Spinal Cord (2019) 57:617–625
https://doi.org/10.1038/s41393-019-0304-2

REVIEW ARTICLE

Monitoring spinal cord hemodynamics and tissue oxygenation: a review of the literature with special focus on the near-infrared spectroscopy technique

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Received: 27 February 2019 / Revised: 21 May 2019 / Accepted: 22 May 2019 / Published online: 4 June 2019

Abstract

Study design Review.

Objectives Clinical studies have shown that the hemodynamic management of patients following acute spinal cord injury (SCI) is an important aspect of their treatment for maintaining spinal cord (SC) perfusion and minimizing ischemic secondary injury to the SC. While this highlights the importance of ensuring adequate perfusion and oxygenation to the injured cord, a method for the real-time monitoring of these hemodynamic measures within the SC is lacking. The purpose of this review is to discuss current and potential methods for SC hemodynamic monitoring with special focus on applications using near-infrared spectroscopy (NIRS).

Methods A literature search using the PubMed database. All peer-reviewed articles on NIRS monitoring of SC published from inception to May 2019 were reviewed.

Results Among 125 papers related to SC hemodynamics monitoring, 26 focused on direct/indirect NIRS monitoring of the SC.

Discussion Current options for continuous, non-invasive, and real-time monitoring of SC hemodynamics are challenging and limited in scope. As a relatively new technique, NIRS has been successfully used for monitoring human cerebral hemodynamics, and has shown promising results in intraoperative assessment of SC hemodynamics in both human and animal models. Although utilizing NIRS to monitor the SC has been validated, applying NIRS clinically following SCI requires further development and investigation.

Conclusions NIRS is a promising non-invasive technique with the potential to provide real-time monitoring of relevant parameters in the SC. Currently, in its first developmental stages, further clinical and experimental studies are mandatory to ensure the validity and safety of NIRS techniques.

Introduction

Spinal cord injury

Spinal cord injury (SCI) can result in permanent morbidity due to critical complications and multi-organ dysfunction that impairs the quality of life of people with SCI and their immediate family members. Consequently, advancing the treatment of patients with acute SCI to minimize their long-term neurological deficits is of great importance to patients, health care providers and society as a whole worldwide.

Acute SCI involves primary and secondary pathological cascades. The physical traumatic impact causes the immediate "primary injury" and SC tissue destruction. "Secondary injury" mediated by excitotoxicity, ischemia,

Supplementary information The online version of this article (https://doi.org/10.1038/s41393-019-0304-2) contains supplementary material, which is available to authorized users.

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hypoxia, inflammation, and oxidative stress follows in the subsequent hours to days, leading to progressive SC damage. The primary and secondary injury cascades both contribute to the ultimate SC damage and resultant neurologic deficits after acute SCI [1].

Unfortunately, neuroprotective treatment options to contain secondary injury are currently limited. Immediate surgical decompression of the injured cord, and comprehensive supportive care are the principal interventions to attenuate the effects of injury [2]. However, unlike primary tissue destruction, the effects of secondary injury can be modified. In addition to reducing cord compression and inflammation, optimizing the perfusion and oxygenation of the injured cord through proactive, aggressive hemodynamic management can significantly reduce ischemia and hypoxia at the site of injury, limiting irreversible neuronal damage and potentially significantly improving neurologic recovery [3–7]. Therefore, the hemodynamic management of newly injured patients currently provides an important clinical opportunity to improve function after acute SCI.

