Near infrared spectroscopy: clinical and research uses

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BACKGROUND: Pulse oximetry is routinely used to measure hemoglobin saturation and is currently the gold standard to assess oxygenation in patients. Due to attenuation of infrared light by skin, bone, and other organs, pulse oximetry cannot assess end-organ tissue oxygenation (StO_2). Near infrared spectroscopy (NIS) penetrates a broad range of tissues and utilizes reflection rather than direct transmission between an emitter and receiver pair. NIS is able to measure StO_2 and assess end-organ perfusion in a variety of applications.
STUDY DESIGN AND METHODS: A retrospective review of recent animal and human StO_2 studies was undertaken. StO_2 measurements and outcomes were assessed.
RESULTS: StO_2 measurements identified visceral organ ischemia in animal hemorrhage models. These measurements were also able to guide optimization of resuscitation and end-organ oxygenation. Human studies demonstrated StO_2 changes preceded those seen in traditionally measured parameters such as blood pressure, heart rate, base deficit, serum lactate, and mental status. Additionally, StO_2 thresholds identified trauma patients who required massive transfusions, developed multiple organ dysfunction syndrome, or experienced lower extremity compartment syndrome. StO_2 measurements also demonstrated a benefit in selecting resuscitation fluids, assessing end-organ oxygenation during blood transfusion, and quantifying the oxygen-carrying deficit secondary to the blood storage lesion.
CONCLUSION: StO_2 measurements have been used to guide resuscitation efforts in trauma patients. This technology and its applications continue to evolve and represent a novel change in patient care.

Noninvasive pulse oximetry has been the gold standard measure for hypoxemia in hospital and field settings for decades. Originally developed in 1935 by Dr Karl Matthes, his noninvasive ear probe utilized red and infrared light to account for tissue and blood content variability. Based on the principles of the Beer-Lambert Law (Fig. 1), the incident wave's amplitude, I_o, is exponentially attenuated by the tissue's absorption coefficient, $\varepsilon(\lambda)$, and concentration of absorbing substance, C, over a distance, L. The resultant amplitude, I_L, is an index for tissue oxygenation (StO_2). The inability to differentiate between venous and arterial blood plagued these early devices making them grossly inaccurate. By the early 1970s the accuracy of arterial oxygen saturation improved through heating elements within the probe increasing arterial capillary blood flow. By 1972 Takuo Aoyagi was able to discriminate between arterial and venous flow.[1,2] He developed the first pulse oximeter by targeting light pulsations, isolating the arterial component. This device received worldwide interest from several engineering firms, and subsequently became an invaluable tool for patient care.

In 1977 Dr Frans Jöbsis advanced StO_2 research by establishing near infrared spectroscopy (NIS) as a viable and reliable measurement device.[3] Unlike the pulse oximeter, it utilizes infrared and near infrared light. The near infrared light is not attenuated by skin, bone, or other organs but is absorbed by oxygenated and deoxygenated blood; however, infrared light is only absorbed by deoxygenated blood. Based upon reflected light, the NIS device calculates the tissue's optical density at each wave length,

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doi: 10.1111/trf.12036

TRANSFUSION 2013;53:52S-58S.

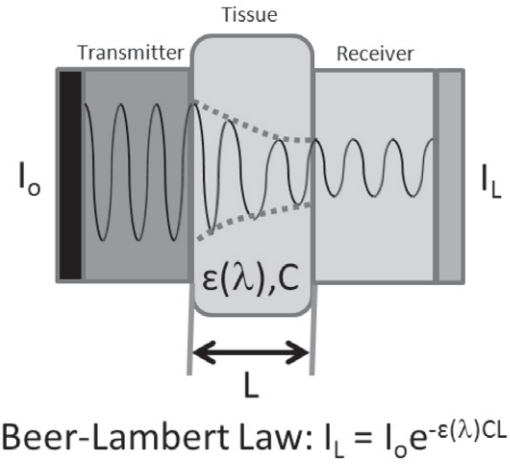

Fig. 1. Beer-Lambert Law—The incident wave's amplitude, I_o, is exponentially attenuated by the tissue's absorption coefficient, ε(λ), and concentration of the absorbing substance, C, over a distance, L. The resultant amplitude, I_L, is an index for tissue oxygenation. The absorbing substance is any tissue—bone, vasculature, RBC, or skin artifact—which reduces the incident wave's amplitude.

OD(λ), by using a variation of the Beer-Lambert Law (Fig. 2). The optical densities are utilized to derive the change in total hemoglobin, Δ[Hgb], and oxygenated hemoglobin, $\Delta[HgbO_2]$; the difference in these values, $\Delta[O_2]$, represents StO_2. Furthermore, Mancini demonstrated that the correlation between NIS and venous oxygenation could act as a surrogate for tissue perfusion.[4] Taken together these findings suggested that NIS affords a continuous noninvasive direct measure of StO_2.

