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Review Article

Non-Invasive Tissue Oximetry—An Integral Puzzle Piece

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Abstract: Non-invasive tissue oximetry is a monitoring method for continuous assessment of tissue oxygenation, which may aid in detection of hemodynamic instability and otherwise unnoticed hypoxia. Numerous studies focused on using non-invasive tissue oximetry intraoperatively, proposing its predictive value in relation to clinical outcome. Tissue oximetry may be part of standard monitoring practice for brain monitoring during cardiac surgery in many clinical centers; however, the monitoring method can be deployed in numerous clinical settings. This succinct overview aims to determine the role of non-invasive tissue oximetry in current clinical practice.
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Comprehensive development of diagnostic and monitoring technologies in modern medicine has helped to better understand the complex pathophysiology of acute circulatory failure in critical cases such as surgical patients or patients admitted to the intensive care unit. In critical care settings, it is vital to assess the patient's hemodynamic status for optimization of end-organ tissue oxygenation to prevent or minimize morbidity and mortality (1). It is, however, challenging to monitor the state of tissue oxygenation accurately. The use of standard hemodynamic parameters such as blood pressure and pulse oximetry for assessing tissue blood flow is less than accurate (2,3). Despite apparently normal macroperfusion (capillary refill, cardiac output, and blood pressure), tissue hypoperfusion can persist as a result of microcirculatory perfusion defects (4). Various approaches have been introduced to avoid such hypoperfusion—mostly with disappointing or controversial results. A randomized trial of protocol-based care for early septic shock showed that the early goal-directed therapy strategy for septic shock not only proves no survival benefits but also might increase the risk of fluid overload (5). Thus, measuring heart rate, cardiac output, arterial blood pressure, and mixed venous oxygen saturation solely provides information regarding the patient's central hemodynamic status, reflecting macroperfusion, and normalization of these hemodynamic variables does not ensure sufficient oxygenation at the peripheral tissue level (6,7). The introduction of near-infrared spectroscopy for assessing the adequacy of regional tissue perfusion was an important landmark in the history of tissue monitoring (8). Since then, monitoring regional tissue oxygenation has gained wide interest, and studies began to address the importance of monitoring tissues susceptible to hypoperfusion. Non-invasive tissue oximetry uses near-infrared light for continuous assessment of tissue oxygenation, which may aid in timely detection of hemodynamic instability and otherwise unnoticed hypoxia. To date, numerous studies (of which mostly observational) focused on the use of non-invasive tissue oximetry in surgical patients, elucidating on its predictive value in relation to clinical outcome (9,10,11). Tissue oximetry may be part of standard monitoring practice for brain monitoring during cardiac surgery in many clinical centers; however the monitoring method can be deployed in various clinical settings.

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Given the diversity of technologies currently available to assess tissue oxygenation status, it is important to consider various applications of non-invasive tissue oximetry. This succinct overview aimed to determine the role of these applications in current clinical practice.