The hemodynamic management of acute SCI patients

SC ischemia and hypoxia are major contributors to secondary damage after acute injury [8]. To mitigate the effects of ischemia on the injured cord, clinicians aim to augment the mean arterial pressure (MAP) in acute SCI patients. Clinical practice guidelines have recommended that MAP be maintained at 85–90 mmHg for 5–7 days post-injury [9, 10] although it is recognized that the evidence that this target MAP improves the neurologic outcome after acute SCI is relatively weak. It does appear, however, that the injured cord is sensitive to changes in blood pressure. Hawryluk and his colleagues demonstrated that even small increases in MAP during the first 3–7 days post-injury can significantly improve neurologic recovery [4]; by analyzing almost one million MAP measurements it was observed that the difference in MAP between patients who improved their spinal injury impairment scale (AIS) and those who did not improve was less than 5 mmHg. This suggests that efforts to improve SC perfusion by even a few mmHg can result in clinically meaningful neurologic improvement. In some individuals, increasing MAP by administration of high-dose vasopressor agents, however, may contribute to drug-related complications [11]. In fact, the hemodynamic management of an acute SCI patient during the first-week post-injury is critical and highly challenging.

While clinical practice guidelines [12–14] make such management appear as simple as setting the MAP target to 85–90 mmHg and maintaining this range via fluid and/or vasopressor agent administration, the first-week post-SCI is, in fact, a very dynamic period, during which many factors influencing cord perfusion are changing. Hence, simply deciding on a MAP target does not mean that this MAP is necessarily achieved. It is also well documented that SCI patients frequently experience acute episodes of significant hypotension, despite being managed by experienced teams that follow the guidelines [7, 12–15]. Furthermore, several studies have shown that the MAP required to achieve the optimal SC perfusion pressure (SCPP) in one patient may be significantly different to that of another patient [12–16]. Hence, while a "one-size-fits-all" MAP target may improve SC perfusion and oxygenation in some patients this approach can be harmful in others.

For this reason, to achieve the adjustment of MAP each individual patient needs to optimize their cord perfusion and oxygenation, a way is ideally required to directly monitor SC hemodynamics in real-time during the 7-day high-risk period after injury. But, in the absence of such monitoring capability, accurate, real-time, non-invasive technologies are needed that can aid in the maintenance of SC perfusion, oxygenation, and pressure. The ability to monitor these parameters will provide clinicians with critical information to use in optimizing the hemodynamic management of each individual patient, and improve the chances of the best possible neurologic outcome being achieved.

NIRS principals, techniques, and fundamentals

Optical techniques for clinical applications were developed after the invention of muscle oximeters by Glenn Millikan in the 1940s [17]. In 1977, the first in vivo application of near-infrared spectroscopy (NIRS) was reported by Jobsis [18]. He found that the relatively high transparency of biological material in the near-infrared (NIR) region (650–1000 nm) [17, 19] made it feasible to non-invasively measure tissue oxygen saturation (SO_2) in real-time using the principles of optical spectrophotometry.

NIRS can differentiate the absorption spectra of three important chromophores: oxygenated hemoglobin (O_2Hb), deoxygenated hemoglobin (HHb), and cytochrome aa3 (cyt). Hence, it can measure relative changes in oxygen concentration using these three chromophores [20]. Different types of NIRS instruments exist. The most clinically applicable and lowest-cost technique is continuous-wave (CW) NIRS [17]. CW NIRS provides high temporal resolution allowing continuous measurements of long duration in real-time [21]. Figure 1 demonstrates setup of a general NIRS system. Typically, the Beer-Lambert law (BLL) algorithm is used to convert raw light intensity into different chromophore concentrations [19]. However, due to scattering phenomena in live tissues, BLL cannot provide exact quantitative spectroscopy of chromophores [22–24]. This issue has been addressed by Cope et al. [25] through a