Since Jöbsis's early work, several animal models have demonstrated and validated the ability to assess visceral organ ischemia through NIS.[5-8] Rhee's group used rabbit models with NIS probes over the stomach, liver, kidney, and hamstring muscles.[8] During partial hemorrhage and resuscitation with autologous blood and crystalloid, they monitored cytochrome oxygenation, cardiac output, and oxygen delivery. During the resuscitation phase, a decrease in mitochondrial cytochrome oxidation, which correlated with cellular oxygenation, was identified. This deficit was readily apparent despite traditional measures indicating adequate resuscitation. Work was subsequently extrapolated to guidance of fluid resuscitation in animal models. Varela's group studied swine models in shock states that underwent either delayed, hypotensive, or aggressive resuscitation.[7] Through measurements of gastric StO_2, blood gasses, and blood flow, it was demonstrated that aggressive resuscitation was detrimental to

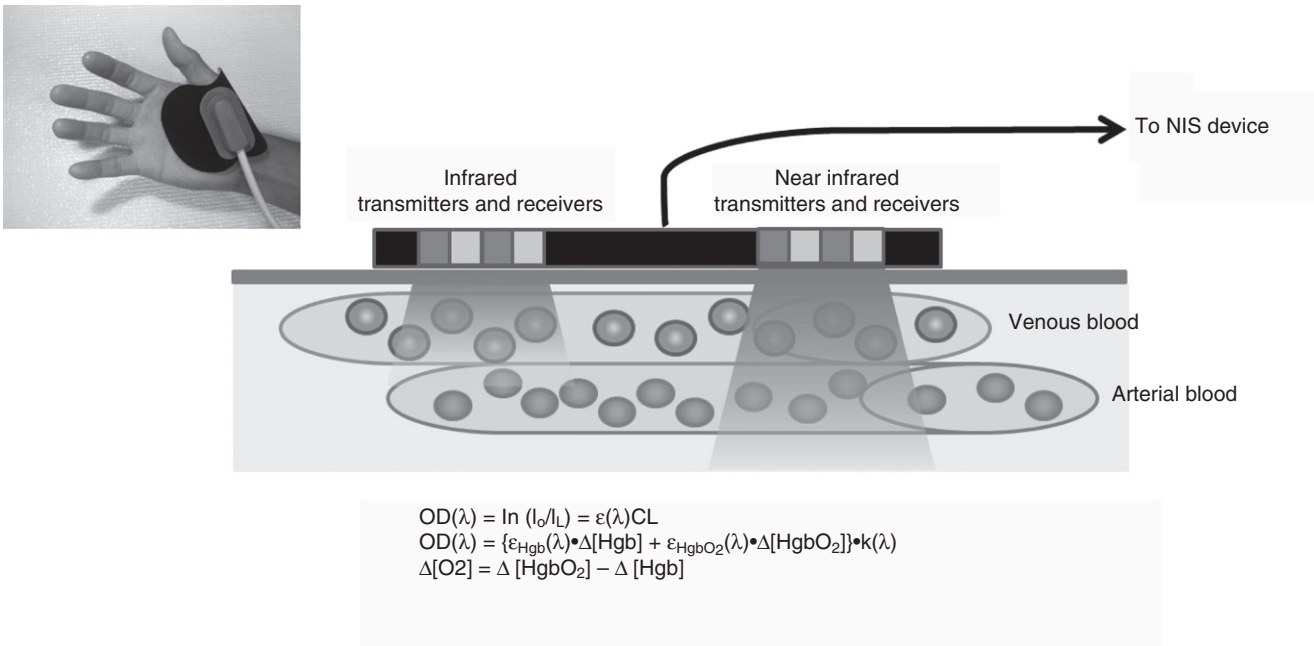

Fig. 2. NIS over the thenar eminence—The device utilizes near infrared light which is absorbed by oxygenated and deoxygenated blood and infrared light which is only absorbed by deoxygenated blood. Based upon reflected light, the NIS device calculates the tissue's optical density at both wave lengths, OD(λ), through a variation of the Beer-Lambert Law. The product of concentration, C, and length, L, equals the change in total hemoglobin, Δ[Hgb], and oxygenated hemoglobin, $\Delta[HgbO_2]$. The constant, k(λ), is a factor representing the total path traveled by the light. The optical densities are utilized to derive Δ[Hgb] and $\Delta[HgbO_2]$; the difference in these values, $\Delta[O_2]$, represents tissue oxygenation, StO_2.

splanchnic perfusion; however, a hypotensive resuscitation protocol was beneficial to both systemic and splanchnic circulations resulting in higher gastric and portal vein oxygenation saturations.

