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TITLE: **Development and Testing of New Noninvasive Monitoring Tools for Prolonged Field Care Goal-Directed Therapy**

PRINCIPAL INVESTIGATOR: Kevin Ward, MD

CONTRACTING ORGANIZATION: University of Michigan, Ann Arbor, MI

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6. AUTHOR(S)

Kevin Ward, MD: keward@umich.edu
Mohamad H. Tiba, MD : tibam@med.umich.edu

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Michigan
Michigan Center for Integrative Research in Critical Care
2800 Plymouth Road, NCRC
Building 10, Room A107
Ann Arbor, Michigan 48109-2800

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14. ABSTRACT

Management of the polytrauma patient with or without TBI in the prolonged field care (PFC) setting especially when prolonged damage control resuscitation (pDCR) is required represents an extraordinary challenge. While there is a desire to develop new therapeutic agents to improve survival and mitigate tissue injury and organ failure, we have not yet developed tools which assist in helping providers maximize use of supportive treatments such blood transfusion, volume expansion, vasopressor use, etc. in a precision manner for goal directed therapy (GDT). The use of goal GDT has been demonstrated to be life saving for both surgical and medical populations with severe hemodynamic compromise but is difficult to implement with current invasive and noninvasive tools because of their lack of precision or form factor and expense. This proposal will scale testing of two novel noninvasive measures that could allow for real-time use of GDT in the PFC/pDCR setting.

These include: 1) Resonance Raman Spectroscopy (RRS) to measure tissue hemoglobin oxygen saturation (StO2) of the buccal mucosa as a substitute for central or mixed venous hemoglobin oxygen saturation (ScvO2) and potentially lactate, and 2) Dynamic Respiratory Impedance Volume Evaluation (DRIVE) of the limb as a substitute for ultrasound of the inferior/superior vena cava and central venous pressure (CVP). RRS-StO2 uses a special wavelength of light to determine how much oxygen a tissue is receiving. DRIVE uses a small amount of electricity passed through tissue to measure blood volume moving in and out of the tissue during breathing.

Hypothesis: The use of noninvasive RRS-StO2 and DRIVE will provide information of sufficient value in complex surgical patients regarding tissue oxygenation and intravascular volume to allow consideration of their use for GDT in PFC and pDCR.

Specific Aims/Objectives:

1) Test and compare RRS-StO2 with other measures and surrogates of tissue oxygenation including lactate and ScvO2 in polytrauma and complex operative and post-operative surgical patients.

2) Test and compare DRIVE to other measures and surrogates of intravascular volume monitoring including ultrasound of the IVC and SVC, CVP, and stroke volume variation (SVV) (when measured) in polytrauma and complex operative and post-operative surgical patients.

3) Compare time series measurement RRS-StO2 and DRIVE to patient outcomes including mortality and organ failure in order to support future clinical intervention trials.

This is a clinical research study examining two prototype noninvasive devices (RRS-StO2 and DRIVE) to compare their performance to a range of standard invasive and noninvasive monitoring that may not be suitable for PFC and pDCR. Trauma and surgical critical care patients undergoing invasive monitoring (CVP, ScvO2 stroke volume variation (SVV), etc.) and noninvasive or minimally invasive monitoring (IVC ultrasound, TEE, etc.) will have these measures compared to RRS-StO2 and DRIVE over time. Responses to treatment such as transfusion, volume loading, vasoactive medication administration, mechanical ventilation, etc. will be tracked and compared. Additional data such as lactate levels, injury severity scores, surgical interventions, organ failure scores, and finally outcome will be compared to understand how DRIVE and RRS-StO2 perform compared to other traditional measures. An attempt will be made to enroll 200-300 subjects.

15. SUBJECT TERMS

Tissue Oxygenation, Resonance Raman Spectroscopy, Bioimpedance, Intravascular Volume, Hemodynamics, Goal Directed Therapy

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1. INTRODUCTION:

Trauma frequently leads to a state of shock usually through significant hemorrhage. Hemorrhage continues to be the leading cause of death on the battlefield. The ability is lacking to both quickly determine the severity of hypoperfusion and tissue hypoxia after injury as well as during resuscitation as a means to guide therapy and optimally resuscitate victims early in their care and between echelons of care. Cellular dysfunction, organ damage, coagulopathy and death are known to occur proportional to the degree of shock. Early goal directed therapy (GDT) is a resuscitation strategy developed over the last decade based on the physiologic principle of reversing tissue dysoxia, and restoring basic oxygen transport metrics to a level that meets the body's oxygen demands in an early and individualized targeted fashion.

Management of the polytrauma patient with or without TBI in the prolonged field care (PFC) setting especially when prolonged damage control resuscitation (pDCR) is required represents an extraordinary challenge. While there is a desire to develop new therapeutic agents to improve survival and mitigate tissue injury and organ failure, we have not yet developed tools which assist in helping providers maximize use of supportive treatments such blood transfusion, volume expansion, vasopressor use, etc. in a precision manner for GDT. The use of goal GDT has been demonstrated to be life saving for both surgical and medical populations with severe hemodynamic compromise, but is difficult to implement with current invasive and noninvasive tools because of their lack of precision or form factor and expense. This proposal will scale testing of two novel noninvasive measures that could allow for real-time use of GDT in the PFC/pDCR setting. These include:

1) Resonance Raman Spectroscopy (RRS) to measure tissue hemoglobin oxygen saturation (StO_2) of the buccal mucosa as a substitute for central or mixed venous hemoglobin oxygen saturation ($ScvO_2$) and potentially lactate
2) Dynamic Respiratory Impedance Volume Evaluation (DRIVE) of the limb as a substitute for ultrasound of the inferior/superior vena cava and central venous pressure (CVP).

RRS-StO2 uses a special wavelength of light to determine how much oxygen a tissue is receiving. DRIVE uses a small amount of electricity passed through tissue to measure blood volume moving in and out of the tissue during breathing.

2. KEYWORDS:

Tissue Oxygenation, Resonance Raman Spectroscopy, Bioimpedance, Intravascular Volume, Hemodynamics, Shock, Resuscitation, Goal Directed Therapy

3. ACCOMPLISHMENTS:

3.1. What were the major goals of the project?

- **Major Task 1:** Test and compare RRS-StO_2 with other measures and surrogates of tissue oxygenation including lactate and $ScvO_2$ in polytrauma and complex operative and post-operative surgical patients. Months 0-36
- **Major Task 2**: Test and compare DRIVE to other measures and surrogates of intravascular volume monitoring including ultrasound of the IVC and SVC, transthoracic echo, CVP, and SVV in polytrauma and complex operative and post-operative surgical patients. Months 0-36
- **Major Task 3:** Compare time series measurement RRS-StO_2 and DRIVE to patient outcomes including mortality and organ failure in order to support future clinical intervention trials. Months 6-36

3.2. What was accomplished under these goals?

Major Task 1: Test and compare RRS-StO_2 with other measures and surrogates of tissue oxygenation including lactate and $ScvO_2$ in polytrauma and complex operative and post-operative surgical patients. Months 0-36

Specific objectives:

Protocol [HRPO Assigned Number]: A-20596Title: Development and Testing of New Noninvasive Monitoring Tools for Prolonged Field Care Goal Directed Therapy
Target required for clinical significance: 275
Target approved for clinical significance: 1500

a) IRB approval January 22, 2013
b) HRPO approval November 15, 2017
c) Patient recruitment: 19 additional patients were recruited since last quarterly report

Report amendments submitted to the IRB and USAMRMC HRPO for review:

Amendment No.	Description	Status	Status Date
Ame00106451	**Removing and adding staff.** **Adding electronic and remote consent forms**	**Completed**	**11/14/2020**
Ame00107536	**Adding staff**	**Completed**	**12/9/2020**
Ame00107909	**Changes in ICF**	**Completed**	**1/6/2021**
Ame00109313	**Adding and removing staff**	**Completed**	**2/9/2021**
Ame00109880	**Updating the billing grid**	**Completed**	**3/8/2021**
Ame00110495	**Adding arm circumference**	**Completed**	**04/07/2021**
CR00085184	**Continuing review**	**Completed**	**10/18/2020**

One hundred and seventy-one patients were recruited from multiple intensive care units across the University of Michigan's hospital. The patients had a mean (Standard Deviation) age and weight of 60 (15) years and 97.3 (30) kg respectively. One hundred and seventeen (68%) of the patients were recruited from the cardiovascular ICU, nine (5%) from the Critical Care Medicine Unit, twenty-seven (16%) from Emergency Department and the Emergency Critical Care Center (EC3), and the rest are from the Cath lab, trauma and burn ICU, Cardiac ICU, and the surgical ICU. The RRS probe was covered in a sterile sleeve and placed on the buccal mucosa of the patient. Data were collected for 20 minutes. Both sides of the buccal mucosa were tested independently. Near the end of testing, 3cc of mixed venous blood was collected from the pulmonary artery port of the central line and the reading from the Raman spectrophotometer was recorded for comparison. Blood was tested for $ScvO_2$ and compared to tissue oxygen saturation (StO_2) as measured by RRS.

Significant results:

Preliminary Data analysis: Descriptive statistics are expressed as means and standard deviations. Linear regression was used to quantify the relationships between RRS-StO_2 and $ScvO_2$. Summary statistics using receiver operating characteristic (ROC) and area under the curve (AUC) values were used for pooled data to assess performance of RRS-StO_2 at different thresholds of $ScvO_2$. Table 1 lists Descriptive Statistics of RRS-StO_2, $ScvO_2$ and the difference between the two (RRS-StO_2 - $ScvO_2$).