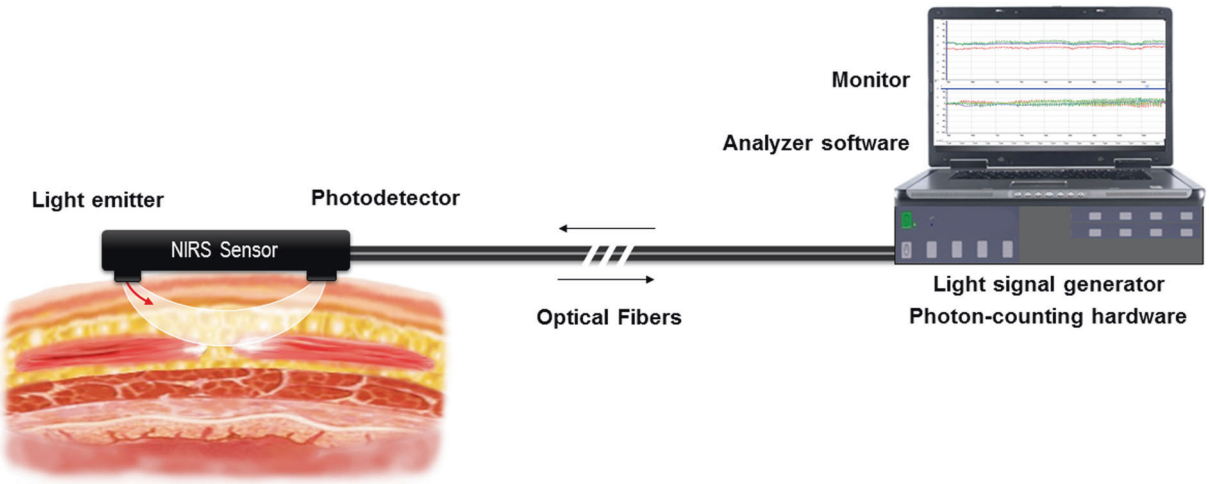

Fig. 1 A diagram of a general NIRS setup

Table 1 Inclusion and exclusion criteria on the selected papers

Selected papers	Inclusion criteria	Exclusion criteria
Clinical condition	• Traumatic and non-traumatic SCI	• Cerebral oxygenation and ischemia
	• Animal or human	• Non-monitoring applications of NIRS in SC tissues
	• English-written	
Monitoring technique	• Near-infrared spectroscopy	• Other monitoring tools e.g., somatosensory evoked potentials (SSEP), motor evoked potentials (MEP) and laser doppler flowmetry (LDF)

modified BLL (MBLL) equation. In this review, we discuss current options for monitoring SC hemodynamics and oxygenation that focus on techniques using NIRS.

Methods

A computerized literature search using the PubMed database was performed on papers published by May 2019 focused on intraoperative or post-operative SC hemodynamics and oxygenation using NIRS techniques. To cover all published manuscripts, several combinations of keywords were utilized including "near-infrared spectroscopy, spinal cord" with other phrases such as "oxygenation", "hemodynamics", and "monitoring". In addition, to avoid missing relevant publications, a manual cross-reference search of the selected full papers was also conducted. Overall, through our search strategy, we found 125 papers. After abstract screening and applying exclusion criteria to our search results, 59 papers were selected; among these, 26 articles focused on direct/indirect monitoring of SC blood flow (SCBF) and oxygenation; these were then reviewed in detail. The inclusion and exclusion criteria are presented in Table 1.

Discussion

NIRS is a promising method for intraoperative and post-operative monitoring of SC tissue hemodynamics and oxygenation. It can offer a safe, portable, simple to operate, and relatively low-cost means of clinical monitoring. Based on the theory of diffuse optical spectroscopy (DOS) [26], NIRS can provide direct and real-time information of tissue and organ physiology and function non-invasively, making this optical technique a unique and useful tool in clinical diagnostics and monitoring interventions. To the best of authors' knowledge, there is no previously published paper presenting concise information of the experiments and studies performed on SC oxygenation and hemodynamics monitoring using NIRS technique and, we believe that since NIRS technique is getting more popular among researchers, therefore, such review could put together all the previous attempts as well as initiate organizing future efforts and studies in this area.