NIS has since transitioned to human studies and subsequently has been utilized with increasing frequency in clinical and surgical applications such as stroke and subarachnoid hemorrhage management,[9-12] cerebral monitoring during cardiovascular procedures,[13,14], and detection of lower extremity compartment syndrome.[15-19] NIS is also uniquely designed to assess and direct trauma patient care. In the setting of hemorrhagic shock, accurate real-time knowledge of end-organ perfusion could provide lifesaving and goal-directed measures, guiding patient management. Traditional resuscitation algorithms utilize parameters such as: changes in blood pressure, heart rate, urine output, base deficit, serum lactate, or mental status to guide treatment. However, changes in these parameters may be delayed with respect to an evolving physiologic stressor and therefore are not ideal in the acute setting. For example, hypotension, systolic blood pressure less than 100 mmHg, usually seen in Stage 3 shock, may not occur until a significant amount of blood, 30%-40% of a patient's circulating volume, is lost. Also a base deficit or lactate value may be normal in the early stages of hemorrhagic shock even though occult hypoperfusion may be present. These concerns were examined by Putman's group during evaluation of cardiopulmonary bypass patients by comparing traditional baseline laboratory measures to NIS readings.[20] StO_2 changes associated with cardiopulmonary bypass preceded the rise in lactate and base deficit by nearly 90 minutes. These findings suggest delayed changes in traditional measures of perfusion can underestimate inadequate oxygen delivery resulting in end-organ ischemia.

The necessity for timely data has been heralded by civilian and combat surgical teams. In these acute settings critical lifesaving interventions are predicated on physician experience and rapid acquisition and interpretation of data. Early NIS results have demonstrated a benefit to trauma patients.[21-23] Beekley's group performed a prospective, blinded observational study in 147 combat casualties during the Iraqi conflict to determine if NIS-derived tissue oxygenation was an indicator of early shock.[21] A multivariate logistic regression analysis showed that systolic blood pressure (SBP), international normalized ration (INR), tissue hemoglobin index, and hematocrit were able to predict the need for blood transfusions. However, StO_2 was found to be an independent predictor for blood transfusion in the study population with a SBP > 90 mmHg. This would imply that StO_2 was able to identify wartime casualties requiring blood transfusion as well as other possible lifesaving interventions in those who would normally be triaged to a more conservative tier of care given their initial vital signs.[21]

Similarly, Moore's group performed a prospective StO_2 study to identify patients requiring a massive transfusion.[22] Seven US trauma centers enrolled 383 trauma patients. Those requiring a massive transfusion demonstrated significant differences in their SBP and INR 2 hours after emergency department (ED) admission as compared with the nonmassive transfusion group. Upon initial ED admission, however, the StO_2 was lower in the massive transfusion group, suggesting that StO_2 can be utilized as an early noninvasive sign for a possible lifesaving intervention. Analogously, Cohn's group performed a multicenter observational study of over 350 trauma patients investigating the relationship between StO_2, standard trauma parameters, and outcome.[23] When StO_2 was less than 75%, there was a 78% sensitivity for the development of multiple-organ dysfunction syndrome (MODS). The sensitivity of a base deficit >6 meq/L and systolic blood pressure <90 mmHg was similar for the subsequent

