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13. SUPPLEMENTARY NOTES

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- StO_2 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-StO₂ 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-StO₂ with other measures and surrogates of tissue oxygenation including lactate and ScvO₂ in polytrauma and complex operative and post-operative surgical patients. Months 0-36

1) *Specific objectives:*

- a) IRB approval January 22, 2013
- b) HRPO approval November 15, 2017
- c) Patient recruitment: 12 additional patients were recruited since last quarterly report

One hundred and thirty-eight patients were recruited and tested from multiple intensive care units across the University of Michigan's hospital. The patients had a mean (Standard Deviation) age and weight of 62(13) years and 90.3(26) kg respectively. Sixty-two (45%) of the patients had central venous catheter (CVC) in place at the time of testing, thirty (22%) patients had pulmonary artery catheter (PAC) in place and Forty-six (33%) patients had both CVC and a PAC simultaneously. One hundred and thirteen (82%) of the patients were recruited from the cardiovascular ICU, nine (6%) from the Critical Care Medicine Unit, five (4%) from Emergency Critical Care Center (EC3), and the rest are from the Cath lab, trauma and burn 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 ScvO₂ and compared to tissue oxygen saturation (StO₂) as measured by RRS.

2) *Significant results:*

Data analysis

Descriptive statistics are expressed as means and standard deviations. Linear regression was used to quantify the relationships between RRS-StO₂ and ScvO₂. Bland-Altman analysis is utilized to quantify agreement (bias and limits of agreement) between RRS-StO₂ and ScvO₂ using Tukey's mean-difference plot (20, 21). Summary statistics using receiver operating characteristic (ROC) and area under the curve (AUC) values were used for pooled data to assess performance of RRS-StO₂ at different thresholds of ScvO₂. Clinical adjudication and utility of RRS-StO₂ and ScvO₂ were conducted by asking 5 blinded Critical Care Physicians to indicate, based on RRS-StO₂ and ScvO₂ values, if they would management of their patients to include therapies that aims to increase their oxygen delivery and thus oxygen consumption. Agreement and disagreement between paired RRS-StO₂ and SCVO₂ were calculated for each rater.

Results

Table 1 lists Descriptive Statistics of RRS-StO₂, ScvO₂ and the difference between the two (RRS-StO₂ - ScvO₂).

	RRS-StO ₂ (%)	ScvO ₂ (%)	Difference (t-cv) (%)
Number of values	138	138	138
Mean	64	65	-1.0
Std. Deviation	7.61	9.14	7.53
Std. Error of Mean	0.648	0.778	0.641
95% CI of the mean	63, 66	64, 67	-2.3, 0.2
Minimum	39	44	-19
25% Percentile	60	60	-7
Median	64	65	-2
75% Percentile	69	72	5
Maximum	83	87	14

Mean(SD) of pooled RRS-StO₂ and ScvO₂ were 64(7.6) and 65.3 (9.1)% respectively. A linear regression of the type ($ScvO_2 = \beta_0 + \beta_1 \times RRS-StO_2 + \gamma$) showed a significant correlation between StO₂ and ScvO₂ ($r=0.611$, $p < 0.0001$) (Figure 1).

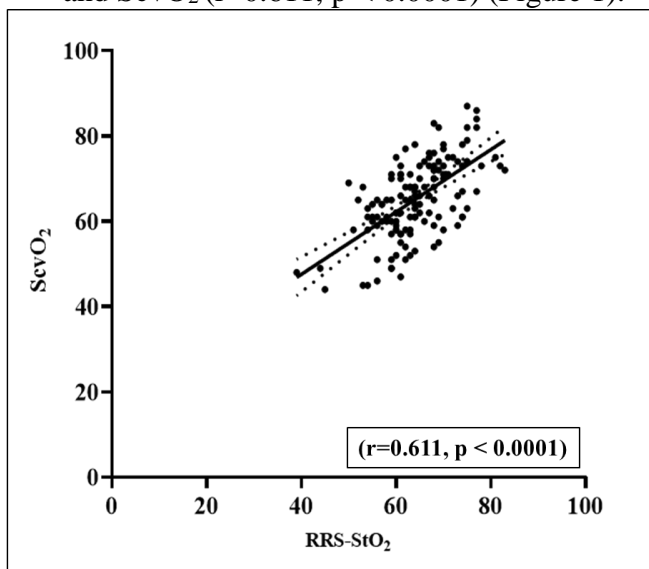


Figure 1: Linear regression model demonstrating the relationship between RRS-StO₂ and ScvO₂. RRS-StO₂: Resonance Raman spectroscopy-tissue hemoglobin oxygen saturation. ScvO₂: Central venous hemoglobin oxygen saturation

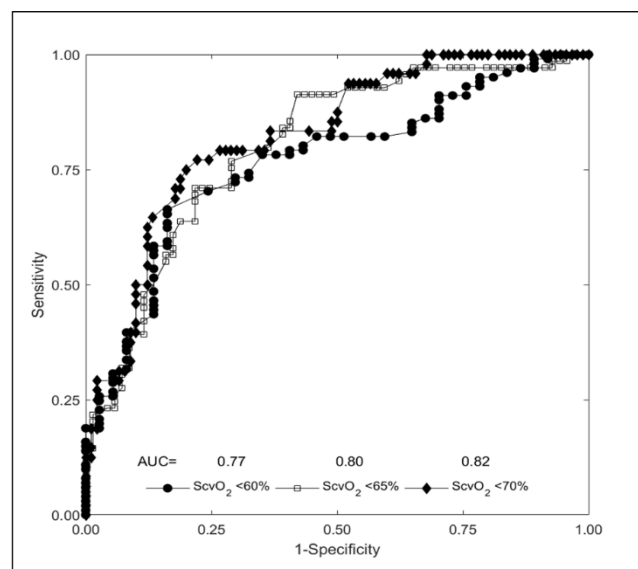


Figure 2: Receiver operator characteristics and area under the curve values for RRS-StO₂ at different thresholds of ScvO₂ (60%, 65%, and 70%). RRS-StO₂: Resonance Raman spectroscopy-tissue hemoglobin oxygen saturation. ScvO₂: Central venous hemoglobin oxygen saturation