CEREBRAL OXIMETRY AS A TOOL TO PREVENT NEUROLOGICAL COMPLICATIONS

Cerebral oximetry, in particular, is a commonly used application of tissue oximetry with its focus on prevention of neurological complications following cardiac surgery. These complications, including stroke, are highly complex in nature and elicited by a multitude of preoperative and perioperative factors. Hypoperfusion resulting in intraoperative cerebral hypoxia is generally accepted as a factor contributing to the risk of adverse neurologic outcomes (12,13). Although the exact etiology is not yet completely understood, continuous assessment of tissue perfusion may aid in a better understanding of the role of tissue hypoxia in the development of postoperative cognitive complications. Although the incidence of neurological complications may appear relatively low, the effects on the patient's physical and psychological health are tremendous with serious implications for the quality of life (14). The reported incidence of stroke following cardiac surgery varies around 1.6–2.3% (15,16). Postoperative stroke entails prolonged hospital stays of, on average, 7 days with an incremental increase of hospital resources (17,18). In the United States, for each affected patient, the estimated added costs make up to $18,552, of which $1,000 is attributable to each additional day of hospitalization (19). Another type of neurological complication that may emerge following cardiac surgery is delirium, which is characterized by a state of confusion and inattention. Although often seen as a reversible condition, delirium contributes to permanent functional decline and significant morbidity and mortality risk (20). Postoperative delirium is associated with only four extra hospitalization days, but is far more common as compared with stroke, with incidence rates varying around 55% (21,22). If non-invasive tissue oximetry could help prevent a part of the neurologic complications, such as hypoxia-related stroke or delirium (13,23), the odds of an uncomplicated prosperous recovery would increase and a substantial proportion of hospital costs could be saved. The costs of performing the measurement itself includes the purchase of disposable self-adhesive sensors (usually two, for bilateral measurement of tissue oxygenation), which in the United States cost around $200 per patient (24), and a one-time investment for purchasing the oximeter device. The costs for routine application of clinical oximetry, however, are only marginal compared with the major additional expenses associated with ischemic stroke and delirium (25,26), let alone the deleterious long-term effects of these complications, i.e., the decrease in quality of life.

THE ROLE OF MODIFIABLE FACTORS IN PREVENTING COMPLICATIONS

The pathophysiology of neurologic postoperative complications is complex and multifactorial in nature. Therefore, some neurologic complications are nearly impossible to prevent because of iatrogenic events occurring in the perioperative period (e.g. aortic cross-clamping and embolism originated from the cardiopulmonary bypass circuit) and the role of certain patient characteristics is not subject to change (pre-existing co-morbidities and positive family history of adverse neurovascular events). Another substantial proportion with less of a complex etiology is caused by modifiable factors, and therefore theoretically concerns preventable cases. For example, hemodynamic instability is known to affect the risk of hypoxia. Moreover, hypercapnia and excessive hemodilution are thought to alter the risk of neurologic complications (27,28). The cardiopulmonary bypass protocol is, therefore, an important factor in enabling and maintaining adequate tissue perfusion and should be critically evaluated to minimize the risk of neurologic complications. Strict monitoring routines concern another factor of importance in preserving hemodynamic integrity, specifically monitoring at the tissue level because general hemodynamic factors may not adequately represent local tissue oxygenation status (6).

With non-invasive tissue oximetry on the rise and being increasingly applied as a brain monitor, the tool appears to be a viable assessment method for diverting adverse neurologic outcome (29). On that note, cerebral oximetry showed to adequately reflect real-time changes in tissue oxygenation readings following several iatrogenic events (10). Despite the abundance of studies implying that oxygen desaturations detected by cerebral oximetry predict neurological outcome, evidence for a causal relationship remains scarce. Part of the explanation can be found in the fact that the development of neurological complications is a complex process, which is still not entirely understood. Deoxygenation episodes detected by cerebral oximetry should be considered as a contributor, rather than an independent causative factor for clinical neurologic damage and evident changes in neurocognitive function (30). In addition, cerebral oximetry solely focuses on regional concentrations of oxygenated and deoxygenated hemoglobin, and therefore, inherently because of its measurement principle, cannot account for cerebrovascular autoregulatory activity. Cerebral autoregulation (CA) ensures a constant cerebral blood flow despite fluctuations in perfusion pressure by continuous control and modification of cerebrovascular resistance. The autonomous cerebral protective system provides protection against hypoxia and

hyperoxia resulting from hypoperfusion and hyperperfusion. Although often unacknowledged, disturbances in autoregulatory function have been shown to result in neurologic complications and thus should be avoided at all times (31).

Although cerebral oximetry has been shown to contribute to early detection of hypoxia, its measurement values can potentially be deceptive because disturbances in CA can remain unnoticed. This is illustrated by the observation of seemingly normal cerebral oximetry readings during cerebral hyperperfusion (i.e., "brain luxury perfusion"), while the cerebral autoregulatory activity is impeded (32).