Unlike somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs), current standard methods for functional monitoring of neuro-electrophysiological activity of the SC during vascular and spinal surgery, NIRS provides direct information of SC hemodynamics and

oxygenation with high temporal resolution, making it well suited for real-time intra- and post-operative monitoring of the SC [20, 27, 28]. Since physiologic changes in blood flow occur before damage to neurological tissue, clinicians with access to real-time NIRS-derived hemodynamics measurements can intervene in a timely manner to prevent further injury [20, 29]. Non-invasive application of NIRS, advances this optical technique over other invasive methods such as laser doppler flowmetry (LDF) [29–35], C-anti-pyrene, hydrogen clearance technique, and radioactive microspheres [30]. Lastly, NIRS does not require extensive off-line computerization of the original data [22] as opposed to single photon emission computed tomography (SPECT) [31] and magnetic resonance imaging-based arterial spin labeling (MRI-ASL) [32–35] methods.

Common clinical applications

In 1993, NIRS was approved by the U.S. food and drug administration (FDA) for non-invasive, continuous monitoring of cerebral and somatic tissue oxygenation [19, 36]. Since then, NIRS has been widely utilized for monitoring regional tissue oxygen saturation (rSO_2) in brain tissues in various clinical scenarios [19, 22, 26, 36–38]. Despite the great success of NIRS techniques in cerebral monitoring, similar applications for SC have been limited to date. Although recently, researchers have started to use NIRS in various applications relevant to SC tissues, patients with SCIs, or SC blood perfusion. For instance, Wolf [39] employed a NIR reflectometry method to provide real-time direct measurements of SC position in both static and dynamic motion states [39]. Multiple studies have employed NIRS for monitoring skin/muscle and blood oxygenation [40–50], or cardiovascular and metabolic responses [51, 52] in the lower limbs of patients with SCI. By comparing their performance with able-bodied groups, researchers were able to propose methods for improving physical activity of patients with SCIs through various exercise protocols.

NIRS applications in SC monitoring

Limited studies have applied NIRS for SC hemodynamics and oxygenation monitoring in animal and human models. Studies in experimental animals include monitoring SC tissue ischemia and hypoxia throughout various interventions, while human studies have focused on patients undergoing thoracoabdominal aortic aneurysm (TAAA) repair. Our search strategy revealed 17 articles [20, 26, 27, 53–66] studying NIRS applications for SC monitoring in animals and 9 articles [67–75] focusing on human patients; these are discussed below, the comprehensive list of these papers are presented as a table in the Supplementary file.

NIRS in the experimental settings

In 2002, Macnab and colleagues [20], were the first to demonstrate the feasibility of using NIRS to monitor the SC. They manipulated oxygen saturation and blood flow in the SC of three pigs and showed immediate corresponding changes in the concentration of oxygenated, deoxygenated and total hemoglobin in the cord. Chromophore changes indicative of hypoxia and ischemia were detected by NIRS sensors placed either directly on the skin over the spinous processes, or over the surgically distracted spinal lamina, and then directly on the exposed SC. Thus, they concluded that NIRS monitoring could help surgeons prevent cord damage by providing real-time detection of the onset of ischemia and hypoxia, and hence allow intervention capable of restoring perfusion and oxygen delivery so as to prevent irreversible neuronal injury.

Two years later, Kunihara et al. [53] continuously monitored rSO_2 in dogs using both NIRS sensors in the esophagus and evoked SC evoked potentials. Comparing measurements from seven animals by both methods, they reported that the NIRS response to SC ischemia is not only consistent, but more immediate than the evoked potential response (which is to be expected, given that the electrophysiologic responses are secondary to the ischemic insult). The same researchers then studied fourteen male rabbits [54], where SC oxygenated hemoglobin was measured through NIRS probes positioned on the posterior side of the lower lumbar vertebrae, and evoked potentials with catheters inserted into the upper thoracic and lumbar epidural spaces. They confirmed the reproducibility of their previous findings and concluded that NIRS can detect SC ischemia earlier than evoked potentials [54].