A paired *t-test* revealed no significant difference between RRS-StO₂ and ScvO₂ with a mean(SD) of the difference between RRS-StO₂ and ScvO₂ of 1.04 (7.5)% (95% CI: 0.22-2.3%, $p=0.11$). ROC analysis yielded a mean(SD) area under the curve for RRS-StO₂ of 0.8(0.029) (95% CI: 0.7 – 0.88, $p<0.0001$) at different thresholds of ScvO₂ (60%, 65%, and 70%) (Figure 2).

Since StO₂ and ScvO₂ are not identical measures, we are experimenting with various means to compare the two since being fundamentally different, utilization of such techniques as Bland-Altman and simple correlations are not useful. Figure 3 shows Bland-Altman analysis by plotting the mean of both RRS-StO₂ and ScvO₂ against their difference. The analysis yielded a mean(SD) of the difference (Bias) of 1(7.5)% and limits of agreement between 14 and 16%.

We have also produced a randomized list of StO_2 and SvO_2 values obtained from over 138 subjects and provided them to surgical critical care and trauma subject matter experts who are considered experts in the use of goal directed resuscitative therapy which incorporates the utilization of SvO_2 values in treatment decision making. These experts are blinded to the source of the values (Raman derived versus co-oximeter derived SvO_2 or $ScvO_2$ values). The subject matter experts have been given the following scenario to react to:

“Please consider each saturation value reported as being reported from a central or pulmonary artery catheter from a critically injured/ill patient. Using principles of goal directed therapy driven by central or mixed venous hemoglobin oxygen saturation values, please if you would treat the patient with therapies to increase their central or mixed venous hemoglobin oxygen saturation values

Five blinded critical care physicians clinically adjudicated the values of $RRS-StO_2$ and $ScvO_2$ in regard to management of patients based on the saturation values. Agreement between $RRS-StO_2$ and $ScvO_2$ adjudication was performed for each rater separately. Post-adjudication pairing of each of the raters’ assessments yielded a significant mean (SD) agreement of 0.73(0.045) ($p < 0.001$) for all raters.

A) Probe enhancement

Probe and clip holder enhancement is currently underway to allow faster and more stable placement of the probe (Figures 4 and 5).

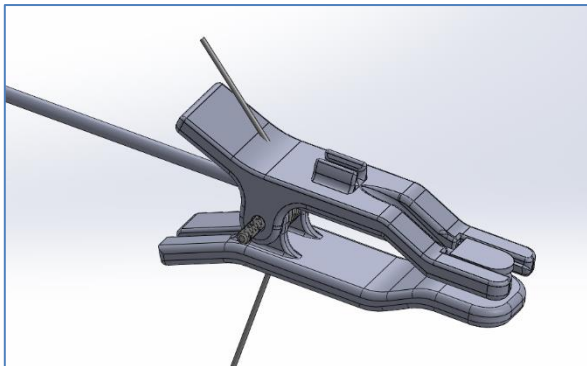


Figure 4: New probe holder configuration



Figure 5: RRS Probe

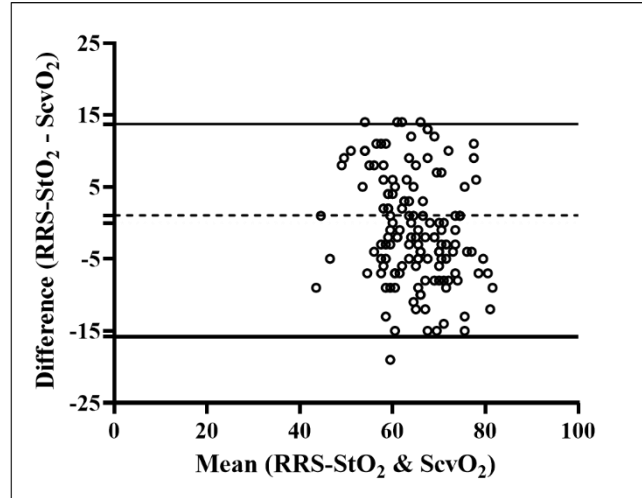


Figure 3: Bland-Altman analysis demonstrating relationship between paired ($RRS-StO_2$ and $ScvO_2$)’s mean vs. the difference between the two. The dotted line represents the bias (mean of difference and solid lines represent the limits of agreement which are $Bias \pm 2SD$. $RRS-StO_2$: Resonance Raman spectroscopy-tissue hemoglobin oxygen saturation. $ScvO_2$: Central venous hemoglobin oxygen saturation

indicated based on the provided value

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*

1) *Specific objectives:*

- a) IRB approval January 22, 2013
- b) HRPO approval November 15, 2017
- c) Patient recruitment: 3 additional patients were recruited since last quarterly report

Patients who were admitted to the University of Michigan trauma ICU, emergency department, or emergency critical care center were consented and enrolled into the study. In cases where the patient was unable to consent, the legally authorized representative consented on their behalf. A signed copy of the informed consent document was provided. Subjects underwent an abdominal ultrasound to measure changes in IVC diameter during normal tidal breathing as well as during respiratory maneuvers such as deep breathing and sniff. Of these patients, a small subset was selected for bioimpedance monitoring with a new portable prototype device. These subjects were monitored using the prototype for 15-30 minutes, using a bipolar electrode array. The amplitude of the cardiac and respiratory components of the bioimpedance signal was quantified and compared to changes in IVC diameter as measured by ultrasound. The bioimpedance signal, comprised of distinct cardiac and respiratory components, was quantified by taking the ratio of the amplitude of these components. A new prototype device that will no longer require the use of a laptop and cart is currently being developed (New Vital Signs, Inc) and tested alongside the Biopac system. The improvements in this device will allow greater mobility and reduce reliance on electricity.