	RRS-StO_2 (%)	**$ScvO_2$ (%)**	**Difference (RRS-cv) (%)**
Mean	63.1	63.8	-0.75
Std. Deviation	7.808	11.41	9.211
Std. Error of Mean	0.5852	0.8556	0.6904

Lower 95% CI	61.9	62.2	-2.1
Upper 95% CI	64.3	65.5	0.6
Minimum	38.8	28.1	-23.5
Maximum	82.8	87.2	32.2

There was a significant correlation between StO_2 and $ScvO_2$ (r=0.592, p < 0.0001) (Figure 1). A paired *t-test* revealed no significant difference between RRS-StO_2 and $ScvO_2$ with a mean(SD) of the difference between RRS-StO_2 and $ScvO_2$ of 0.75 (9.2)% (95%CI: 0.62, 2.2%, *p*=0.281). ROC analysis yielded a mean(SD) area under the curve for RRS-StO_2 of 0.82(0.029) (95% CI: 0.75 – 0.88. p<0.0001) at different thresholds of $ScvO_2$ (60%, 65%, and 70%) (Figure 2).

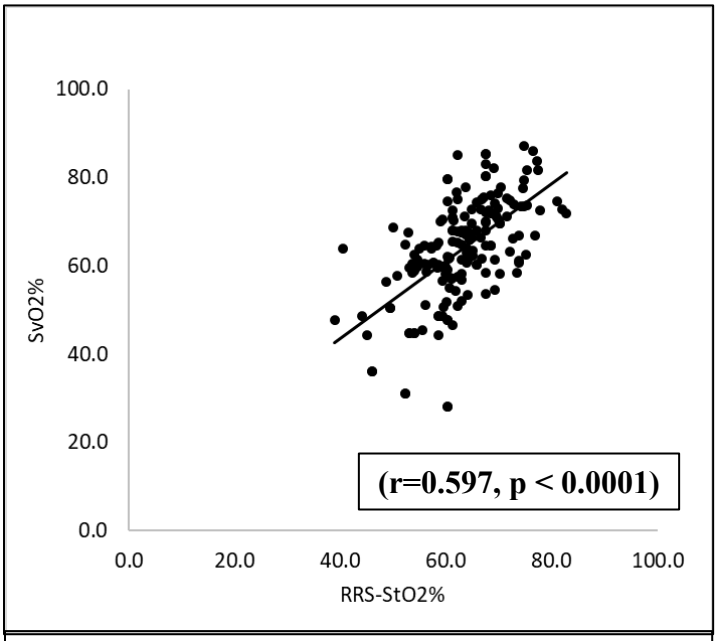

Figure 1: Linear regression model demonstrating the relationship between RRS-StO_2 and $ScvO_2$. RRS-StO2: Resonance Raman spectroscopy-tissue hemoglobin oxygen saturation. ScvO2: Central venous hemoglobin oxygen saturation

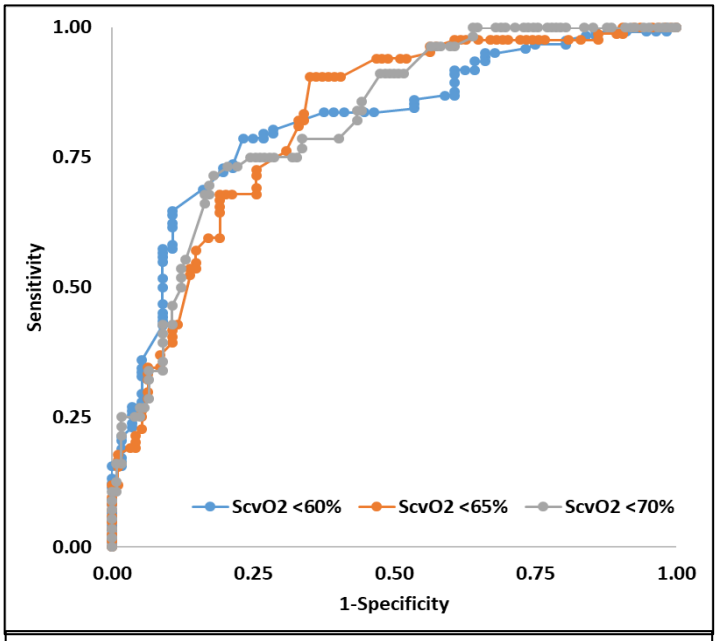

Figure 2: Receiver operator characteristics and area under the curve values for RRS-StO2 at different thresholds of ScvO2 (60%, 65%, and 70%). RRS-StO2:

Since StO_2 and $ScvO_2$ are not identical measures, we are experimenting with various means to compare the two since being fundamentally different, utilization of such techniques Clarke Error Grid was constructed to quantify the clinical accuracy of R-StO_2 when compared to the gold standard ($ScvO_2$). The plot places the data into different zones (A, B, C, D, and E) based on their utility. Zones A represent values that are considered accurate (difference is less than 7%) in this study. Zone B represent acceptable values that will not lead to change in management. Zone C could be viewed to represent false positive values that might lead to unnecessary corrections (normal $ScvO_2$ and low R-StO_2). Zone D may be viewed to represent false negatives as failure to detect low $ScvO_2$ (low $ScvO_2$ but normal R-StO_2) resulting in failure to address tissue hypoxia. And finally, zone E represent erroneous measurement. The Clarke Error Grid showed significant clinical accuracy of R-StO_2 with 87.5% of the data residing within the accurate

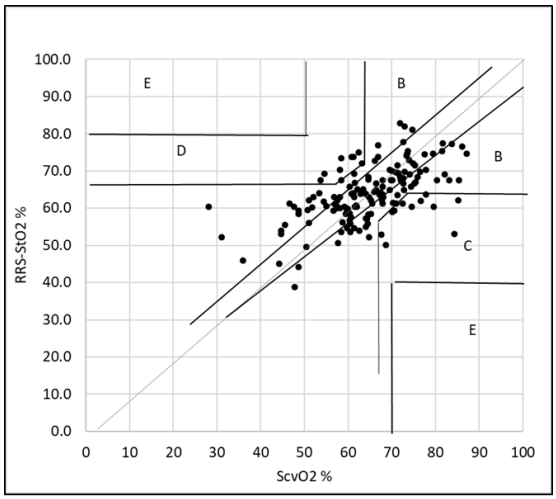

Figure 3: Modified Clarck's Error Grid

and acceptable grids (A and B), 7.2% in the false positive grid (C), and 5.3% in the false negative grid (D) (Figure 3).

Major Task 2: *Test and compare DRIVE to other measures and surrogates of intravascular volume monitoring including ultrasound of the IVC and SVC, transthoracic echo, CVP, and SVV in polytrauma and complex operative and post-operative surgical patients. Months 0-36*

Specific objectives:

a. IRB approval January 22, 2013
b. HRPO approval November 15, 2017
c. Patient recruitment: 18 patients were recruited since last quarterly report

As indicated in previous reports, we continue to examine respiratory induced changes in both impedance and in photoplethysmography signals as a means to assess central volume status. For the remainder of the project we are now also studying a more robust impedance methodology we previously developed to measure central venous pressure. We have previously developed an impedance based noninvasive method of central venous pressure (NICVP) monitoring. This NICVP method shares many important features with DRIVE. Its combination with DRIVE would allow a unique static and dynamic measure if intravascular volume. Central venous pressure (CVP) is static measure of central circulatory volume. While controversial, it has recently enjoyed a renaissance demonstrating value in assessing critically ill and injured patients and in reducing the incidence of acute renal failure. Figure 4 below demonstrates how this technology works along with data from a previously published study by Ward et al. (Shock 33(3): 269-273, 2010. PM19487978) demonstrating the ability of the technology to potentially replace invasively

1- Ward KR, Tiba MH, Draucker GT, Proffitt EK, Barbee RW, Gunnerson KJ, Reynolds PS, Spiess BD: A novel noninvasive impedance-based technique for central venous pressure measurement Shock 33(3): 269-273, 2010. PM19487978"
2- Irwin Gratz, Vinay Kudur, Francis Spitz, Smith Jean, Isabel Elaine Allen, Julia E. Seaman and Edward Deal. Comparison of Invasive vs. Noninvasive CVP Monitoring in Patients Undergoing Major Intra-Abdominal Surgery: A Prospective Comparative Pilot Study. J Anesth Clin Res 2018, 9:11. DOI:10.4172/2155-6148.1000866

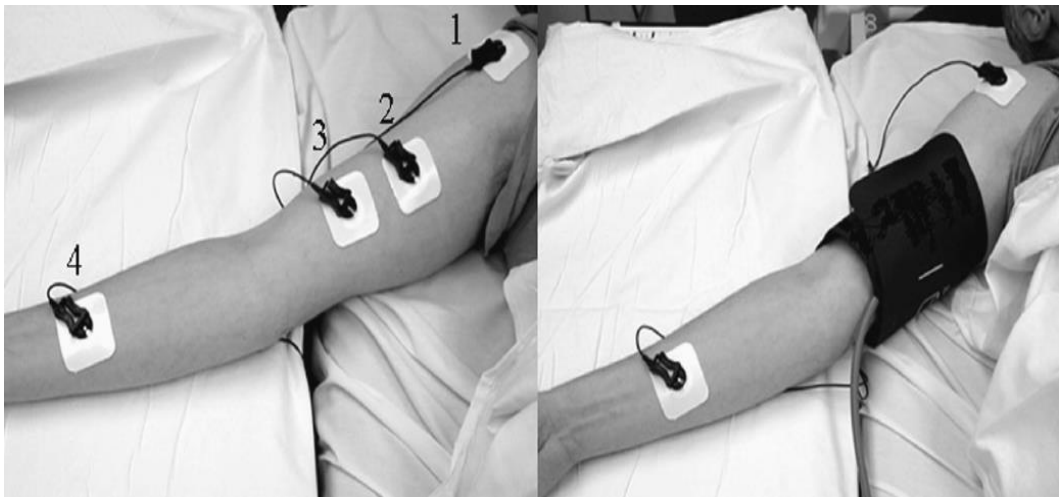

Figure 4: Orientation of electrodes used for tetra-polar impedance plethysmography. Electrodes 1 and 4 inject current toward electrodes 2 and 3, respectively. Ward et al 2010.