In 2005, Radhakrishnan et al. [55] investigated the feasibility of NIRS as a SC monitoring technique by placing sensors on the SC and sciatic nerve of fourteen rats, while also quantifying the scattering properties of NIRS light in the SC. Based on differential light scattering properties of various SC tissues, they proved their technique could differentiate between healthy and demyelinated peripheral nerves. They also showed that the scattering coefficient is higher in rat SC lumbar regions and lower at the center of the cord near blood vessels. Later, they demonstrated that applying peripheral electrical stimulation on the SC of eight rats resulted in significant changes in both light scattering and saturation of O_2Hb through analyzing the optical reflectance spectra of NIRS and visible spectroscopy, respectively [56].

One year later, LeMaire et al. [57] employed transcutaneous sensors over the pig's upper and lower cord to demonstrate the capability of NIRS to detect SC ischemia in real-time during intercostal and lumbar artery ligation. Their histopathological observation showed that although baseline

rSO_2 was similar in the upper and lower cord, oxygenation levels were significantly reduced in the lower cord after ligation. This difference was confirmed microscopically where fewer ischemic neurons were detected in the upper cord compared to the lower cord sections.

In 2010, Goguin et al. [58] developed a low-cost diffused optical imaging system for in vivo measurement of hemodynamic changes and functional activity. Studying two cats at the L5 level, they demonstrated a strong correlation between SC neural activities and hemodynamic changes. In a subsequent experiment on a pig model a spectrometer was used to determine the reflectance and transmittance properties of SC tissue, and a NIRS-based opto-electrical tool to assess autonomic function in the SC. Using photoplethysmographic monitoring the authors showed hemodynamic changes during rest and stimulation phases in the SC [59, 60].

Recently, a group of researchers including Mesquita et al. [27] and Kogler et al. [61] developed a NIRS-based fiber-optic device for "direct" continuous monitoring of the SC. They demonstrated that this device detects SC ischemia in sheep models in real-time and its temporal resolution is much higher than MEP [62]. Their results were also validated with multicolored microspheres.

In 2016, von Aspern and colleagues investigated the correlation between paraspinal NIRS measurements and SC blood flow by comparing data from NIRS sensors with LDF in seven pigs [63]. Two pairs of subcutaneous paravertebral NIRS sensors were positioned at thoracic and lumbar levels to assess paraspinal muscle oxygenation as an "indirect" indicator of SC hemodynamics. Simultaneously, two pairs of LDF sensors were placed on paravertebral muscle and the SC at the same SC levels. Ultimately, they observed that muscle oxygenation in the thoracic region measured via NIRS was significantly different from LDF measurements, whereas in the lumbar region a significant positive correlation was evident. This achievement showed a direct relationship between the blood flow and oxygenation of surrounding tissues with the lumbar region of the cord. The conclusion was that paraspinal NIRS measures can function as a suitable non-invasive monitoring modality for "indirect", real-time SC hemodynamics assessment, which conforms with previous studies performed on human models [67, 68].

In 2017, two independent experiments on SC hemodynamics monitoring in animal models were conducted. In the first study, Shadgan et al. [64] designed and utilized a multi-wavelength NIRS sensor with an extradural probe for non-invasive and real-time monitoring of SC oxygenation and blood volume around the injury site in a pig model of acute SCI. A miniaturized NIRS sensor was positioned directly on the surgically exposed T10. Simultaneously, the same parameters were measured through invasive intraparenchymal sensors inserted directly into the SC where it was shown that NIRS was more sensitive in monitoring changes in SC tissue oxygenation than intraparenchymal sensors. Later, the same researchers conducted another study on six pigs and evaluated the sensitivity of their NIRS sensor as a way to monitor the oxidation state of SC mitochondrial cytochrome aa3 (CCO), which reflects subcellular damage of SC tissue [65]. They observed a consistent drop in CCO chromophore concentration in SC tissue following SCI, confirming cellular oxidative damage in the SC.