Therefore, it is important to consider CA when performing cerebral oximetry. A perfusion protocol that includes maintaining modifiable factors such as arterial partial gas pressure to carbon dioxide and intraoperative hematocrit factors within the physiologic range confers to the observed low incidence of neurological complications by enabling intact autoregulatory function (27,28). Rather than solely focusing on preserving cerebral regional tissue oxygen saturation (rSO_2) within certain predefined limits, maintaining intact CA should be of primary importance in minimizing neurologic complications. Similar to most non-invasive monitoring tools and methods, tissue oximetry readings should be interpreted in the context of all clinical information available.

PROSPECTIVE APPLICATIONS OF TISSUE OXIMETRY

Besides its original intended use (i.e., brain monitoring), non-invasive tissue oximetry is increasingly applied in somatic tissue monitoring. One example is assessment of distal limb perfusion in patients supported by veno-arterial extracorporeal life support (VA-ECLS). Femoral access techniques are often used in VA-ECLS and may compromise limb perfusion, therefore predisposing the patient to concomitant tissue damage with potential disastrous effects (33,34). Tissue oximetry performed at the calf muscle proved effective for identification of endangered limb perfusion by showcasing aberrant tissue oximetry readings before any other clinical parameters showed any evident change (34).

Another example of somatic tissue oximetry applies to monitoring autologous breast reconstructive surgery, in which abdominal wall tissue is transplanted to the chest area using microsurgical anastomoses. Graft failure, in the worst case, could lead to loss of the entire tissue flap with a major additional risk of physical and psychological burden for the patient. By immediately depicting deviant measurement values as compared with the expected physiological tissue response, tissue oximetry appears superior to other applied monitoring techniques, which solely provide delayed timing of alarm signals. Tissue oximetry could aid in timely detection of circulatory compromise and thereby lower the rate of complications resulting from ischemic tissue damage (35). Successively, avoiding complications contributes to minimizing postoperative morbidity and mitigating health-care costs. As is the case in brain monitoring, the costs for performing tissue oximetry are only marginal compared with the costs associated with postoperative complications. In case of arterial or venous thrombosis, surgical re-intervention is necessary to increase the chance of successful flap salvage. This will add around $76,000 per hour spent in the operating room to the hospital costs (36). Also, patients experiencing complications generally consume two extra hospital days, leading to another $7,000 in added costs per patient operated in the United States (36). In uncomplicated cases, tissue oximetry eliminates the need for prolonged intensive monitoring with savings of $1,337 (or 6.3% (37)) that far outweigh the costs associated with routine use of tissue oximetry (37,38). The relationship between aberrant tissue oximetry readings and clinical outcome appears to be more clear in the somatic applications of tissue oximetry. Complications arising from peripheral tissue ischemia (e.g., the distal limb and autologous breast flaps) are elementary in nature because of the absence of an intrinsic homeostatic autoregulatory system. In cerebral oximetry, one attempts assessing an entire organ system that is only represented by a regional assessment of tissue oxygenation in the prefrontal cortex. In somatic tissue oximetry, on the other hand, the readings appear more representative of clinical outcome.

Another application of non-invasive tissue oximetry in which the regional measurement is applied to assess an organ system is renal oximetry. Particularly in children and infants undergoing cardiac surgery, in whom acute kidney injury is a dreadful complication contributing to increased morbidity and mortality. Although typical assessment of renal function is performed using serum creatinine levels and urine output, changes in these markers may be severely delayed (39,40). On the other hand, lowered renal oximetry readings have been shown to correlate with acute kidney injury (39,40) and other parameters representing renal dysfunction such as peak creatinine level (39).