We now have the new prototype (Figure 5). The new prototype will allow the combined measure of both DRIVE and NICVP with no additional need for extra personnel or significant change in workflow or protocol. We anticipate the addition of NICVP will provide significant value to the volume assessment of critically ill and injured patients. As indicated in the last report the underlying theory involves a well-founded and studied method incorporating impedance plethysmography. Specifically, a small amount of current, 400 µA @ 28 kHz sine wave is applied to the patient's arm through standard ECG electrodes. A blood pressure cuff on the patient's arm is inflated to ~40 mm Hg, blocking venous return but below diastolic arterial pressure. After 45-60 sec, the pressure is rapidly deflated for a period of approximately 30 seconds and the impedance is measured by the processing unit while simultaneously measuring the pressure in the cuff. Changes in bioimpedance, resulting from the changes in volume and velocity of blood in the arm are directly related to the

pressure within the large veins of the upper arm. Pressures in these veins are essentially the same as pressures in the large central veins in which they empty into. Maximum blood volume changes in the upper arm detected by impedance are matched to the pressure in the blood pressure cuff during deflation.

The pressure in the blood pressure cuff at this time is pressure within the large vein in the upper arm and this pressure is substituted for CVP. The NICVP device measures impedance in ohms over time (Figure 6-1). The initial change in impedance seen in Figure 6-1 is due to the arm filling with blood when venous return is impeded by the cuff. The change in impedance over time is calculated by the processing unit and a waveform is generated (Figure 6-4). This waveform of the rate of change in impedance over time is an indirect measurement of blood flow under the blood pressure cuff. The cuff pressure, graphed in (Figure 6-2), that is observed at the minimum point in this delta impedance waveform has been found to correlate to the patient's CVP, as measured with a catheter (6-3). The cuff pressure reading is reported as the NICVP parameter value by the device.

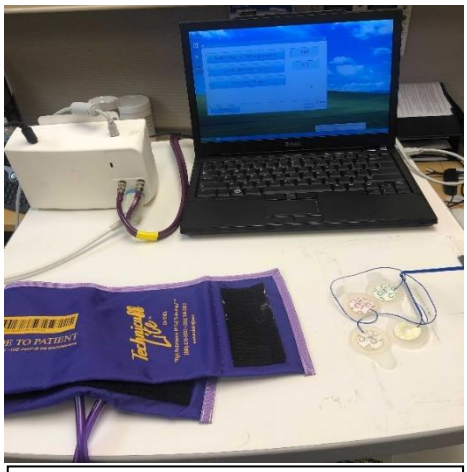

Figure 5: Prototype device to measure central venous pressure non-invasively using bioimpedance

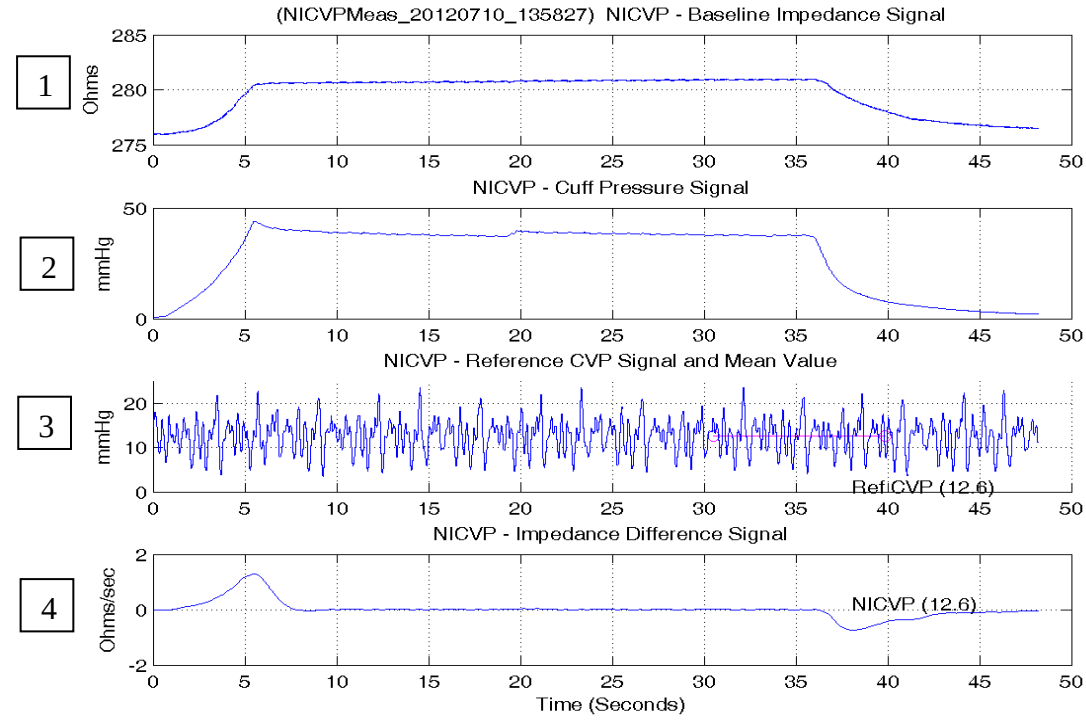

Figure 6: Early prototype device to measure central venous pressure non-invasively using bioimpedance. *Shock 33(3): 269-273, 2010. PM19487978*

Elven patients have been recruited from different ICUs across the University of Michigan's Hospital. The patients had a mean (Standard Deviation) age and weight of 63 (16.5) years and 85.9(19) kg respectively. Nine patients have been recruited from the Cardiac ICU, 9 patients have been recruited from the Cardiovascular Center ICU, 2 patients have been recruited from the Surgical ICU. Patients' NICVP was measured as described above while their CVP was recorded at the

same time of NICVP measurement. Each patient's NICVP was measured 3 to 4 times. Patients NICVP has been shown to be highly correlated with their CVP ($r = 0.836$, $p < 0.0001$) (Figure 7). A Bland-Altman analysis showed a bias (average of the differences between each NICVP and CVP reading) of 0.65 with a standard deviation of 2.76 (Figure 8). Such low bias provides a strong indication that the two reading might be exchangeable.

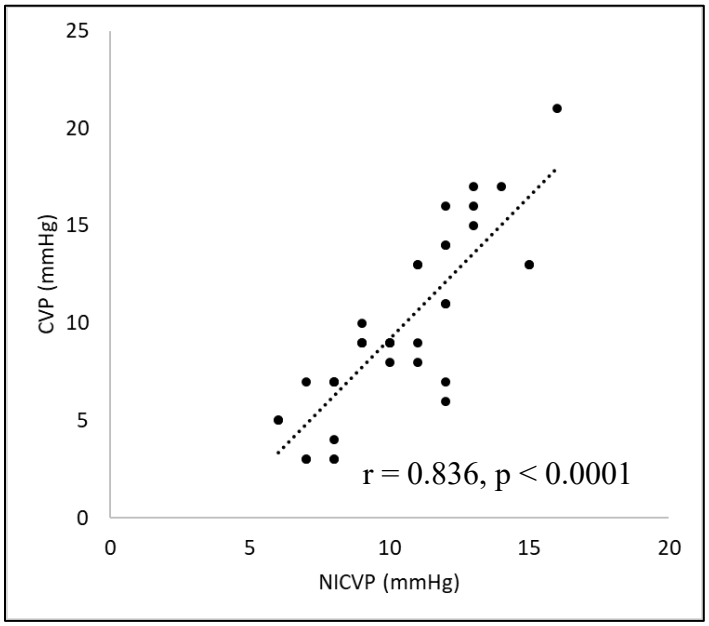

Figure 7: Correlation between NIVCP and CVP

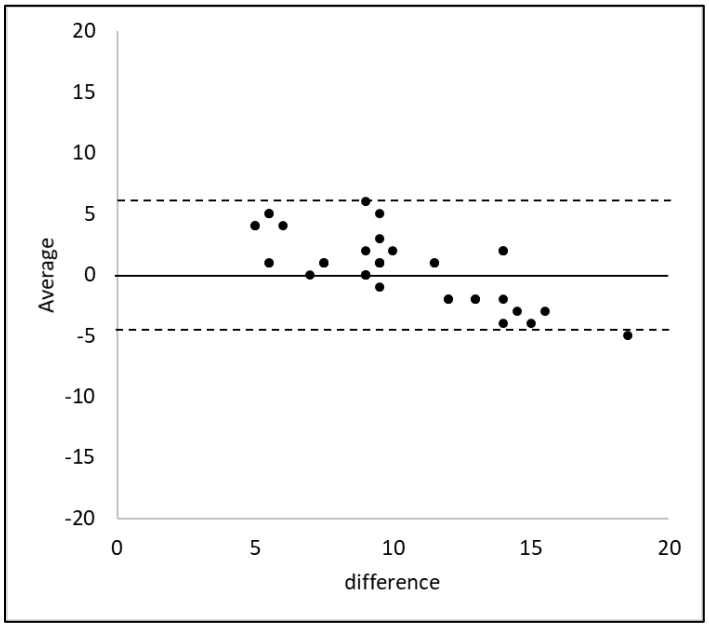

Figure 8: Bland-Altman plot. Average vs. difference

4. OTHER ACHIEVEMENTS

Development of a reduced size device prototype with a handheld tablet in collaboration with New Vital Signs (NVS). The unit is currently being tested alongside Biopac. This prototype has received positive feedback from patients for comfort and ease of application. This prototype will be used during patients testing in conjunction with Biopac system. We will work with New Vital Signs to discuss licensing and incorporation of the NICVP method into the DRIVE technology.