Second, Suehiro et al. [26] reported an experiment on four swine where their results contrast with earlier reports by Lemaire et al. [57] regarding the ability of transcutaneous NIRS to detect SC ischemia. They suggested that the transcutaneous paraspinal muscle rSO_2 values measured by NIRS cannot be a correct indicator for the onset of SC ischemia, since histopathological examination showed that significant ischemia in the SC, which was not reflected by the NIRS system, occurred before tissue oxygenation changes in the paraspinal muscles. Such findings accentuate the need for further research and analysis to ensure that perfusion and oxygenation in SC tissue truly correlate with those surrounding subcutaneous and muscular tissues. Most recently, another study has been conducted by Shadgan and his colleagues [66], where they demonstrated that a multi-wavelength miniaturized NIRS sensor placed directly over the dura can detect and measure real-time changes in SC oxygenation in response to episodes of acute respiratory hypoxia and alteration of MAP with a high degree of sensitivity and specificity.

To examine the safety of direct application and placement of NIRS sensors in contact with the SC tissue, Busch and his colleagues conducted an animal experiment in 2018 [62]. They exposed the SC to laser light utilizing a custom fiber-optic epidural probe in a survival animal surgery on eleven adult Dorset sheep as well as ex vivo SC samples. They reported no functional neurological sequelae, histopathologic evidence of laser-related injury to the SC and no significant temperature changes in ex vivo samples upon prolonged exposure to the laser source of their NIRS optical probes placed within the epidural space.

NIRS in clinical applications

One of the first NIRS clinical applications in humans was performed by Berens and colleagues in 2006 [69]. NIRS monitoring continuously monitored rSO_2 above and below the aortic cross-clamp on 26 pediatric patients who underwent aortic coarctation repair. Transcutaneous sensors were placed on both cerebral and somatic thoracodorsal (T10-L2) sites on the patients. A significant decline in somatic rSO_2 was observed in all patients and a significantly greater decline in neonates and infants <1 year compared to older

children; this was presumed due to a lack of adequate collateral circulation in younger age groups.

In 2011, Badner and colleagues [70] used NIRS and MEP techniques for the first time for intraoperative SC monitoring in two patients undergoing TAAA repair. In both cases, two transcutaneous NIRS sensors were placed over the spine in the midline. They noticed that NIRS signal did not change as fast as the MEP signal. While they reported that NIRS enabled them to prevent one patient from developing neurologic deficits, in a second patient they were unable to keep blood flow in a safe range which resulted in paraplegia.

Concurrently, Moerman and colleagues [71] also reported success using NIRS during endovascular TAAA repair. NIRS sensors were positioned on the left and right forehead, and at two locations over the spinal column for continuous monitoring of tissue oxygenation. A linear relationship was found between tissue oxygenation and MAP, that represented the dependency of SC perfusion on blood pressure after stent deployment.

In 2013, Demir and colleagues [72], investigated NIRS monitoring of spinal regional perfusion in aortic dissection surgery by positioning two NIRS sensors percutaneously on the SC thoracic regions of two patients. They concluded that compared to SSEPs and MEPs, NIRS is a practical and time-saving technique capable of real-time monitoring of the SC and provides early detection of ischemia and hypoxia.

Understanding of SC perfusion has evolved since the introduction of the "paraspinal collateral network" concept [76]. This states that blood supply to the SC is provided by a rich network of paraspinous arterial collaterals which are also shared with surrounding tissues [71, 73, 77]. To prove this, several NIRS experiments were performed using paraspinal muscle monitoring. Etz and colleagues [68] studied twenty individuals undergoing TAAA repair. For the first time, the feasibility of non-invasively and "indirectly" monitoring SC hemodynamics by positioning NIRS sensors on paraspinal thoracic and lumbar regions was evaluated. Paraspinal muscle oxygenation in lumbar regions was found to respond to aortic cross-clamping but demonstrated a delay [73]. As a result, a statistically significant differences in lumbar paraspinal muscle oxygenation were observed between patients who developed SC ischemia vs. patients who did not. Luehr and colleagues [73] repeated this experiment on one patient examining the correlation between regional paraspinal muscle oxygenation and SC perfusion, and also showed the feasibility of using NIRS for "indirect" surveillance of the SC based on the paraspinal collateral network concept through TAAA repair.