2) *Significant results*

A) Data analysis

As previously stated, the objective of the Dynamic Respiratory Impedance Volume Estimation (DRIVE) technology is to noninvasively assess intravascular volume status using limb bioimpedance. Bioimpedance represents the cumulative effect of individual bodily tissues, however, blood has a unique and distinct effect on the bioimpedance signal. Blood is a relatively good conductor, and the volume of blood in a localized area such as the limb varies with respiration and the cardiac cycle. We hypothesize that these respiratory and cardiac variations present in the bioimpedance signal (as presented in Figure 6) contain information which is predictive of the patient's intravascular volume status.

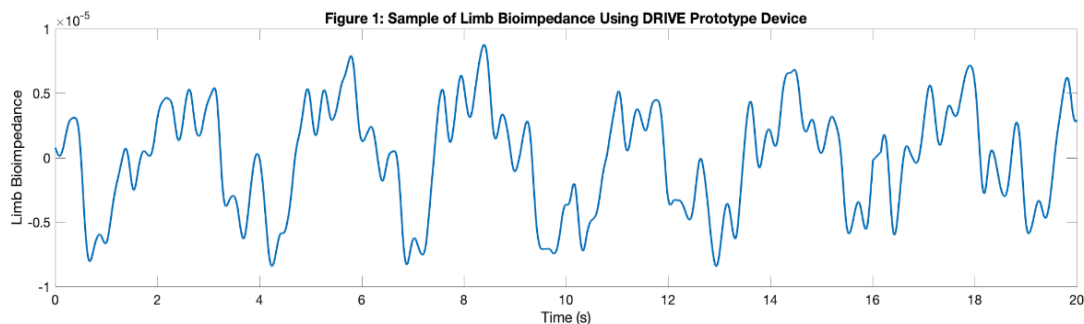


Figure 6: Sample bioimpedance waveform. Note the prevalent respiratory cycle (low frequency) and the higher-frequency cardiac component. This sample signal was obtained from a human subject using the prototype device.

During this quarter, we have tested the prototype on 3 additional patients this quarter. Based on last quarter’s investigation into electrode placement, we have identified the tetrapolar array to provide the most consistent high-quality signal. This arrangement also allows indexing of the respiratory-induced signal changes to a baseline level of impedance, which we are currently investigating as a way to further estimate volume status.