4.1. What opportunities for training and professional development has the project provided?

One undergraduate students participated in the RRS portion of this project as a part of university Undergraduate Research Opportunity Program (UROP) The student helped with data collection.

4.2. How were the results disseminated to communities of interest?

1. Peer reviewed publication: Tiba MH, Awad AB, Pennington A, Fung CM, Napolitano LM, Park PK, Machado-Aranda DA, Gunnerson KJ, Romfh P, Ward KR. Resonance Raman Spectroscopy Derived Tissue Hemoglobin Oxygen Saturation in Critically Ill and Injured Patients. Shock. 2020 Nov 17. doi: 10.1097/SHK.0000000000001696. Epub ahead of print. PMID: 33208679.

2. An abstract was submitted and accepted for presentation at the 2020 MHSRS. Due to COVID-19, the conference has been cancelled, however the abstract will still be published. Full Citation: Abdelrahman Awad, MD; Varisha Essani; Claire Roberge; Kyle Gunnerson, MD; Mohamad Hakam Tiba, MD, MS; Kevin Ward, MD, Monitoring of Tissue Microvasculature Oxygenation Using Resonance Raman Spectroscopy. Military Health System Research Symposium (MHSRS), June 2020. Abstract # MHSRS-20-01069.

3. An abstract was submitted for presentation consideration at the 2021 MHSRS.
   Full Citation: Mohamad H. Tiba, MD, MS, Abdelrahman B. Awad, MD, Christopher M. Fung, MD, Lena M. Napolitano, MD, Pauline K. Park, MD, David A. Machado-Aranda, MD, Kyle J. Gunnerson, MD, Padraic Romfh, BS, MBA, Kevin R. Ward, MD. Resonance Raman Spectroscopy-Derived Tissue Hemoglobin Oxygen Saturation for the Management of the Critically Ill and Injured Patients. Military Health System Research Symposium (MHSRS), Abstract # MHSRS-21-02936

   Manuscript and abstract will be provided with the appendices.

4.3. **What do you plan to do during the next reporting period to accomplish the goals?**

The COVID-19 pandemic has caused considerable disruption and delay in research activities particular during the Summer and Fall of 2020. However, the University of Michagan and the Office of Research have implemented a plan for research reactivation. We are now able to recruit patients however with few restrictions. For the next quarter, we will aim to

- Continue in the recruiting and testing human subjects.
- Continued data analysis.
- Data presentation (national and local).
- Technology and signal processing refinement.
- Continue testing of impedance based NICVP.
- Monitor Raman derived StO2 for longer periods of time in subjects and collect additional oximetric derived ScvO2/SvO2 values.
- Capture additional critically ill and injured subjects who demonstrate evidence of instability (injury patterns, low hemoglobin, low blood pressure, high lactate levels) to capture Raman derived StO2 values who may not be instrumented for ScvO2 or SvO2 monitoring.
- Continue to closely with Pendar Medical to map next regulatory pathway steps for clinical use. We are currently developing a strategy to engage the FDA in a pre-submission meeting.
- Continue to utilize new data capture platform to compare Raman and NICVP values to other patient physiologic parameters.

5. IMPACT:

5.1. **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report at this time as we are still in testing phase. However, we are expecting a high level of impact by the end of the project on the understanding of central venous pressure and tissue oxygenation and the ability to monitor and track these events noninvasively using bioimpedance and resonance Raman spectroscopy. The principle disciplines expected to be impacted by successful completion include the clinical disciplines of emergency medicine, surgery, anesthesiology, critical care, nursing, and paramedical professionals.

5.2. What was the impact on other disciplines?

Nothing to report at this time, but we feel that in the future that the biomedical engineering and data science disciplines will also be impacted

5.3. What was the impact on technology transfer?

The RRS technology has been licensed to Pendar Technologies. RRS data and the performance of the device is being shared with Pendar to allow for continuous improvement and to develop regulatory approval and commercialization strategies. We anticipate to start working with Pendar Medical towards scheduling pre-submission meetings with the FDA to develop a rapid regulatory approval pathway that will place the technology on a path towards commercialization.

The NICVP technology has been licensed to NuMedx. NICVP data and performance of the prototype device is being utilized to support continuous improvement of the technology and approaches to develop regulatory approval and commercialization strategies.

5.4. What was the impact on society beyond science and technology?

While there has been no direct societal impact of the project to date, the *long-term* impact of this research is expected to result in the development and deployment of technologies that noninvasively measure tissue oxygenation and volume status at earlier points of care that may:

- Allow for rapid point of care diagnostic indicators of compensated shock states allowing for significantly earlier intervention in more far forward echelons of care.
- Allow for improved therapeutic allocations by helping to drive therapy to objective measurable endpoints thus optimizing use of important resources such as resuscitation fluids including blood.
- Allow for a greater uninterrupted continuum of care as casualties move from lower to higher levels of care including en-route care.
- Allow for improved outcomes by preventing the early under or over-resuscitation of casualties.
- Reducing iatrogenic and nosocomial complications associated with invasive monitoring.
- Allow for improved resource allocation by providing indications for invasive monitoring.
- Allow earlier termination of the use of invasive monitoring (when they are indicated) by transitioning invasive monitoring for noninvasive monitoring.
- Allow for additional diagnostic and therapeutic end-points for casualties in intermediate care settings.
- Allow for the eventual development of simpler closed-loop and decision assist algorithms and devices for early and late echelon of care settings including en-route care.

6. CHANGES/PROBLEMS:

6.1. Changes in approach and reasons for change

We are expanding our impedance based knowledge and technology to allow incorporation of a very similar technology we have previously developed to allow noninvasive measurement of central venous pressure (NICVP) to complement the dynamic impedance signals measured by DRIVE. This will provide both an important static measure of volume status monitoring which is now enjoying a renaissance.

6.2. Actual or anticipated problems or delays and actions or plans to resolve them

The University of Michigan clinical research office has approved our request to reactivate the study as tier 2 while applying some restrictions that aim to mitigate the spread of COVID-19 disease. Necessary amendments with IRB have been reviewed and approved by the IRB. To help mitigating the spread of COVID-19 among susceptible population, research staff were not allowed to approach the following populations for recruitment purposes:

- Patients 65 years or older (restriction left on September 30th, 2020).
- Immunocompromised patients.

These restrictions resulted in a decreased pool of eligible subjects, hence a decrease in recruited subjects for the study. We will continue to recruit for eligible patients at full capacity while following the previously mentioned policies and restrictions.

6.3. Changes that had a significant impact on expenditures

The COVID-19 pandemic has and will moderately effect expenditures.

6.4. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

6.5. Significant changes in use or care of human subjects: None to report

6.6.Significant changes in use or care of vertebrate animals: None to report

6.7. Significant changes in use of biohazards and/or select agents: None to report

7. PRODUCTS:

7.1. Publications, conference papers, and presentations

7.1.1. **Journal publications.** Nothing to report
Tiba MH, Awad AB, Pennington A, Fung CM, Napolitano LM, Park PK, Machado-Aranda DA, Gunnerson KJ, Romfh P, Ward KR. Resonance Raman Spectroscopy Derived Tissue Hemoglobin Oxygen Saturation in Critically Ill and Injured Patients. Shock. 2020 Nov 17. doi: 10.1097/SHK.0000000000001696. Epub ahead of print. PMID: 33208679.

7.1.2. **Books or other non-periodical, one-time publications.** Nothing to report

7.1.3. **Other publications, conference papers, and presentations.**

An abstract was submitted and accepted for presentation at the 2020 MHSRS. Due to COVID-19, the conference has been cancelled, however the abstract will still be published. Full Citation: Abdelrahman Awad, MD; Varisha Essani; Claire Roberge; Kyle Gunnerson, MD; Mohamad Hakam Tiba, MD, MS; Kevin Ward, MD, Monitoring of Tissue Microvasculature Oxygenation Using Resonance Raman Spectroscopy. Military Health System Research Symposium (MHSRS), June 2020. Abstract # MHSRS-20-01069.

An abstract was submitted for presentation consideration at the 2021 MHSRS.
Full Citation: Mohamad H. Tiba, MD, MS, Abdelrahman B. Awad, MD, Christopher M. Fung, MD, Lena M. Napolitano, MD, Pauline K. Park, MD, David A. Machado-Aranda, MD, Kyle J. Gunnerson, MD, Padraic Romfh, BS, MBA, Kevin R. Ward, MD. Resonance Raman Spectroscopy-Derived Tissue Hemoglobin Oxygen Saturation for the Management of the Critically Ill and Injured Patients. Military Health System Research Symposium (MHSRS), Abstract # MHSRS-21-02936

7.2. **Website(s) or other Internet site(s)**
https://mcircc.umich.edu/microvascular-oximetry

7.3. **Technologies or techniques**
The new DRIVE RMS and noise/movement detection analysis is new and will be reviewed in the near future for their potential/need for intellectual property protection. Discussion regarding these analytic techniques will take place with New Vital Signs in order to consider their incorporation into the DRIVE prototypes.

We are actively exploring the addition of the impedance based NICVP technology for noninvasive evaluation of volume status.

The new RRS clip will continue to be utilized and evaluated for ease of use. These were designed and 3-D printed by our team. Their final utilization and incorporation into the RRS system will be discussed with Pendar Technologies.

7.4. **Inventions, patent applications, and/or licenses.**

- United States Patent 7,113,814: Ward KR, R. RW, Terner J, Ivatury RR, Hawkridge F. Tissue Interrogation Spectroscopy
- United States Patent 14/445,926: Ward KR, Tiba MH, Blum M. Evaluating cardiovascular health using intravascular volume.