In 2013, Amiri et al. [74] for the first time showed the feasibility of intraoperatively monitoring physiological changes in the SC in humans during spine surgery using NIRS accompanied by indocyanine green (ICG) as a tracer. Transdural and translaminar sensors were used on eighteen patients to measure the SC carbon dioxide (CO_2) reactivity index which indicates changes in perfusion associated with increases in CO_2. The authors concluded that their technique can detect increases in SC perfusion if hypercapnia occurs which conforms with changes in the cerebral blood flow.

In 2015, Boezeman et al. [67] stated that NIRS might be a promising non-invasive technique for "indirect" detection of SC ischemia in TAAA repair after using MEP and NIRS on fifteen patients to monitor paraspinal muscle oxygenation. Continuous measurement of rSO_2 at the thoracic vertebrae T3 (sensor 1, reference spot) and T12 (sensor 2) were made via skin sensors. T12/T3 ratios were calculated and compared with the MEP measurements. While no patients showed clinical signs of SC ischemia, they found NIRS-derived paraspinal T12/T3 ratios were significantly lower in the MEP ratios less than 50% compared with the MEP ratios 50% or higher. This result indicates a potential association of paraspinal NIRS measurements with MEP [63, 68]. Following previous experimental findings, Grus et al. [75] also employed a transcutaneous NIRS oximetry device to continuously monitor the SC and prevent ischemia at the lumbar region in a patient diagnosed with infectious aneurysms.

Although promising, NIRS monitoring of SC is subject to certain challenges. The unknown pathlength taken by NIR photons through the SC tissue, the difficulty in achieving a high signal-to-noise ratio (SNR) while maintaining enough light penetration, being sensitive to movement, and avoiding thermal tissue damage [27, 61] are among main challenges. Another particular and controversial challenge is how to arrange the sensors so as to achieve optimal spatial resolution and sensitivity [23, 63]. As described in this review, various types of sensors and placement sites have been used for monitoring SC hemodynamics and oxygenation. Thus far, all approaches for sensor positioning have shown promising results in detecting SC ischemia. However, the propagation of light through tissues with multiple layers of the nonhomogeneous medium is complex, and how effectively this is achieved with NIRS depends on the density, optical characteristics and metabolic activity of each layer. Therefore, it is logical to assume that the most accurate method for monitoring the SC will be where there is the least amount of tissue between the sensor and the cord. In practice, this would be achieved by placing the sensor directly on the extradural surface of the cord [64]. Direct contact between the NIRS sensor and the dura at the site of injury is particularly essential when monitoring traumatic SC tissue [66]. Correct placement and fixation of the NIRS sensor in epidural space is also a critical challenge in patients with subacute phase of SCI and those undergo TAAA repair [61, 67].

Conclusions

The importance of hemodynamic management with vigilant maintenance of MAP has been acknowledged for many years to be an integral entity for improving neurologic recovery after acute SCI. However, without real-time and continuous monitoring of the injured SC, the optimal hemodynamic management of a recently injured patient is difficult—if not impossible—to achieve. In this review, we have described the NIRS approach for monitoring SC hemodynamics and oxygenation. While showing clear promise, it is evident that further technical advances, followed by clinical trials with large cohort studies, are required to confirm the clinical validity of NIRS as a viable technique for accurate monitoring in patients with acute SCI.

Acknowledgements BS holds a Scholar Award from the Michael Smith Foundation for Health Research. BKK is the Canada Research Chair in Spinal Cord Injury and the Dvorak Chair in Spine Trauma.

Author Contributions TR was responsible for conducting the study and manuscript preparation. AM contributed to the study by analyzing the findings and drafting the manuscript. AC contributed to the study by article searching and manuscript preparation. AS contributed to the study by manuscript and graphic preparations. BK contributed the study by analyzing the findings, guiding the discussions, and reviewing the manuscript. BS was responsible for proposing and supervising the study and drafting the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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