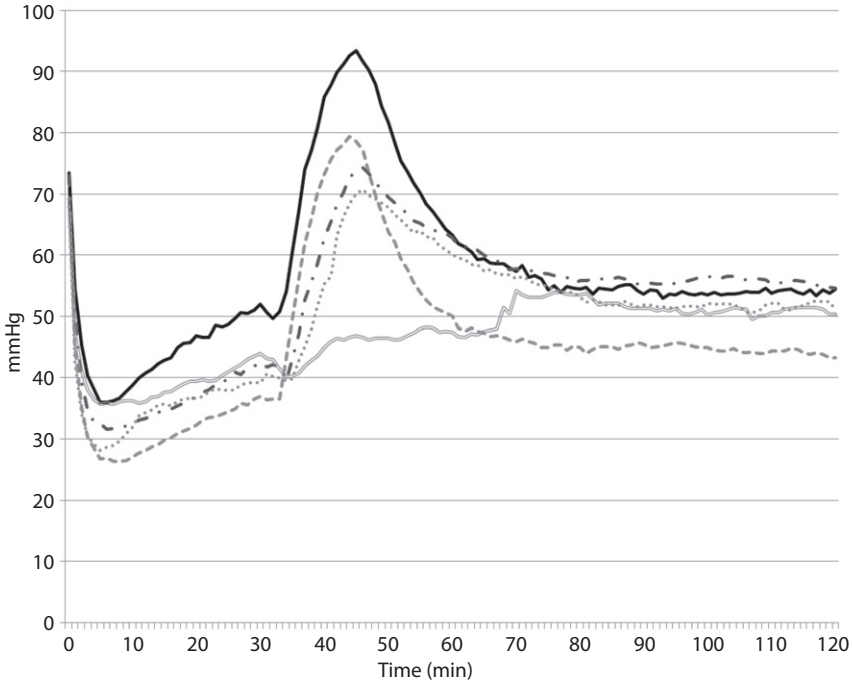

Fig. 3. Continuous MAP recording during Grade V liver injuries—The initial injury was followed by a 30-minute hemorrhage and bolus resuscitation. At the 1-hour time mark, there was no difference between LR, HEX, and HTS. At the 2-hour time mark, the decreased MAP after NS administration was statistically significant. ----, NS; ——, LR; – · –, HEX; ·····, HTS; ——, NF.

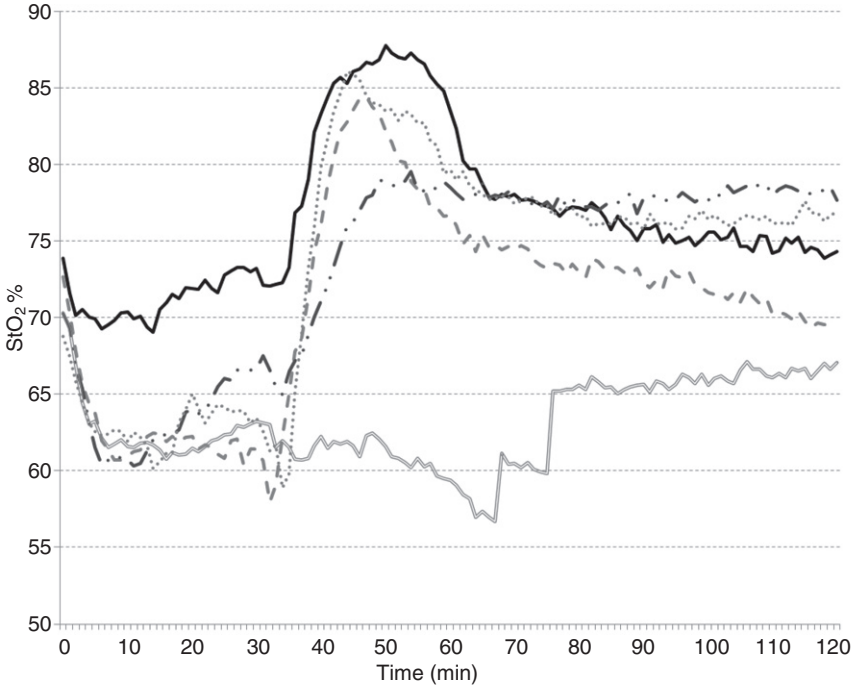

Fig. 4. Continuous StO_2 recording during Grade V liver injuries—The NF group was significantly different than all groups at the 1-hour time mark; however, no difference could be seen between NS and NF at the 2-hour time mark. A difference was not seen among LR, HEX, and HTS at the 1- and 2-hour time mark. ----, NS; ——, LR; — -, HEX; ·····, HTS; ——, NF.

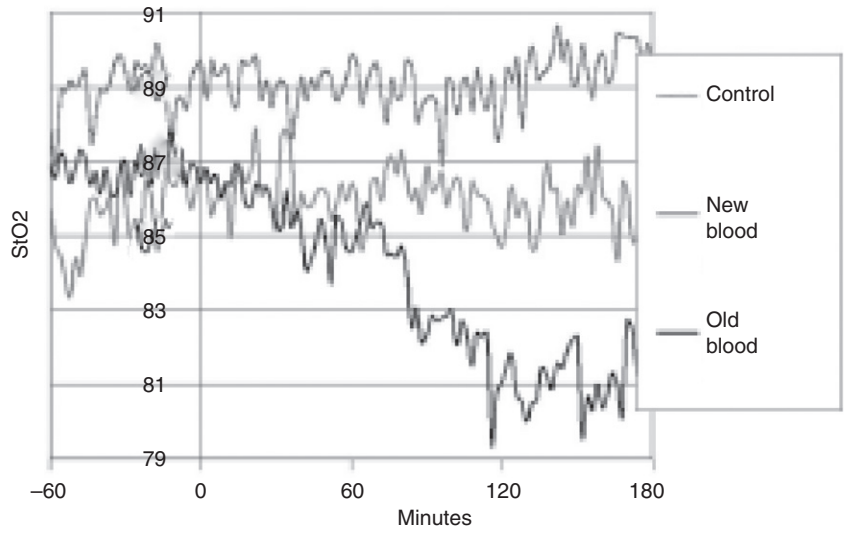

Fig. 5. Tissue oxygenation during transfusion with old (≥21 days) versus new (<21 days) blood—A significant decline in StO_2 is noted after transfusion with the old blood. An increase in StO_2 was not appreciated when RBCs less than 21 days old were given.

development of MODS. Tissue oxygenation and base deficit were found to have a higher negative predictive value for MODS than hypotension; therefore during resuscitation, an StO_2 greater than 75% was not associated with development of MODS. Both studies clearly show that StO_2 is an early and reliable indicator of patients requiring a lifesaving intervention compared with traditional vital signs or laboratory measures.