The versatility of tissue oximetry in the clinical setting broadens the scope for future studies to focus on new potential applications. One prospective application is assessment of microcirculatory function (41). Intraoperative monitoring of peripheral microvascular reactivity enables early detection of alterations in microcirculatory function and may contribute to preventing impaired tissue perfusion and adverse patient outcome. In general, microvascular alterations associated with microcirculatory dysfunction are predominant factors in the process of tissue hypoxia,

and if left untreated result in ischemic tissue damage. Combining continuous non-invasive tissue oxygenation monitoring with a reproducible ischemia reperfusion challenge allows dynamic assessment of vascular reactivity and potentially early recognition of altered vascular reactivity and function. Parameters resulting from a so called vascular occlusion test include the occlusion slope, reperfusion slope, and the hyperemic area which provide information regarding the current status of local tissue metabolism (42), the local reperfusion reserve (42), and tissue oxygen consumption (43), respectively. Because microcirculatory dysfunction precedes tissue hypoxia, adopting tissue oximetry as a part of standard microcirculatory monitoring may prove to be the next big frontier in critical care management. The clinical relevance of alterations identified by dynamic measurements of peripheral tissue oxygenation, however, remains to be further explored. The current literature describes a variety of measurement protocols and calculation methods (41,42,44); thus, further studies are warranted to determine the optimal approach in performing tissue oximetry combined with a vascular occlusion test.

CONSIDERATIONS IN TISSUE OXIMETRY: A WORK IN PROGRESS

Despite the need for superior continuous and non-invasive monitoring methods in patient care, tissue oximetry is not yet part of standard routine practice. A multitude of anecdotal reports and recent reviews have tempered the enthusiasm for routine use of rSO_2 by questioning whether it leads to improved patient outcomes or not (45). One of the causative factors is the lack of intervention-guided trials linking disturbances in tissue oxygen saturation to adverse clinical outcome. Although multiple studies reported an association between tissue oxygen desaturation and post-surgical complications, it remains unclear whether this is part of a causal relationship or just a reflection of overall morbidity.

Furthermore, cerebral oximetry data has been implemented as part of the Society of Thoracic Surgeons Adult Cardiac Surgery Database effective from January 2008 to provide evidence, potentially improving patient outcome (46).

An important factor precluding routine use of tissue oximetry is the lack of clear application-specific rSO_2 thresholds requiring immediate intervention. In previous attempts to determine a clear threshold or change in rSO_2 necessitating prompt intervention, published studies were insufficient in taking the limitations of the measurement into account. Clinical oximetry devices are destined for either trend or absolute rSO_2 monitoring, using an algorithm that requires the assumption of a fixed ratio of arterial to venous blood in the vascular bed in the area of interest. This algorithm, however, cannot adapt to all possible applications of tissue oximetry. Hence, one must be cautious when interpreting absolute rSO_2 values derived from measurements performed in different areas. To date, there are no clear indications when intervention to correct rSO_2 is warranted. One may argue that this is partially because of the fact that studies up until now failed to demonstrate a causal relationship between tissue oxygen desaturations identified by tissue oximetry and adverse clinical outcome. In addition, the use of different monitoring devices across studies makes standardized application of cerebral oximetry even more challenging. Oximetry devices from different manufacturers each use different algorithms for estimation of local oxygen content, and use varying numbers and wavelengths of near-infrared light. Furthermore, because every device differs in terms of hardware and software (data acquisition, filtering, and processing), each device should be used in accordance with a device-specific and application-specific set of desaturation thresholds. Not only the specific measurement device but also the different applications in tissue oximetry directly affect the measurement and derived rSO_2 values. Development of standardized desaturation thresholds for the different applications will aid in interpretation of rSO_2 values and thereby establish routine use of tissue oximetry.

With the limitations of non-invasive assessment of tissue oxygenation being identified, future studies should focus on interpretation of measured data and aim at determining clinically relevant and application-specific threshold values for tissue desaturation-related injury. Furthermore, the types of interventions necessary for correcting tissue oxygenation values and its effects on clinical outcome require further clarification.

CONCLUSION

Overall, non-invasive tissue oximetry is a promising tool for (regional) assessment of tissue oxygenation. The measurement readings should be considered as an integral source of information, a puzzle piece that together with all clinical information aids in decision-making and minimizing the risk of complications.

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