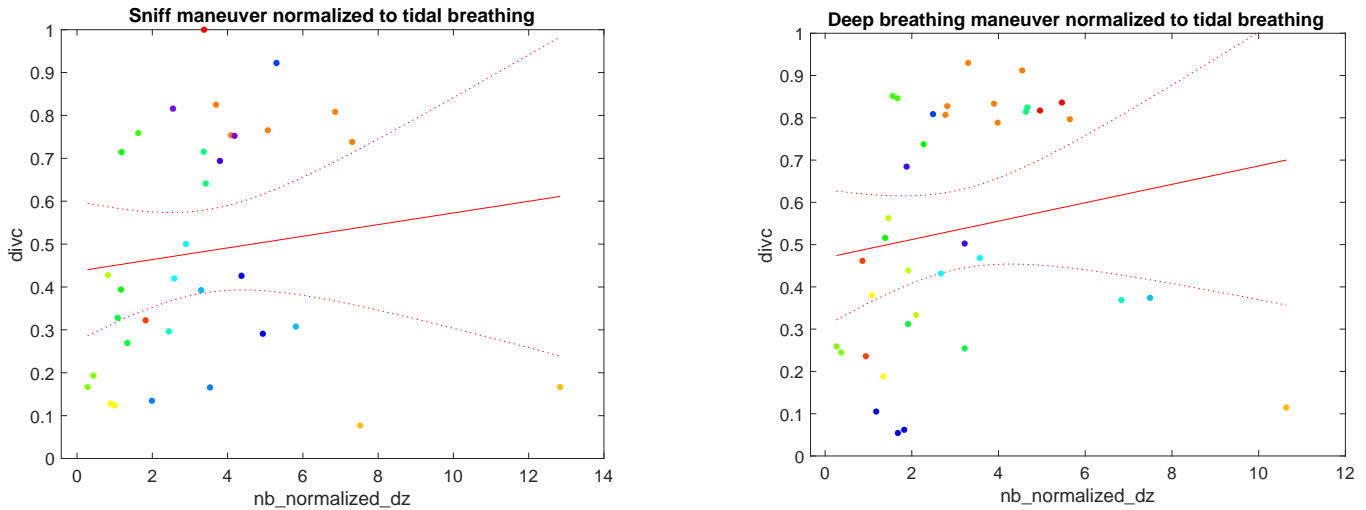
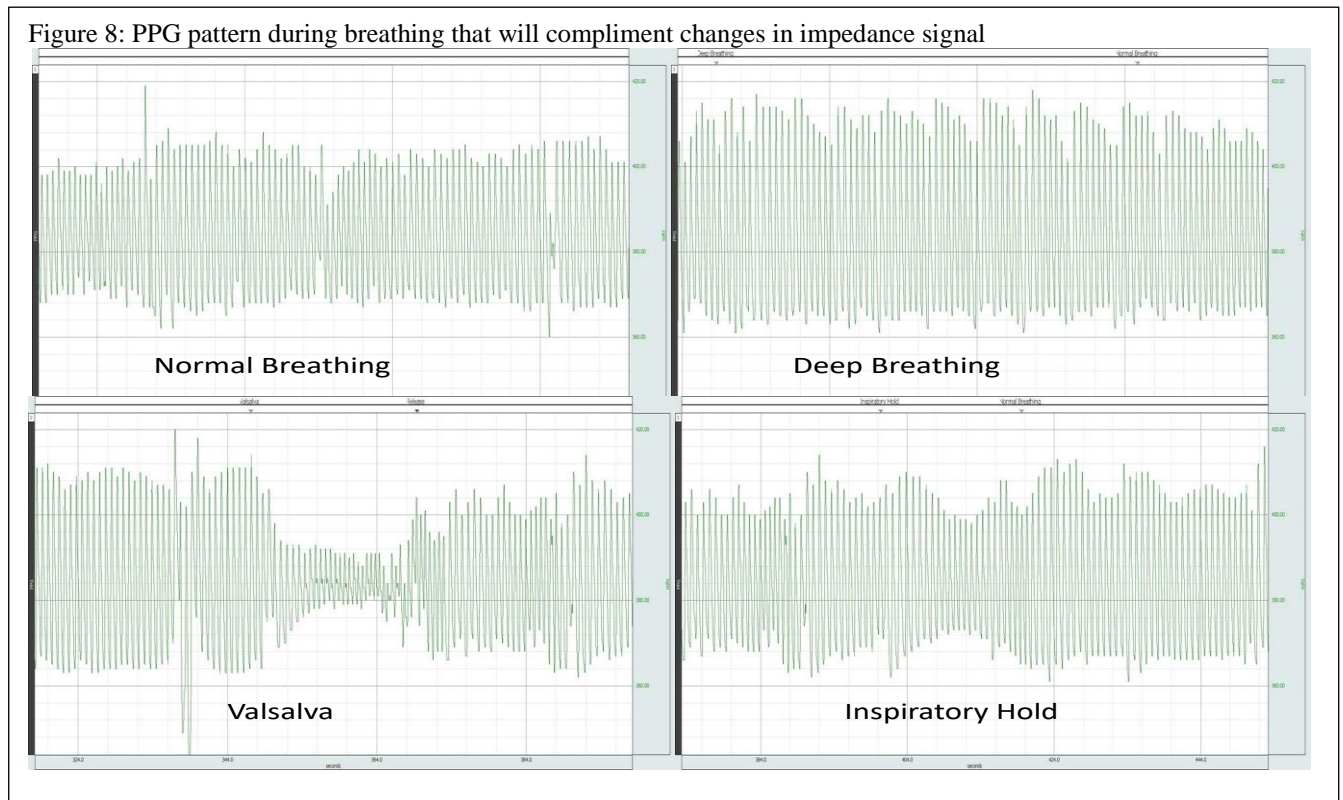


Figure 7: Bioimpedance vs. dIVC. For all patients in our cohort with a viable bioimpedance signal and IVC image, “nb_normalized_dz” was calculated as the respiratory variability during a maneuver (sniff in the leftmost panel, or deep breathing on the right) divided by the respiratory variability during a normal spontaneous breath. With the exception of the right-handed outliers, the correlation between our bioimpedance measure and dIVC is moderate- to high (R value). With the exception of the right-handed outliers, the correlation between our bioimpedance measure and dIVC is significant at a 5% level in both cases. We are currently investigating the cause of these outliers to understand why they deviate so far from the trend.

Additionally, we are examining optimal electrode placement sites ranging from whole arm to upper arm to forearm. As delineated above, these metrics are compared to inferior vena cava (IVC) collapsibility index (dIVC) as a gold standard of volume status. The IVC is visualized longitudinally via B-mode ultrasound by a trained emergency medicine physician. Video clips of the IVC are recorded as the patient undergoes various breathing exercises, such as deep breathing. IVC collapsibility during such a maneuver is believed to be indicative of volume status and responsiveness. The minimum and maximum diameter of the IVC during the exercise is recorded by the physician, and the collapsibility index (dIVC) is described as the relative change in IVC diameter during these respiratory maneuvers. In addition, we have also continued to explore how these respiratory maneuvers may be standardized across patients. One technique we have been investigating is to index the impedance change noted during the respiratory maneuver to a baseline measurement taken moments prior. The figure below displays the result of this index from deep breathing and sniff as compared to dIVC measurements.

Preliminary data supports that using a dIVC of 50% may produce DRIVE values that are more consistent with critical decision making. In addition, we have noted significant noise in the impedance signal especially when subjects repeat the maneuvers of deep breathing. Due to this noise, we have also been challenged in using the impedance signal to track breathing patterns of subjects prior to the breathing maneuver. We believe this variability plays a significant role in the impedance signal variability of the outliers. In an attempt to reduce noise, add critical redundancy, and preserve the value of the venous component of the impedance signal, we are planning to add a photoplethysmographic (PPG) signal to the impedance methodology. The use of PPG is anticipated in both our issued patent and covered in the approved IRB protocol and simply incorporates the use of a pulse oximeter signal. What is new is our ability now to record and capture both signal from approximately the same region of



tissue. We are also able to manipulate the AC and DC component of the signal to maximize the PPG signal for changes in blood volume.

Figure 8 above demonstrates compressed PPG signals (beat to beat) during various respiratory maneuvers. The PPG signal capture both arterial and venous components of volume whereas changes in impedance are mainly reflective of changes in venous volume. Our plan is to combine the two signals in the future to increase the fidelity of the venous signal in order to match changes in dIVC. Simultaneous use of the PPG will assist in developing noise mitigation/cancellation strategies and understanding patient breathing patterns during and in between maneuvers.