A recent publication from our laboratory utilized NIS technology and StO_2 measures to investigate the hemodynamic and physiologic benefits of common initial resuscitation strategies in civilian and military settings.[24] Swine underwent Grade V liver injuries and were allowed to freely bleed for 30 minutes, followed by peri-hepatic packing. After hemorrhage, animals were given a 12-minute intravenous fluid resuscitation with either 2 L of normal saline (NS), 2 L of Lactated Ringer's (LR), 500 mL of Hextend (HEX), 250 mL of 7.5% hypertonic saline with 3% Dextran (HTS), or no fluid (NF). Following injury, both mean arterial pressure (MAP) and StO_2 dropped rapidly (Figs. 3 and 4). However, after reaching a nadir, a spontaneous increase in MAP occurred even in the absence of fluid resuscitation. This was not seen with the StO_2, suggesting that the elevation in blood pressure is not associated with increased perfusion. Our previous work revealed that this period of "autoresuscitation" is attributed to an increase in systemic vascular resistance.[25] Furthermore, it was notable that in the resuscitated animals their respective MAPs were lower than baseline whereas the StO_2 measures were higher or the same. Despite a lower MAP, the StO_2 indicates that the animals may have been adequately resuscitated. These studies illustrate how StO_2 and blood pressure reflect different information during hemorrhagic shock and resuscitation.

In the event resuscitation with colloid and crystalloid is unsuccessful, transfusion with red blood cells (RBCs) is the next option. The intention of transfusing RBCs is to increase end-organ perfusion and oxygenation.[26,27] RBCs, however, undergo structural and functional transformations known as the storage lesion. These transformations detrimentally impact the RBCs' oxygen-carrying capacity, ability to transverse the capillary network, capacity to

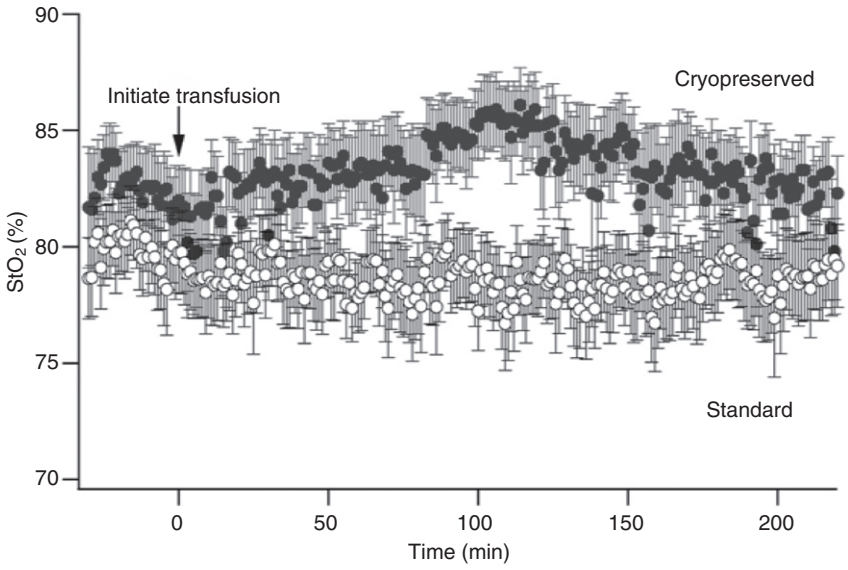

Fig. 6. Cryopreserved and standard RBC transfusion versus StO_2—The standard transfusion results remained near baseline while those receiving cryopreserved RBCs demonstrated a statistically significant increase in StO_2 ($p = 0.03$).

vasoregulate via altered nitric oxide mechanisms,[28-31] and oxygen off-loading.[32] These changes restrict perfusion and impair end-organ oxygenation.[33-37] Using NIS, our laboratory investigated the effect of RBC age on StO_2 in trauma patients. Patients receiving blood that was greater than or equal to 21 days old (old blood) were compared with patients who received blood that was less than 21 days old (young blood).[38] The intent of the 21-day threshold was to ensure the storage lesion's morphologic and biochemical changes were manifest.[39,40] The group that received old blood demonstrated a significant decrease in StO_2 compared with baseline measurements (Fig. 5). Conversely, the control group and the group that received younger blood did not demonstrate a significant change in StO_2 after transfusion. These findings suggest that changes associated with the storage lesion reduce tissue perfusion and may explain why transfusion of older blood is associated with worse outcomes.