7.5. **Other Products**
Nothing to report

7.6. Research material (e.g., Germplasm; cell lines, DNA probes, animal models);
Nothing to report

8. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

8.1. What individuals have worked on the project?

Name:	***Kevin Ward, MD***
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	*Oversight of data collection and analysis*
Funding Support:	

Name:	***Mohamad Hakam Tiba, MD, MS***
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2*
Contribution to Project:	*Oversight of data collection and analysis*
Funding Support:	

Name:	***Kyle Gunnerson, MD***
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2*
Contribution to Project:	*medical consultation*
Funding Support:	

Name:	***Lena Napolitano, MD***
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2*

Contribution to Project:	*medical consultation*

Name:	***Pauline Park, MD***
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*medical consultation*

Name:	***Nik Theyyunni, MD***
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Perform ultrasounds*
Funding Support:	

Name:	***Christopher Fung, MD***
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Perform ultrasounds*
Funding Support:	

Name:	***Michael Cover, MD***
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2*
Contribution to Project:	Perform ultrasounds
Funding Support:	

Name:	***Joseph Blackmer***
Project Role:	*Research Staff*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*4*
Contribution to Project:	Data analysis
Funding Support:	

Name:	***Christopher Gillies, PhD***
Project Role:	*Data Scientist*
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	*3*
Contribution to Project:	*data analysis*
Funding Support:	

Name:	***Guan Wang, MS, ME***
Project Role:	*Application programmer* / Analyst
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6
Contribution to Project:	Software engineering and system administration
Funding Support:	

Name:	***Jonathan Motyka***
Project Role:	*Data scientist*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Data analysis
Funding Support:	

Name:	***Brandon Cummings, BS***
Project Role:	*Research Staff*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	9
Contribution to Project:	Data analysis
Funding Support:	

Name:	***Nicholas Greer, BS***
Project Role:	*Research Staff*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*data analysis*
Funding Support:	

Name:	***Denise Poirier***
Project Role:	*Administrative Staff*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	*Scheduling of meetings*
Funding Support:	

Name:	***Abdelrahman Awad***
Project Role:	*Clinical Coordinator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*7*
Contribution to Project:	*Screening and consenting patients, data collection*
Funding Support:	

Name:	***Nicholas Sautter, BS***
Project Role:	*Research Staff*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Screening and consenting patients, data collection*
Funding Support:	

Name:	***Erin Bisco, BS***
Project Role:	*Research Staff*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2*
Contribution to Project:	*Screening and consenting patients, data collection*
Funding Support:	

8.2. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
Nothing to report

8.3. **What other organizations were involved as partners?**
Pendar Technologies and New Vital Signs as manufacturers and commercial partners in developing the RRS and DRIVE technologies respectively.

8.4. **Other.**
Nothing to report

9. SPECIAL REPORTING REQUIREMENTS

9.1. COLLABORATIVE AWARDS:
None

9.2. **QUAD CHARTS:** Included with this report before the appendices

10. APPENDICES:

a. Publication
b. 2020 MHSRS abstract
c. 2021 MHSRS abstract

Shock, Publish Ahead of Print

DOI : 10.1097/SHK.0000000000001696

Resonance Raman Spectroscopy Derived Tissue Hemoglobin Oxygen Saturation in Critically Ill and Injured Patients

Mohamad H. Tiba,[1,4] Abdelrahman B. Awad,[1,4] Amanda Pennington, [1,4] Christopher M. Fung,[1,4] Lena M. Napolitano,[2,4] Pauline K. Park,[2,4] David A. Machado-Aranda,[2,4] Kyle J. Gunnerson,[1,4], Padraic Romfh,[5] Kevin R. Ward[1,3,4]

1. Department of Emergency Medicine. University of Michigan, Ann Arbor, Michigan.

2. Department of Surgery. University of Michigan, Ann Arbor, Michigan.

3. Department of Biomedical Engineering. University of Michigan, Ann Arbor, Michigan.

4. Michigan Center for Integrative Research in Critical Care. University of Michigan, Ann Arbor, Michigan.

5. Pendar Technologies, LLC. Cambridge, Massachusetts

Corresponding Author

Kevin R. Ward, MD

University of Michigan Department of Emergency Medicine

Michigan Center for Integrative Research in Critical Care

2800 N. Plymouth Road

North Campus Research Complex Building 26-323N

Ann Arbor, MI, 48109

keward@umich.edu

Phone: (734) 764-6702

Fax: (734) 764-4940

Address for reprints

Same as corresponding author's address

Conflicts of Interest and Source of Funding

Authors KRW and PR have intellectual property on Raman spectroscopy. The technology is licensed to Pendar Technologies, LLC. where author PR is a Co-Founder and Director of Clinical Business Development. The rest of the authors declare no conflict of interest.

This work has been supported by a grant award from the Department of Defense Joint Program Committee 6 (JPC-6) Combat Casualty Care (CCC) Research (W81XWH-18-1-0078). The study sponsor did not have any role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. KW is a LTC in the U.S. Army Reserve MC. His views do not necessarily reflect the view of the U.S. Army or Department of Defense.

Running Head Tissue Hemoglobin Oxygen Saturation Monitoring

Abstract:

Background: In this study, we examined the ability of resonance Raman spectroscopy to measure tissue hemoglobin oxygenation ($R\text{-}StO_2$) noninvasively in critically ill patients and compared its performance with conventional central venous hemoglobin oxygen saturation ($ScvO_2$). **Methods:** Critically ill patients (n=138) with an indwelling central venous or pulmonary artery catheter in place were consented and recruited. $R\text{-}StO_2$ measurements were obtained by placing a sensor inside the mouth on the buccal mucosa. $R\text{-}StO_2$ was measured continuously for 5 minutes. Blood samples were drawn from the distal port of the indwelling central venous catheter or proximal port of the pulmonary artery catheter at the end of the test period to measure $ScvO_2$ using standard co-oximetry analyzer. A regression algorithm was used to calculate the $R\text{-}StO_2$ based on the observed spectra. **Results**: Mean(SD) of pooled $R\text{-}StO_2$ and $ScvO_2$ were 64(7.6) % and 65(9.2) % respectively. A paired *t-test* showed no significant difference between $R\text{-}StO_2$ and $ScvO_2$ with a mean(SD) difference of -1(7.5) % (95% CI: -2.2, 0.3 %) with a Clarke Error Grid demonstrating 84.8% of the data residing within the accurate and acceptable grids. Area under the receiver operator curve for $R\text{-}StO_2$'s was 0.8(0.029) (95% CI: 0.7, 0.9 $p<0.0001$) at different thresholds of $ScvO_2$ (• 60%, • 65%, and • 70%). Clinical adjudication by five clinicians to assess the utility of $R\text{-}StO_2$ and $ScvO_2$ yielded Fleiss' Kappa agreement of 0.45 ($p<0.00001$). **Conclusions:** $R\text{-}StO_2$ has the potential to predict $ScvO_2$ with high precision and might serve as a faster, safer, and non-invasive surrogate to these measures.

Keywords

Resonance Raman spectroscopy; hemoglobin; Tissue hemoglobin oxygen saturation; noninvasive monitoring; Central venous oxygen saturation

Introduction

Ensuring adequate oxygen delivery and preventing tissue hypoxia in the care of the critically ill and injured continues to be of paramount importance (1). However, identifying imbalances in the delivery and consumption of oxygen through measurement and monitoring of tissue oxygenation continues to be a challenge with no clearly established and adopted technologies allowing for continuous or point of care measurement. While the use of lactate monitoring is of significant value in identifying oxygen delivery dependent states of oxygen consumption, it changes relatively late and cannot be used as a continuous measure (1-3).

While central venous oxygen saturation ($ScvO_2$) can play a significant role in the management of critically ill and injured patients as a means to assess the adequacy of whole body oxygen delivery, $ScvO_2$ measurements are invasive and thus difficult to use as a screening or point-of-care tool in the early care of patients (4-6). In an attempt to overcome these issues, optical based noninvasive technologies such as near infrared spectroscopy (NIRS) have been developed as a means to measure tissue hemoglobin oxygen saturation (StO_2) as an indicator of tissue oxygenation as well as a surrogate to $ScvO_2$ (7-10). The basis for such approaches is that 70-80% of blood volume in tissue is venous and thus aggregate measures of blood hemoglobin oxygenation in a target tissue predominately represents the post-extraction compartment, and thus may mirror the balance of oxygen delivery and consumption similar to $ScvO_2$ (10, 11). However, techniques like NIRS are not without challenges related to the presence of interfering chromophores such as myoglobin from muscle tissue which have a vastly different P50 limiting its clinical utility as a surrogate of more established measures like $ScvO_2$ (10, 12, 13).

To overcome some of these barriers we have developed a StO_2-measurement modality that utilizes the principles of resonance Raman spectroscopy (RRS) (14-16). RRS uses the well-established phenomenon of Raman inelastic scattering of light (17). Inelastic scattering is the result of photons interacting with the molecule and exciting it to a new vibrational state which cause the photon to lose or gain energy. The resulting shift in the scattered photon's wavelength give a signature spectrum for the excited molecule (17-19). The Raman spectroscopic basis of our determination of StO_2 (R-StO_2) lies in the resonance vibrational enhancement of hemoglobin and deoxy-hemoglobin in the near ultraviolet region (15-20). This allows for simultaneous identification of the proportion of oxy and deoxy-hemoglobin in a concentration-dependent manner using a single wavelength of light which creates a spectral fingerprint of both species of hemoglobin (Fig. 1) (17, 19, 20). In this study, we explored R-StO_2 measurements obtained from the buccal mucosa in critically ill adult ICU patients and compared them to spot measures of $ScvO_2$ values. We hypothesized that R-StO_2 could potentially be a noninvasive surrogate of $ScvO_2$ as an indicator of tissue oxygenation.

Methods and Materials:

This prospective, non-interventional observational study was conducted under approval of the University of Michigan Institutional Review Board ((HUM00067675). Patients or their legally authorized representatives were consented for the study.