Lastly, our group has previously developed an impedance based noninvasive method of central venous pressure (NICVP) monitoring. The method had been licensed through Virginia Commonwealth University (VCU) to NiVasc Inc. This NICVP method shares many important features with DRIVE. Its combination with DRIVE would allow a unique static and dynamic measure of intravascular volume. To date, NiVasc had been unwilling to collaborate but recently returned the technology to VCU. The University of Michigan has now secured the rights from VCU to develop and license the NICVP technology to commercial entities. Central venous pressure (CVP) is a 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. The graphic below demonstrates how this technology works along with data from a previously published study [1] demonstrating the ability of the technology to potentially replace invasively measured CVP.

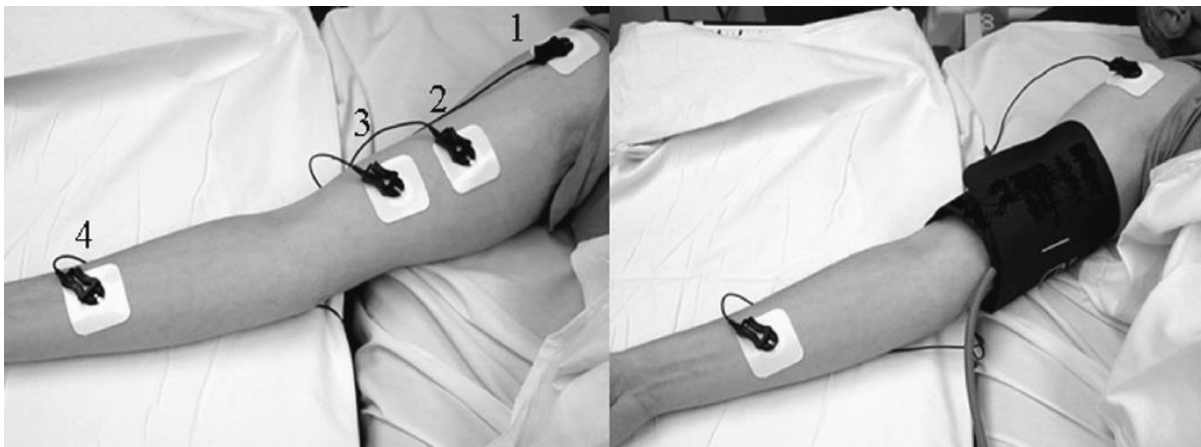
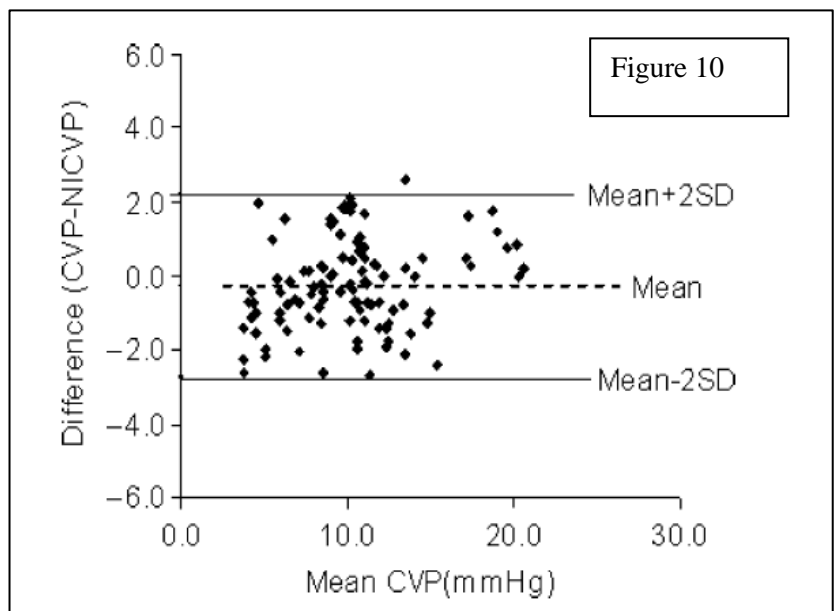


Figure 9: Orientation of electrodes used for tetra-polar impedance plethysmography. Electrodes 1 and 4 inject current toward electrodes 2 and 3, respectively, allowing for detection of volume changes in the segment of tissue underlying the blood pressure cuff [1].

Figure 10 demonstrates our NICVP technologies performance when compared to invasive CVP measure (Gold standard) using Bland-Altman plot. Of all 108 measures in 36 subjects (three measures per subject). Mean bias was -0.26 mmHg (95% CI: $-0.67, 0.15$). Limits of agreement were -2.7 and 2.2 mmHg with the 95% CI for the lower limit of agreement ($-3.4, -2.0$ mmHg) and for the upper limit of agreement ($1.5, 2.9$ mmHg) demonstrating that the technique can be used to replace the invasive method [1].



“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”

We have inherited a new prototype (Figure 11) from the previous licensee (NiVASC) and tested signals on ourselves (no patients) obtained with a tetrapolar arrangement of electrodes to that obtained with a bipolar arrangement demonstrating no significant change in signal quality when compared to previous studies (figure 12). Our current IRB protocol allows testing of this method but will need to be changed to reflect the new prototype. 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.

The underlying theory involves a well-founded and studied method incorporating impedance plethysmography. Specifically, a small amount of current, 400 μ A @ 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 sec 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.