Cryopreservation (CP) prolongs the shelf life of RBCs and virtually eradicates the storage lesion. CP completely arrests these biochemical and morphological pathways,[41-44] resulting in maintenance of the preprocessing RBCs' membrane integrity and their oxygen-carrying capacity.[45] The only variable that contributes to the storage lesion is the duration of time from donation to deep freeze. Our laboratory again utilized NIS to compare transfused cryopreserved blood with standard RBCs in a trauma population. Immediately following the initiation of transfusion, there was an increase in StO_2 in the CP group that did not occur in the standard liquid preserved RBC group (Fig. 6) (unpublished data). As opposed to the previous study, which showed a tissue oxygenation deficit after transfusion with standard preserved RBCs greater than 21 days old, our latest data suggest a tissue oxygenation benefit was conferred with cryopreserved blood. The StO_2 measurements helped identify the failure to increase tissue oxygenation with transfusion of standard liquid RBCs most likely due to the storage lesion.

Aside from NIS providing insight into the assessment of trauma patients and their resuscitation efforts, identifying time-related deficits in traditional laboratory values, and optimizing RBC transfusions, the technology has been integrated into other areas of patient management. For example, StO_2 has been measured in patients with chronic exertional compartment syndrome.[18,19] Giannotti's group demonstrated a prefasciotomy oxygenation deficit based upon decreased StO_2, and subsequent resolution to the normal range after procedure.[46] Similarly, van den Brand's group investigated a larger military population with chronic exertional compartment syndrome through which lower extremity fasciotomy normalized StO_2.[18] Finally, Shuler's group studied StO_2 levels in trauma patients with unilateral lower extremity trauma.[16] When normalized for the uninjured leg, NIS was able to identify the extremity with lower perfusion pressure and possible acute or chronic compartment syndrome. One caveat to this technique is that NIS readings can potentially be altered by subcutaneous fluid collections or hematomas. Overall these studies demonstrate consistent results and the benefit of noninvasive analysis versus intra-compartmental pressure measurements or costly magnetic resonance imaging analysis.

Opportunities for early interventions were also seen during monitoring of cerebral oxygenation in patients undergoing abdominal procedures.[47] Through the use of bilateral forehead probes, over 120 patients were evaluated. Those randomized to the treatment arm were managed based upon regional cerebral oxygenation saturation (rSO_2). Values less than 75% were initially addressed by checking the ventilator and patient position, increasing the FiO_2, and providing intravenous fluids and vasopressors as needed. If these maneuvers were unsuccessful and did not increase the rSO_2, a bolus of propofol was given to decrease the cerebral oxygen requirement. Patients randomized to the nontreatment arm were managed based upon their vital signs. Those who received treatment intraoperatively according to their rSO_2 values had a decreased postoperative care unit stay, a shorted hospitalization, and improved postoperative Day-7 Mini Mental State Examination. This intraoperative monitoring technique

affords real-time feedback of cerebral oxygenation, decreases the opportunity of cerebral hypoxic events, and allows for early goal-directed interventions.

NIS is a developing technology with numerous applications. It is a noninvasive, portable device that can be easily adapted to numerous settings including the emergency room or far-forward deployed military medical unit for triage of casualties, an operating room for refinement of anesthesia, or a hospital ward for bedside monitoring. Its potential uses are well documented in the recent literature that focuses on early goal-directed diagnosis and intervention as compared with traditional measures and laboratories. NIS technology is becoming an adjunct to first-line assessment and care, and could represent a paradigm shift in patient management.

CONFLICT OF INTEREST

There is no conflict of interest or financial involvement with this manuscript.