Study Population: One hundred and thirty-eight patients were recruited from multiple intensive care units across Michigan Medicine (formerly the University of Michigan Health System). The hospital serves as a major quaternary care facility for the state of Michigan for critically ill and injured patients. Patients had a mean (SD) age of 62(13) years old and weight of 90(26) Kg. There were 93(68%) males and 45(32%) females with racial makeup of White (88%), Black (11%), and Asian (1%). Units included surgical (cardiovascular, surgical, trauma-burn (86%), medical (11%) and emergency department (5%). Inclusion criteria included adults 18 years and older critically ill ICU patients while patients under 18 years old, pregnant women and prisoners were excluded. Seventy-six (55%) of the patients had central venous catheter (CVC) in place at the time of testing, while, sixty-two (45%) patients had pulmonary artery catheter (PAC). Patients had a mean (Standard Deviation) age and weight of 62(13) years and 90.3(26) kg respectively.

Tissue oxygen saturation measurements and data collection: R-StO_2 measurements were performed by placing a small sensor fitted with a clip inside the mouth on the buccal mucosa. The sensor is connected to an experimental microvascular oximeter (Pendar Technologies, LLC, Cambridge, MA). The microvascular oximeter uses a 405nm, 4mW laser to illuminates an area of tissue that is approximately $12mm^2$. The laser light excites both oxyhemoglobin and deoxy-hemoglobin in the interrogated tissue's microvasculature into distinct vibrational states causing differential wavelength shift of the scattered light (15). The spectrum of the scattered light is then used by a regression algorithm to calculate R-StO_2 as the relative ratio of concentration of oxygenated hemoglobin to that of total hemoglobin based on a library of known hemoglobin spectra. The oximeter calculates StO_2 every 1 second based on a running average of spectra from the previous 30-180 seconds. The buccal mucosa was the chosen tissue site of interrogation since light at a wavelength of 405nm penetrates only 2-3 mm (15). At this depth enough microvasculature and thus blood is encountered to derive an RRS signal for calculation of StO_2. In addition, the mucosa is largely void of other potentially contaminating chromophores such a skin pigment and myoglobin. Lastly the oral mucosa is known to be sensitive to changes in tissue perfusion (15, 21-23) and is relatively insensitive to environmental temperature, unlike skin. R-StO_2 was collected and measured continuously over 15 to 20 minutes. An average R-StO_2 over 5-minute at the time of blood sample acquisition (below) was used to compare R-StO_2 to the value of $ScvO_2$.

Central venous blood gas samples: At the conclusion of each testing session, a blood sample was collected from the distal port of the central venous catheter or the proximal port of the pulmonary artery catheter using standard clinical protocols and collected in blood gas syringes for measurement of $ScvO_2$. Blood hemoglobin oxygen saturation was directly measured in the Michigan Medicine's critical care clinical laboratories using a multi-wavelength co-oximeter (GEM Premier 5000: Instrumentation laboratory, Bedford, MA).

Statistical Analysis: Descriptive statistics are expressed as means and standard deviations. Linear regression was used to quantify the relationships between R-StO_2 and $ScvO_2$. A modified Clarke Error Grid was constructed to quantify the clinical accuracy of R-StO_2 when compared to the gold standard ($ScvO_2$) (24). Summary statistics using receiver operator characteristic (ROC) and area under the curve (AUC) values were used for pooled data to

assess performance of R-StO_2 at different thresholds of $ScvO_2$. Clinical utility of R-StO_2 and $ScvO_2$ were conducted by asking 5 blinded medical and surgical intensivists to indicate if they would consider changing management of a theoretical patient to increase oxygen delivery based on R-StO_2 and $ScvO_2$ values provided to them. R-StO_2 and $ScvO_2$ values were randomly presented (blinded to source). Percentage of agreement or disagreement between paired R-StO_2 and $ScvO_2$ for management decisions were calculated for each rater individually. In addition, Fleiss' Kappa (25) was calculated to test overall agreement between the five raters. Data analysis was performed on GraphPad Prizm8 (GraphPad Software, Inc., La Jolla, CA). Statistical significance was set at • < 0.05.

Results

Table 1 lists descriptive statistics of R-StO_2, $ScvO_2$ and the difference between the two (R-StO_2 – $ScvO_2$). Mean(SD) of pooled R-StO_2 and $ScvO_2$ were 64(7.6) and 65(9.2) % respectively. A linear regression of the type ($ScvO_2$ = • $_0$ + • $_1$*S-StO_2 + •) showed a significant correlation between StO_2 and $ScvO_2$ (r=0.611, p < 0.0001) (Fig. 2). A paired *t-test* revealed no significant difference between R-StO_2 and $ScvO_2$ with a mean(SD) of the difference between R-StO_2 and $ScvO_2$ of -1(7.5) % (95% CI: -2.2, 0.3 %, *p*=0.11). The Clarke Error Grid showed significant clinical accuracy of R-StO_2 with 84.8% of the data residing within the accurate and acceptable grids (A and B), 8% in the false positive grid (C), and 7.2% in the false negative grid (D) (Fig. 3).

ROC analysis yielded a mean(SD) area under the curve for R-StO_2 of 0.8(0.029) (95% CI: 0.7, 0.9 p<0.0001) at different thresholds of $ScvO_2$ (• 60%, • 65%, and • 70%) (Fig. 4). These $ScvO_2$ thresholds were examined as general examples of "actionability" in the setting of critical illness and injury assuming actions would be taken or not taken above or below these thresholds to increase oxygen delivery.

The blinded critical care physicians clinically adjudicated the values of R-StO_2 and $ScvO_2$ regarding management of patients based on saturation values. For each value of R-StO_2 or $ScvO_2$, the raters answered the question of "would you change your management plan based on such value" by yes or no. Overall agreement between all 5 raters was highly significant (Fleiss' Kappa 0.45, p<0.00001). In addition, agreement between R-StO_2 and $ScvO_2$ utility to management decision was performed for each rater separately. Post-adjudication pairing of each of the raters' assessments yielded a mean(SD) a (yes, no) agreement of 0.73(0.045) for all raters with a range of 0.69 to 0.81.

Discussion

Management strategies for critically ill and injured patients continue to evolve. Prevention of tissue hypoxia continues to be a fundamental principle in the initial resuscitation and ongoing care of patients to limit further accumulation of oxygen debt in sepsis, trauma, heart failure, complex surgeries and others (1, 26-30). However, assessment of the adequacy of tissue oxygenation in critically ill patients remains a challenge, especially in the early phases of emergency and critical care. The value of $ScvO_2$ monitoring is likely highest when used early and may find greater value when coupled with lactate measures (3, 31-35).

Implementation of $ScvO_2$ monitoring, however, can be challenging especially in early echelons of care, in part, due to the invasive nature of the measure. Even when used, in many institutions (including ours) the use of catheters capable of continuous oximetry measurement is inconsistent and clinical management varies with experience and levels of training, and therefore, at best, only intermittent $ScvO_2$ measurements are available which may not provide adequate information to carefully titrate fluid/blood infusions and inotropic/vasopressor support. In addition, invasive $ScvO_2$ monitors require accurate placement of the catheter, calibration and bedside clinical validation, all of which can result in delays of intervention. In contrast, noninvasive methodologies, which could be easily applied and allow for point-of-care or continuous monitoring of tissue oxygen saturation as a surrogate to $ScvO_2$ would potentially be of significant value in the management of the critically ill.

In this study, R-StO_2 was measured from the buccal mucosa and predicted $ScvO_2$ with moderately high precision of statistical and clinical significance. Our data shows that R-StO_2 and $ScvO_2$ are highly correlated with no significant difference when compared using a paired *t-test*. Furthermore, the ROC analysis using $ScvO_2$ as a gold standard revealed a high predictive performance of R-StO_2 at different levels of $ScvO_2$ with high area under the curve enforcing its potential as a clinical metric to guide management. Although, as shown in figure 2, the correlation coefficient might appear to be moderate, it gives a good indication regarding the positive relationship between the two measurements and when combined with the more rigorous statistics such as a t-test (interchangeability and equality of means), Clark's error grid (Strength and accuracy of our measurement) and the Receiver Operator Characteristic curve (Predictive performance of our measurement), it gives an additional indication of the robustness of our measurement of tissue oxygenation.

To assess the clinical accuracy of the R-StO_2 measurement, we constructed a modified Clarke Error Grid plot (24). The plot places the data into different zones (A, B, C, D, and E) based on their utility. Zones A represent values that are considered accurate (difference is less than 7%) in this study. Zone B represent acceptable values that will not lead to change in management. Zone C could be viewed to represent false positive values that might lead to unnecessary corrections (normal $ScvO_2$ and low R-StO_2). Zone D may be viewed to represent false negatives as failure to detect low $ScvO_2$ (low $ScvO_2$ but normal R-StO_2) resulting in failure to address tissue hypoxia. And finally, zone E represent erroneous measurement. Of note is that 84.8% of out R-StO_2 data resides in zones A and B showing the accuracy of clinical utility of the RRS measurement. In addition, the low false positive measurements in zone C (8% of readings) and the low false negative measurements in zone D (7.2% of readings) indicate a high specificity and sensitivity of the measurement. It is interesting to consider zone C where R-StO_2 values are lower than $ScvO_2$ values by 13-27%. Such differences could indicate that R-StO_2 is identifying tissue hypoxia earlier than $ScvO_2$. Studies using video microscopy of the oral microcirculation have demonstrated changes indicating tissue hypoperfusion prior to changes in traditional oxygen transport metrics and despite (21, 22, 36). Such change is closely dependent on the type of circulatory shock (sepsis, cardiogenic, hemorrhagic) and is related to changes in the buccal mucosa's

microcirculatory blood flow. However, such changes are usually an early indication and reflective of global hypoperfusion (37, 38).

