42]. This is usually achieved with an esophageal Doppler monitor to evaluate changes in flow in response to fluid challenges [43–45]. Markers of tissue perfusion have also been used as endpoints for resuscitation. These include SvO_2, $ScvO_2$, lactate, base excess and gut mucosal pH using gastric tonometry. The use of these endpoints is attractive, because ensuring optimal blood flow to the vital organs is the ultimate aim of hemodynamic resuscitation. Those patients who spontaneously achieve target hemodynamics fall into a low mortality group and those who are non-achievers despite treatment have a high mortality. These differences must be due to the underlying fitness of patients [46]. Protocolized care plans should use best evidence, aim to reverse those processes known to increase morbidity and mortality, and at the same time be simple enough to be applied across care centers.

Another such protocol that lends itself to this approach is referred to as Functional Hemodynamic Monitoring, because it asks of the monitoring information what treatments should be given, not what is the diagnosis [47]. One needs to first know that a patient is unstable with tissues at risk or existing in an ischemic state. Once this has been identified, then how to treat the patient can be greatly

simplified. Fundamentally there are only three questions asked of the cardiovascular system regarding response to resuscitation efforts during shock. First, will blood flow to the body increase (or decrease) if the patient's intravascular volume is increased (or decreased), and if so, by how much? Second, is any decreased in arterial pressure due to loss of vascular tone or merely due to inadequate blood flow? And third, is the heart capable of maintaining an effective blood flow with an acceptable perfusion pressure without going into failure? If taken in this order, one can develop a logical treatment algorithm. If the patient is hemodynamically unstable and preload-responsive, then treatment must include immediate volume expansion as part of its overall plan. However, if the patient is also hypotensive and has reduced vasomotor tone, then even if cardiac output were to increase with volume expansion, arterial pressure may not increase in parallel. Thus, vital organ blood flow may remain compromised despite increasing cardiac output. Since the goal of resuscitation is to restore tissue perfusion, knowing that perfusion pressure will decrease despite an increasing cardiac output, defines that the physician should also start a vasopressor agent in tandem with the initial fluid resuscitation so that both pressure and flow increase. If the patient is not preload-responsive but has reduced vasomotor tone, then a vasopressor alone is indicated, since fluid resuscitation will not improve organ perfusion and may precipitate RV or LV overload. In the patient with circulatory shock who is neither preload-responsive or displaying reduced vasomotor tone, the problem is the heart and both diagnostic and therapeutic actions must be taken to address these specific problems (e.g., echocardiography, dobutamine). The exact cause of cardiac compromise is not addressed by this approach. For example massive pulmonary embolism (acute cor pulmonale), acute hemorrhagic tamponade and massive myocardial infarction would all fall into this category but would have markedly different treatments. However, since the diagnostic development can rapidly default to this group within minutes of initiating the algorithm, appropriate diagnostic approaches could then be used in a highly focused fashion. Although this simplified algorithm has not been used in clinical trials, it has the advantage of being easy to defend on physiological grounds, as well as being simple and easy to apply at the bedside across patient subgroups.

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