REFERENCES

1. Severinghaus JW, Honda Y. History of blood gas analysis. VII. pulse oximetry. J Clin Monit 1987;3:135-8.
2. Severinghaus JW. Takuo Aoyagi: discovery of pulse oximetry. Anesth Analg 2007;105(Suppl.):S1-4; tables of contents.
3. Jöbsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 1977;198:1264-7.
4. Mancini DM, Bolinger L, Li H, Kendrick K, Chance B, Wilson JR. Validation of near-infrared spectroscopy in humans. J Appl Physiol 1994;77:2740-7.
5. Beilman GJ, Groehler KE, Lazaron V, Ortner JP. Near-infrared spectroscopy measurement of regional tissue oxyhemoglobin saturation during hemorrhagic shock. Shock 1999;12:196-200.
6. Cohn SM, Varela JE, Giannotti G, Dolich MO, Brown M, Feinstein A, McKenney MG, Spalding P. Splanchnic perfusion evaluation during hemorrhage and resuscitation with gastric near-infrared spectroscopy. J Trauma 2001;50:629-34; discussion 634-5.
7. Varela JE, Cohn SM, Diaz I, Giannotti GD, Proctor KG. Splanchnic perfusion during delayed, hypotensive, or aggressive fluid resuscitation from uncontrolled hemorrhage. Shock 2003;20:476-80.
8. Rhee P, Langdale L, Mock C, Gentilello LM. Near-infrared spectroscopy: continuous measurement of cytochrome oxidation during hemorrhagic shock. Crit Care Med 1997; 25:166-70.
9. Moerman A, Wouters P. Near-infrared spectroscopy (NIRS) monitoring in contemporary anesthesia and critical care. Acta Anaesthesiol Belg 2010;61:185-94.
10. Terborg C, Groschel K, Petrovitch A, Ringer T, Schnaudigel S, Witte OW, Kastrup A. Noninvasive assessment of cerebral perfusion and oxygenation in acute ischemic stroke by near-infrared spectroscopy. Eur Neurol 2009;62: 338-43.
11. Yokose N, Sakatani K, Murata Y, Awano T, Igarashi T, Nakamura S, Hoshino T, Kano T, Yoshino A, Katayama Y, Ohmae E, Suzuki T, Oda M, Yamashita Y. Bedside assessment of cerebral vasospasms after subarachnoid hemorrhage by near infrared time-resolved spectroscopy. Adv Exp Med Biol 2010;662:505-11.
12. Zweifel C, Castellani G, Czosnyka M, Carrera E, Brady KM, Kirkpatrick PJ, Pickard JD, Smielewski P. Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid hemorrhage. Stroke 2010;41:1963-8.
13. Vernieri F, Silvestrini M, Tibuzzi F, Pasqualetti P, Altamura C, Passarelli F, Matteis M, Rossini PM. Hemoglobin oxygen saturation as a marker of cerebral hemodynamics in carotid artery occlusion: an integrated transcranial Doppler and near-infrared spectroscopy study. J Neurol 2006;253:1459-65.
14. La Monaca M, David A, Gaeta R, Lentini S. Near infrared spectroscopy for cerebral monitoring during cardiovascular surgery. Clin Ter 2010;161:549-53.
15. Shuler MS, Reisman WM, Cole AL, Whitesides TE, Jr, Moore TJ. Near-infrared spectroscopy in acute compartment syndrome: case report. Injury 2011;42:1506-8.
16. Shuler MS, Reisman WM, Kinsey TL, Whitesides TE Jr, Hammerberg EM, Davila MG, Moore TJ. Correlation between muscle oxygenation and compartment pressures in acute compartment syndrome of the leg. J Bone Joint Surg Am 2010;92:863-70.
17. Shuler MS, Reisman WM, Whitesides TE, Jr, Kinsey TL, Hammerberg EM, Davila MG, Moore TJ. Near-infrared spectroscopy in lower extremity trauma. J Bone Joint Surg Am 2009;91:1360-8.
18. van den Brand JG, Nelson T, Verleisdonk EJ, van der Werken C. The diagnostic value of intracompartmental pressure measurement, magnetic resonance imaging, and near-infrared spectroscopy in chronic exertional compartment syndrome: a prospective study in 50 patients. Am J Sports Med 2005;33:699-704.
19. van den Brand JG, Verleisdonk EJ, van der Werken C. Near infrared spectroscopy in the diagnosis of chronic exertional compartment syndrome. Am J Sports Med 2004;32: 452-6.
20. Putnam B, Bricker S, Fedorka P, Zelada J, Shebrain S, Omari B, Bongard F. The correlation of near-infrared spectroscopy with changes in oxygen delivery in a controlled model of altered perfusion. Am Surg 2007;73:1017-22.
21. Beekley AC, Martin MJ, Nelson T, Grathwohl KW, Griffith M, Beilman G, Holcomb JB. Continuous noninvasive tissue oximetry in the early evaluation of the combat casualty: a prospective study. J Trauma 2010;69(Suppl. 1):S14-25.
22. Moore FA, Nelson T, McKinley BA, Moore EE, Nathens AB, Rhee P, Puyana JC, Beilman GJ, Cohn SM; StO_2 Study