To further assess and understand the utility of the R-StO_2 measure to clinically differentiate between physiologic states requiring intervention, we solicited the post-hoc clinical judgement of critical care and subject matter experts to adjudicate the influence of both R-StO_2 and $ScvO_2$ over the clinicians' management decision. The five raters individually rated the measures based on their potential to indicate the need for therapies that would increase oxygen delivery. All five raters had high agreement between R-StO_2 and $ScvO_2$.

Examining the utility of a tissue oxygenation in this manner when comparing to more established measures may be helpful in understanding both the limits of the measure and how it could be used. For example, an R-StO_2 level of 70% and a $ScvO_2$ level of 85% may be significantly different from a statistical standpoint but neither of these levels are likely to invoke a change in therapy to increase oxygen delivery. Similarly, an R-StO_2 value of 40% and a $ScvO_2$ level of 55% while significantly different would likely result in similar changes in management to increase oxygen delivery.

This study is important as it indicates significant correlation between R-StO_2 and $ScvO_2$ in adult ICU patients. Thus, it may be capable of providing early detection of tissue hypoperfusion providing intensivists and emergency physicians with an opportunity to improve perfusion and potentially improve patient outcomes. The results also align with our previous work in small and large animals as well in-vitro testing demonstrating the validity of R-StO_2 over a wide range of clinically relevant hemoglobin oxygen saturation levels (15, 16, 20). Interestingly, the findings of this study are in contrast to the findings of a pilot study in 16 neonates which reported R-StO_2 was safe and feasible, but reported no correlation between buccal or plantar R-StO_2 with umbilical vein hemoglobin oxygen saturation as a surrogate of $ScvO_2$. However, as indicated in that study, the timing of sample pairing was sometimes different by up to 4 hours and the microcirculation of neonates especially those that are premature is complex (39).

This study has several limitations. First, while the study is a prospective comparison of R-StO_2 and $ScvO_2$, patients were only tested at one point in time during their care without repeated measures of both $ScvO_2$ and R-StO_2 to assess trends, responses to various treatments, or outcomes. Despite this, the investigation represents a necessary first step in the evaluation of RRS utility to measure tissue oxygenation and begin to place it in context to a better-known body oxygenation measure ($ScvO_2$). Further studies will be conducted to assess R-StO_2 performance over a longer period of time with more frequent comparisons to $ScvO_2$ as well as other noninvasive measures such as NIRS to assess its ability to detect changes in response to therapies and to drive patient management. Second, comparison of R-StO_2 and $ScvO_2$ may be over simplified, given that R-StO_2 is a peripheral mixed measure (tissue blood contains arterial, capillary, and venous components) from a single tissue bed and $ScvO_2$ is an aggregate central measure of pure venous blood reflecting contributions from the entire body. The source and composition of the sample is a reason why a traditional Bland-Altman analysis is not appropriate in this case (40). As such we have used the Clarke-Error Grid as more appropriate measure of the R-StO_2 clinical utility (24). Lastly, we restricted sampling

and comparison to $ScvO_2$ and not mixed venous hemoglobin oxygen saturation. While the values from these two sites are similar, we chose to limit our measurement and analysis to $ScvO_2$ which is likely more available in most institutions (5, 33, 41). In regard to this, the tip position of central venous catheter or the proximal port of a pulmonary artery catheter could impact $ScvO_2$ values (superior vena cava, right atrium, inferior vena cava) and thus its comparison to R-StO_2 (42). Too high and the sample may not be adequately mixed with blood from the inferior vena cava. In other cases, being too close to the coronary sinus or in the inferior vena cava can result in lower values. Comparison of R-StO_2 to mixed venous oxygen saturation from a pulmonary artery catheter may have yielded differing results. However, we plan in future studies to collect this data from diverse populations of patients which will allow us to better understand the value of R-StO_2 in this setting and its potential as a surrogate indicator to prevent under- or over-resuscitation of patients especially in the early phases of care. Future observational studies combining time series R-StO_2 measures in conjunction with lactate should further shed light regarding the utility of R-StO_2 as a reliable measure of tissue oxygenation capable of informing and guiding management and impacting clinical outcomes.

Conclusion

R-StO_2 local measurement from the buccal mucosa demonstrated significant agreement with $ScvO_2$ at levels that would potentially allow it to be used to guide clinical management. The use of R-StO_2 may have potential as a suitable noninvasive indicator of systemic oxygenation and as a surrogate metric to $ScvO_2$. Additional testing will be required to assess RRS's longitudinal ability to track changes in tissue oxygenation over time and in response to therapies.

Acknowledgments

The authors would like to thank Danielle Leander as well as the Michigan Center for Integrative Research in Critical Care and Michigan Medicine Intensive Care Units staff for their technical support.

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Figure Legends

Figure 1 Example of a molecule being interrogated by RRS depicting the Raman vibrational spectroscopy phenomena. Deoxy-Hb: Deoxy-hemoglobin. Oxy-Hb: Oxy-hemoglobin.

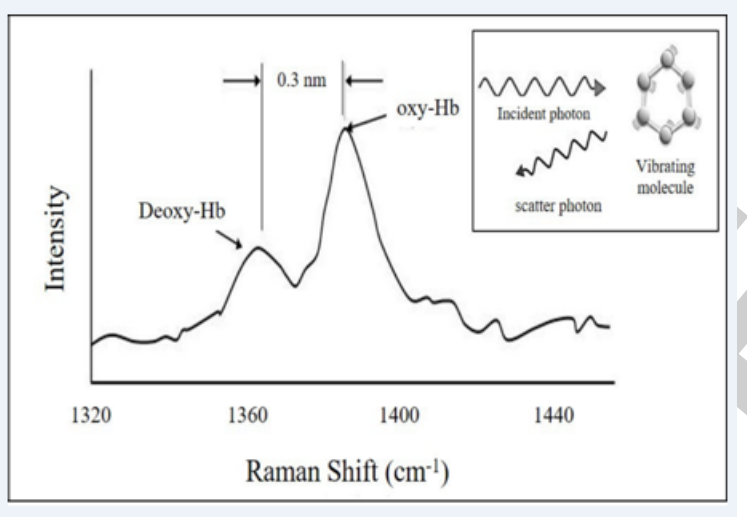

Figure 2:

Linear regression model demonstrating the relationship between R-StO2 and $ScvO_2$. R-StO2: resonance Raman spectroscopy-tissue hemoglobin oxygen saturation. ScvO2: central or mixed venous hemoglobin oxygen saturation.

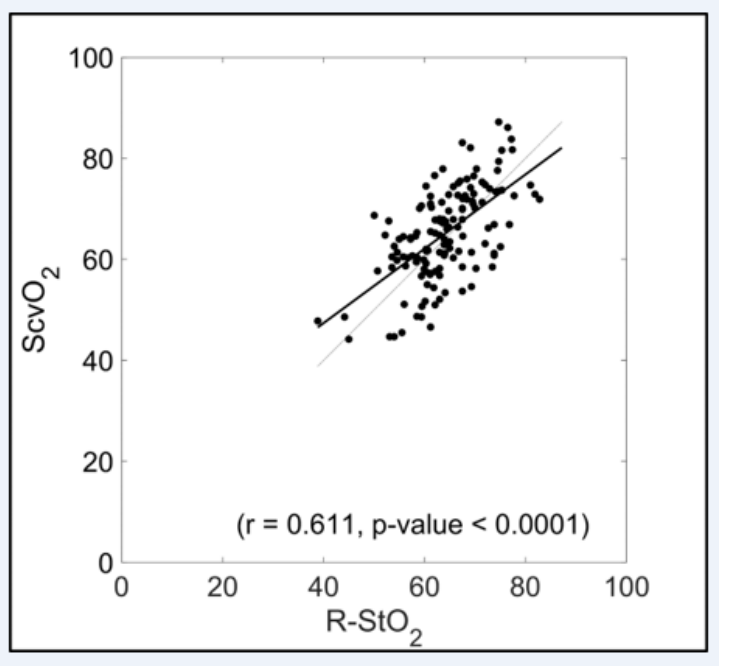

Figure 3: Clarke Error Grid plot to quantify clinical accuracy of estimated R-StO_2. Zone A: Accurate values within clinically acceptable difference. Zone B: Acceptable values. Zone C: represent potential of unnecessary treatment or false positive values. Zone D: represent failure to detect and treat or false negative values. And zone E: represent erroneous measurements. See results and discussion section for details.

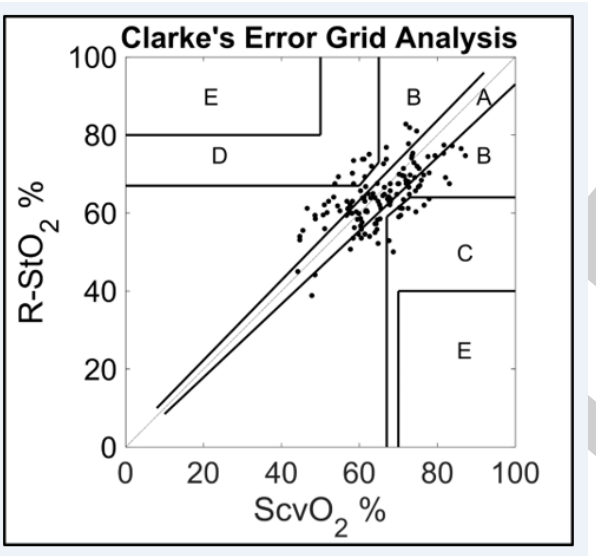

Figure 4: Receiver operator characteristics and area under the curve values for R-StO_2 at different thresholds of $ScvO_2$ (60%, 65%, and 70%). R-StO_2: resonance Raman spectroscopy-tissue hemoglobin oxygen saturation. $ScvO_2$: central or mixed venous hemoglobin oxygen saturation.