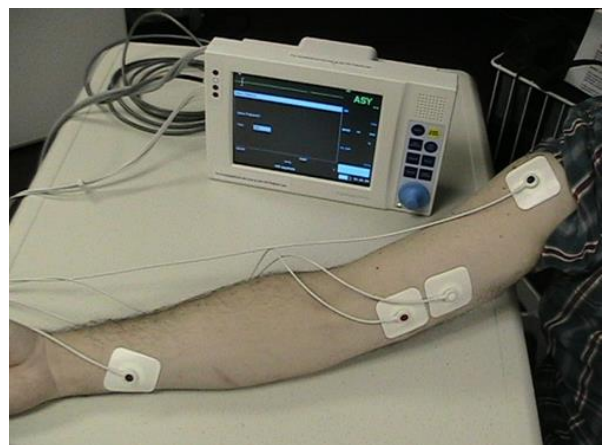


Figure 11: Prototype device to measure central venous pressure non-invasively using bioimpedance

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 12-1). The initial change in impedance seen in Figure 12-A 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 12-4). 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 12-2), that is observed at the minimum point in this delta impedance waveform (see red vertical line in Figure 12) has been found to correlate to the patient’s CVP, as measured with a catheter (12-3). The cuff pressure reading is reported as the NICVP parameter value by the device.

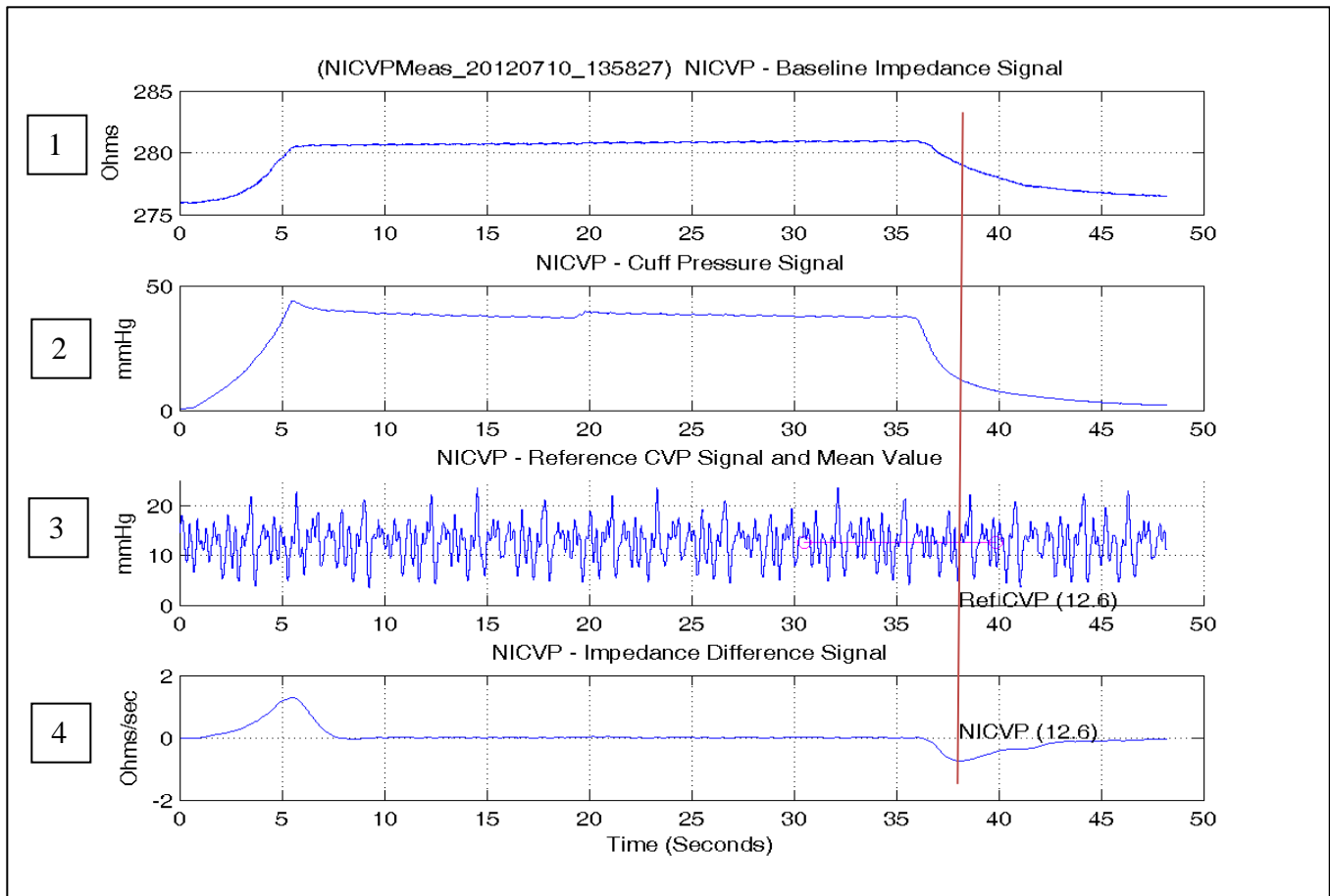


Figure 12: Early prototype device to measure central venous pressure non-invasively using bioimpedance. 1) Bioimpedance changes during cuff inflation. 2) Cuff pressure changes. 3) Invasive CVP measurement (Gold standard). 4) High quality, filtered bioimpedance signal to denote value of non-invasive CVP. The red line indicated pressure in cuff (panel 2) at the point of the impedance derivative (panel 4) which matches the mean CVP value (panel 3) *Shock 33(3): 269-273, 2010. PM19487978*

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?

- A study clinical coordinators presented data in a poster format at the 2019 Annual Military Health Science Research Symposium in Kissimmee, Florida.