Group. Massive transfusion in trauma patients: tissue hemoglobin oxygen saturation predicts poor outcome. J Trauma 2008;64:1010-23.
23. Cohn SM, Nathens AB, Moore FA, Beilman GJ; StO_2 in Trauma Patients Trial Investigators. Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. J Trauma 2007;62:44-54; discussion 54-5.
24. Riha GM, Kunio NR, Van PY, Hamilton GJ, Anderson R, Differding JA, Schreiber MA. Hextend and 7.5% hypertonic saline with dextran are equivalent to lactated Ringer's in a swine model of initial resuscitation of uncontrolled hemorrhagic shock. J Trauma 2011;71:1755-60.
25. Phillips CR, Vinecore K, Hagg DS, Sawai RS, Differding JA, Watters JM, Schreiber MA. Resuscitation of hemorrhagic shock with normal saline vs. lactated Ringer's: effects on oxygenation, extravascular lung water, and hemodynamics. Crit Care 2009;13:R30.
26. Consensus conference. perioperative red blood cell transfusion. JAMA 1988;260:2700-3.
27. Napolitano LM, Corwin HL. Efficacy of red blood cell transfusion in the critically ill. Crit Care Clin 2004;20:255-68.
28. Jia L, Bonaventura C, Bonaventura J, Stamler JS. S-nitrosohaemoglobin: a dynamic activity of blood involved in vascular control. Nature 1996;380:221-6.
29. McMahon TJ, Moon RE, Luschinger BP, Carraway MS, Stone AE, Stolp BW, Gow AJ, Pawloski JR, Watke P, Singel DJ, Piantadosi CA, Stamler JS. Nitric oxide in the human respiratory cycle. Nat Med 2002;8:711-17.
30. González-Alonso J, Mortensen SP, Dawson EA, Secher NH, Damsgaard R. Erythrocytes and the regulation of human skeletal muscle blood flow and oxygen delivery: role of erythrocyte count and oxygenation state of haemoglobin. J Physiol 2006;572(Pt 1):295-305.
31. Mack AK, McGowan Ii VR, Tremonti CK, Ackah D, Barnett C, Machado RF, Gladwin MT, Kato GJ. Sodium nitrite promotes regional blood flow in patients with sickle cell disease: a phase I/II study. Br J Haematol 2008;142:971-8.
32. Valeri CR, Collins FB. The physiologic effect of transfusing preserved red cells with low 2,3-diphosphoglycerate and high affinity for oxygen. Vox Sang 1971;20:397-403.
33. Rumsby MG, Trotter J, Allan D, Michell RH. Recovery of membrane micro-vesicles from human erythrocytes stored for transfusion: a mechanism for the erythrocyte discocyte-to-spherocyte shape transformation. Biochem Soc Trans 1977;5:126-8.
34. McHedlishvili G, Maeda N. Blood flow structure related to red cell flow: determinant of blood fluidity in narrow microvessels. Jpn J Physiol 2001;51:19-30.
35. Langenfeld JE, Livingston DH, Machiedo GW. Red cell deformability is an early indicator of infection. Surgery 1991;110:398-403.
36. Laczkó J, Feó CJ, Phillips W. Discocyte–echinocyte reversibility in blood stored in CPD over a period of 56 days. Transfusion 1979;19:379-88.
37. Card RT, Mohandas N, Mollison PL. Relationship of post-transfusion viability to deformability of stored red cells. Br J Haematol 1983;53:237-40.
38. Kiraly LN, Underwood S, Differding JA, Schreiber MA. Transfusion of aged packed red blood cells results in decreased tissue oxygenation in critically injured trauma patients. J Trauma 2009;67:29-32.
39. Hovav T, Yedgar S, Manny N, Barshtein G. Alteration of red cell aggregability and shape during blood storage. Transfusion 1999;39:277-81.
40. Bennett-Guerrero E, Veldman TH, Doctor A, Telen MJ, Ortel TL, Reid TS, Mulherin MA, Zhu H, Buck RD, Califf RM, McMahon TJ. Evolution of adverse changes in stored RBCs. Proc Natl Acad Sci U S A 2007;104:17063-8.
41. Purdy FR, Tweeddale MG, Merrick PM. Association of mortality with age of blood transfused in septic ICU patients. Can J Anaesth 1997;44:1256-61.
42. Sumida S. Transfusion and transplantation of cryopreserved cells and tissues. Cell Tissue Bank 2006;7:265-305.
43. Huggins C. Preparation and usefulness of frozen blood. Ann Rev Med 1985;36:499-503.
44. Wallach S, Zemp JW, Cavins JW, Jenkins LJ Jr, Bethea M, Freshette L, Haynes LL, Tullis JL. Cation flux and electrolyte composition of frozen-deglycerolized blood. Blood 1962;20:344-54.
45. Krijnen NW, de Wit JJ, Kuivenhoven AC, Loos JA, Prins HK. Glycerol treated human red cells frozen with liquid nitrogen. Vox Sang 1964;9:559-72.
46. Giannotti G, Cohn SM, Brown M, Varela JE, McKenney MG, Wiseberg JA. Utility of near-infrared spectroscopy in the diagnosis of lower extremity compartment syndrome. J Trauma 2000;48:396-9; discussion 399-401.
47. Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Danelli G, Fierro G, De Cosmo G, Servillo G. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. Anesth Analg 2005;101:740-7; table of contents.