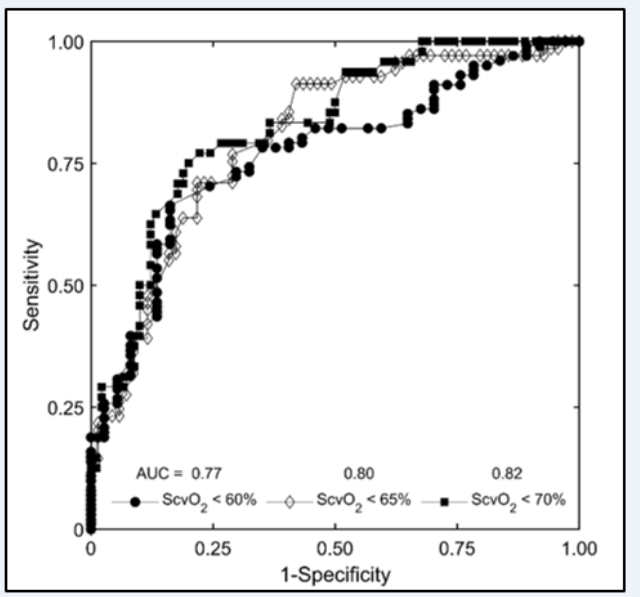

Table 1: Descriptive Statistics

	R-StO_2 (%)	**$ScvO_2$ (%)**	**Difference (R-StO_2-$ScvO_2$) (%)**
Number of values	138	138	138
Mean	64	65	-1
Std. Deviation	7.6	9.2	7.5
Std. Error of Mean	0.65	0.78	0.64
95% CI of the mean	63, 66	64, 67	-2.2, 0.3
Minimum	39	44	-19
25% Percentile	60	59	-7
Median	64	65	-2
75% Percentile	69	72	5
Maximum	83	87	15

Descriptive Statistics of R-StO_2, $ScvO_2$ and the difference between the two. R-StO_2: Resonance Raman Spectroscopy-Tissue oxygen saturation. $ScvO_2$: Central venous oxygen saturation. 95% CI: 95% confidence intervals.

Monitoring of Tissue Microvasculature Oxygenation Using Resonance Raman Spectroscopy

Abdelrahman Awad, MD[1,3]; Varisha Essani[1,3]; Claire Roberge[1,3]; Kyle Gunnerson, MD[1,3]; Mohamad Hakam Tiba, MD, MS[1,3]; Kevin Ward, MD[1,2,3]

[1]Department of Emergency Medicine, University of Michigan, Ann Arbor, Michigan
[2]Department of Biomedical Engineering, University of Michigan, Ann Arbor, Michigan
[3]Michigan Center for Integrative Research in Critical Care (MCIRCC), University of Michigan, Ann Arbor, Michigan

Introduction: Management and treatment of critically ill patients remain a complicated process. Monitoring of the critically ill's tissue oxygenation status provides valuable insight into the effectiveness of their management plan. Current modalities to assess patients' oxygenation status is by obtaining a central venous blood gas sample ($ScvO_2$) which requires the presence of a central venous catheter (CVC) or a Pulmonary Artery Cather (PAC), which not only is considered invasive and non-continuous measurement but also has its own complications and challenges. Resonance Raman Spectroscopy (RRS) is a novel, non-invasive and effective measure to monitor and assess tissue oxygenation (StO_2) as a surrogate for $ScvO_2$. We have developed a portable monitor to measure StO_2 utilizing the well-defined and narrow Resonance Raman spectral fingerprint of oxy and deoxy-hemoglobin in the interrogated tissue. We present data for our investigation into the utility and effectiveness of our monitor comparing our SSR-StO_2 to blood gas measures of $ScvO_2$.
Hypothesis: We hypothesize that RRS-StO_2 will rack and predict patients' $ScvO_2$ with high precision.
Methods: Critically ill patients with a central venous catheter in place were recruited mainly from the cardiovascular ICU and other ICUs at Michigan Medicine. Informed consent was obtained from the patients or their legally authorized representatives prior to any testing. During the test, the RRS sensor was placed on the buccal mucosa for an average of 15 minutes and StO_2 measurements were obtained and collected. At the conclusion of testing, a blood sample was collected from the distal port of the central catheter to measure $ScvO_2$ and the RRS measurement at that time was marked and recorded. GraphPad Prism8 statistical software was used for data analysis to compare StO_2 to $ScvO_2$.
Results: Between 2015 and 2020, a total of 138 critically ill patients were recruited and tested. Average (standard deviation) of patients age and weight were 62(13) years, 90.3(26) kg respectively. Average (SD) of pooled StO_2 and $ScvO_2$ were 64(7.6) and 65.3 (9.1) respectively. There was significant correlation between StO_2 and $ScvO_2$ ($r=0.609$, $p < 0.0001$). A paired *t-test* showed no significant difference between StO_2 and $ScvO_2$ with an average (SD) difference of 1.04 (7.5) % (95%CI: 0.22- 2.3%). Receiver Operator Curve revealed an StO2 area under the curve > 0.8 (95% CI: 0.7 – 0.88. $p<0.0001$) at different thresholds of ScvO2 (60%, 65%, and 70%).
Conclusion: In this study, RRS is showing promise as a non-invasive alternative to $ScvO_2$. Because of its non-invasive nature, RRS may serve as a faster, safer, and more cost-effective way to assess patient tissue oxygenation, aiding in the diagnosis and treatment of conditions such as sepsis, trauma, heart failure and other critical states.

Disclaimer: This research project is supported by the Department of Defense – Combat Casualty Care grant award W81XWH-18-1-0078. KW is an inventor of the technology.

Learning Objectives:
Describe Resonance Raman Spectroscopy and its utility to interrogate tissue oxygenation
Describe current methodology to assess critically ill patients' oxygenation
Compare performance of RRS-StO_2 to measurements of central venous oxygen saturation.

Resonance Raman Spectroscopy-Derived Tissue Hemoglobin Oxygen Saturation for the Management of the Critically Ill and Injured Patients

Mohamad H. Tiba, MD, MS[1,4], Abdelrahman B. Awad, MD[1,4], Christopher M. Fung, MD[1,4], Lena M. Napolitano, MD[2,4], Pauline K. Park, MD[2,4], David A. Machado-Aranda, MD[2,4], Kyle J. Gunnerson, MD[1,4], Padraic Romfh, BS, MBA[5], Kevin R. Ward, MD[1,3,4]

1. Department of Emergency Medicine. University of Michigan, Ann Arbor, Michigan.
2. Department of Surgery. University of Michigan, Ann Arbor, Michigan.
3. Department of Biomedical Engineering. University of Michigan, Ann Arbor, Michigan.
4. Michigan Center for Integrative Research in Critical Care. University of Michigan, Ann Arbor, Michigan.
5. Pendar Technologies, LLC. Cambridge, Massachusetts

Introduction: Management and treatment of critically ill patients remain a challenging process. Monitoring of the critically ill's tissue oxygenation status provides valuable insight into the effectiveness of their management and prognosis. Current assessment of oxygenation status requires obtaining a central venous blood gas sample ($ScvO_2$) which requires the presence of a central venous catheter (CVC) or a Pulmonary Artery Cather (PAC), which not only is considered invasive and non-continuous measurement, but also has its own complications and challenges. In this study, we examined the ability of Resonance Raman Spectroscopy (RRS) to measure tissue hemoglobin oxygenation (R-StO_2) noninvasively in critically ill patients and compared its performance with conventional central venous hemoglobin oxygen saturation ($ScvO_2$)

Hypothesis: We hypothesized that R-StO_2 could potentially be a noninvasive surrogate of $ScvO_2$ as an indicator of tissue oxygenation.

Methods: Critically ill patients (n=138) with an indwelling central venous or pulmonary artery catheter in place were consented and recruited. R-StO_2 measurements were obtained by placing a sensor inside the mouth on the buccal mucosa. R-StO_2 was measured continuously for 5 minutes. Blood samples were drawn from the distal port of the indwelling central venous catheter or the proximal port of the pulmonary artery catheter at the end of the test period to measure $ScvO_2$ using a standard co-oximetry analyzer. A regression algorithm was used to calculate the R-StO_2 based on the observed spectra.

Results: Data is presented as mean and (Standard deviation). Mean (SD) of pooled R-StO_2 and $ScvO_2$ were 64%(7.6%) and 65% (9.2%) respectively. A paired t-test showed no significant difference between R-StO_2 and $ScvO_2$ with a mean(SD) difference of -1% (7.5%) (95% CI: -2.2, 0.3 %). A modified Clarke Error Grid showed significant clinical accuracy of R-StO_2 with 84.8% of the data residing within the accurate and acceptable grids (A and B), 8% in the false-positive grid (C), and 7.2% in the false-negative grid (D). Area under the receiver operator curve for R-StO_2's was 0.8 (0.029) (95% CI: 0.7, 0.9 $p<0.0001$) at different thresholds of $ScvO_2$ ($\leq$60%, $\leq$65%, and $\leq$70%). Five blinded critical care physicians clinically adjudicated the values of R-StO2 and ScvO2 regarding the management of patients based on saturation values. Overall agreement between all 5 raters was highly significant (Fleiss' Kappa 0.45, $p<0.00001$).

Conclusions: R-StO_2 local measurement from the buccal mucosa demonstrated significant agreement with $ScvO_2$ at levels that would potentially allow it to be used to guide clinical management. The use of R-StO_2 may have potential as a suitable noninvasive indicator of systemic oxygenation and as a surrogate metric to $ScvO_2$.

Disclaimer: This research project is supported by the Department of Defense – Combat Casualty Care grant award (W81XWH-18-1-0078). KRW is an inventor of the technology.

Learning Objectives:
Describe Resonance Raman Spectroscopy and its utility to interrogate tissue oxygenation
Describe current methodology to assess critically ill patients' oxygenation
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