Amanda J. Pennington, Mohamad Hakam Tiba, Brandon C. Cummings, Varisha Essani, Claire Roberge, Kyle Gunnerson, Kevin R. Ward. Novel monitoring of tissue microvasculature oxygenation using resonance Raman spectroscopy. Military Health System Research Symposium (MHSRS), August 2019, Kissimmee, Florida

Posters are provided in the appendices

- A manuscript describing the resonance Raman spectroscopy is in the final stages of submission to Critical Care Medicine.

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

Due to COVID-19 pandemic, we are working remotely and patients' recruitment is on hold temporarily. However, we will use this time to continue with data analysis and manuscripts preparation. Details about COVID-19 temporary research ramp-down can be found below. Upon reversal of the research ramp down order, we will

- 4.3.1. Continue patient recruitment
- 4.3.2. Data analysis
- 4.3.3. Data presentation (national and local)
- 4.3.4. Manuscript writing
- 4.3.5. Technology and signal processing refinement
- 4.3.6. Begin incorporation and testing of impedance based NICVP

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 volume status 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.

Upon publication of our Raman results in Critical Care Medicine or other high-impact critical care journal, we anticipate working with Pendar 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 DRIVE technology has been licensed to New Vital Signs. DRIVE data and performance of the new prototype device is being shared with New Vital Signs to support continuous improvement of the technology and approaches to develop regulatory approval and commercialization strategies. New analytic approaches such as the RMS technique described above may be sources of new intellectual property in the future.

We also now will be exploring the utility of combining DRIVE with our previously developed impedance based noninvasive Central Venous pressure monitor (NICVP).

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

As indicated above, 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

In light of the COVID-19 pandemic, University of Michigan clinical research office has placed temporary restrictions on human subjects research effective Saturday, March 14, 2020 that is still in effect to date. Screening and recruitment have been halted since then which will affect the total number of target patients. In late May, the office of research has started a research re-engagement plan for phased reopening of research laboratories. However, patients' recruitment for research is still on hold until further notice. To mitigate the delay in fulfilling our objective, we have put forth plan to request a 12-month no-cost extension of the award. Institutional documentation related to COVID-19 research ramp down and re-engagement will be provided with this report

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

- 6.4.1. **Significant changes in use or care of human subjects:** None to report
- 6.4.2. **Significant changes in use or care of vertebrate animals:** None to report
- 6.4.3. **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
- 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 has been presented at the 2019 Military Health System Research Symposium (MHSRS)

Amanda J. Pennington, Mohamad Hakam Tiba, Brandon C. Cummings, Varisha Essani, Claire Roberge, Kyle Gunnerson, Kevin R. Ward. Novel monitoring of tissue microvasculature oxygenation using resonance Raman spectroscopy. Military Health System Research Symposium (MHSRS), August 2019, Kissimmee, Florida

Abstracts are included in the appendices

- A manuscript highlighting the Resonance Raman Spectroscopy results and clinical adjudication is in the final stages of preparations and will be submitted to Critical Care Medicine journal

7.2. Website(s) or other Internet site(s)

Nothing to report

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

Nothing to report

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?

9. Name:	<i>Kevin Ward, MD</i>
Project Role:	<i>PI</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	<i>Oversight of data collection and analysis</i>
Funding Support:	

Name:	<i>Mohamad Hakam Tiba, MD, MS</i>
Project Role:	<i>Co-I</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	<i>Oversight of data collection and analysis</i>
Funding Support:	

Name:	<i>Kyle Gunnerson, MD</i>
Project Role:	<i>Co-I</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	<i>3</i>
Contribution to Project:	<i>medical consultation</i>
Funding Support:	

Name:	<i>Lena Napolitano, MD</i>
Project Role:	<i>Co-I</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>medical consultation</i>

Name:	<i>Pauline Park, MD</i>
Project Role:	<i>Co-I</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>medical consultation</i>

Name:	<i>Nik Theyyuni, MD</i>
Project Role:	<i>Co-I</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Perform ultrasounds</i>
Funding Support:	

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

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

Name:	<i>Amanda Pennington, MS</i>
Project Role:	<i>Clinical Research Project Manager</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	<i>Subject screening and enrollment, regulatory and compliance management, data collection</i>
Funding Support:	

Name:	<i>Christopher Gillies, MS</i>
Project Role:	<i>Data Scientist</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	<i>data analysis</i>
Funding Support:	

Name:	<i>Brandon Cummings, BS</i>
Project Role:	<i>Research Staff</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	11
Contribution to Project:	Data analysis
Funding Support:	

Name:	<i>Anne Weitzel, BS</i>
Project Role:	<i>Research Staff</i>
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	2
Contribution to Project:	<i>data analysis</i>
Funding Support:	

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

Name:	<i>Abdelrahman Awad, MD</i>
Project Role:	<i>Clinical Coordinator</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	<i>Screening and consenting patients, data collection</i>
Funding Support:	

Name:	<i>Nicholas Greer, BS</i>
Project Role:	<i>Research Staff</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	<i>Data analysis</i>
Funding Support:	

Name:	<i>Erin Bisco, BS</i>
Project Role:	<i>Research Staff</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	<i>Screening and consenting patients, data collection</i>
Funding Support:	

Name:	<i>Nicholas Sautter, BS</i>
Project Role:	<i>Research Staff</i>

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	<i>Screening and consenting patients, data collection</i>
Funding Support:	

Name:	<i>Guan Wang, MS ME</i>
Project Role:	<i>Application programmer / Analyst</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	<i>Software engineering and system administration</i>
Funding Support:	

9.1. 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

9.2. 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.

9.3. Other.

Nothing to report

10. SPECIAL REPORTING REQUIREMENTS

10.1. COLLABORATIVE AWARDS:

None

10.2. QUAD CHARTS: Included with this report before the appendices

11. APPENDICES:

- a. 2019 MHSRS Abstract and poster
- b. COVID-19 new restrictions for human subjects research
- c. Planning Research Re-engagement
- d. Research Re-engagement _ U-M Research

Development and Testing of New Noninvasive Monitoring Tools for Prolonged Field Care Goal Directed Therapy

DM160225 Prolonged Field Care Research Award



PI: Kevin R. Ward, MD

Org: University of Michigan

Award Amount: \$2,998,209

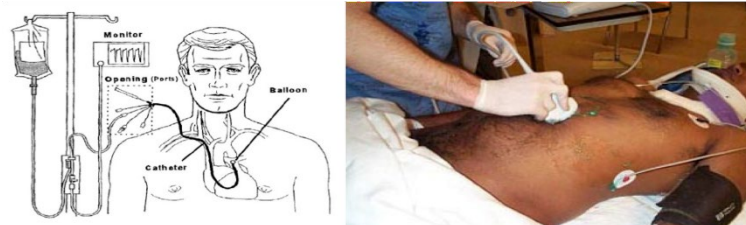
Study/Product Aim(s)

- Test and compare resonance Raman spectroscopy tissue oxygenation (RRS StO2) with other measures of tissue oxygen in polytrauma and complex surgical patients.
- Test and compare dynamic respiratory impedance volume evaluation (DRIVE) to other measures and surrogates of intravascular volume monitoring in polytrauma and complex surgical patients.
- Compare time series measurement RRS StO2 and DRIVE to patient outcomes including mortality and organ failure in order to support future trials supporting their use in PFC and pRDC.

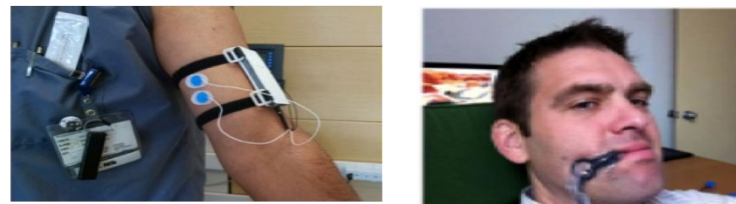
Approach

We will compare two newly developed noninvasive hemodynamic monitoring technologies to traditional hemodynamic monitoring in surgical patients for their suitability in goal directed therapy for potential future use in PFC and pRDC.

Comparing CVP, ScvO2 and IVC Ultrasound monitoring to



DRIVE and RRS StO2 monitoring for GDT in PFC



Clinical comparison of newly developed DRIVE and RRS StO2 buccal mucosa monitoring to traditional CVP, ScVO2, IVC ultrasound and other measures for potential in goal directed therapy in PFC

Timeline and Cost

Activities	CY18	CY19	CY20
Enroll 200-300 Subjects	[Green bar]		
Data comparisons to gold standard monitoring		[Green bar]	
Monitoring comparisons to outcomes and interventions		[Green bar]	
Estimated Budget (\$K)	\$967,249	\$1,003,281	\$1,027,679

Goals/Milestones

CY18 Goal –

- ✓ Patient recruitment
- ✓ Comparison of new tools to standard measures

CY19 Goals –

- ✓ Additional patient recruitment
- ✓ Comparison of new tools to standard measures
- ✓ Begin comparisons of monitoring to outcomes and interventions

CY20 Goal – Production readiness

- ✓ Complete patient enrollment
- ✓ Complete data comparisons of monitors and comparisons to outcomes and interventions
- ✓ Work with industry partners on commercialization, trialing and scaling strategies

Comments/Challenges/Issues/Concerns. None.

Budget Expenditure to Date: \$1,754,873

NOVEL MONITORING OF TISSUE MICROVASCULATURE OXYGENATION USING RESONANCE RAMAN SPECTROSCOPY

Amanda J. Pennington, MS^{1,2}, Mohamad Hakam Tiba, MD, MS^{1,2}, Brandon C. Cummings, BS^{1,2}, Varisha Essani^{1,2}, Claire Roberge^{1,2}, Kyle Gunnerson, MD^{1,2}, Kevin R. Ward, MD^{1,2}

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

² Michigan Center for Integrative Research in Critical Care (MCIRCC), University of Michigan, Ann Arbor, Michigan.

Introduction: The ability to monitor the critically ill patient noninvasively remains a challenge especially in settings outside the intensive care unit. Measurements of oxygenation at the level of a specific tissue might offer sensitive information to guide therapeutic modalities and decision making in the management of the critically ill. We examined the ability of Resonance Raman Spectroscopy (RRS) to monitor tissue hemoglobin oxygenation (StO₂) noninvasively in a post-surgery setting and compared its performance with conventional central venous hemoglobin oxygen saturation (ScvO₂). RRS is a novel optical technique capable of providing information on the vibrational and electronic properties of compounds, including oxy- and deoxyhemoglobin. RRS can be used to interrogate tissue hemoglobin levels (StO₂) by producing signals heavily dominated by venous blood. Thus, the resulting aggregate StO₂ is reflective of the post-extraction compartment of the tissue similar to ScvO₂.

Methods: Post-surgery patients who had a central venous catheter in place were consented and recruited. StO₂ measurements were obtained using RRS with a sensor placed on the buccal mucosa inside the mouth. Simultaneous blood samples were drawn from the indwelling central catheter. An algorithm that utilizes the spectral peaks was used to calculate the StO₂ which were compared to ScvO₂ measured by co-oximetry (gold standard).

Results: Eighteen patients with a mean(SD) age 64(15) years old were consented and recruited. Mean(SD) StO₂ and ScvO₂ were 64(11.1)% and 67(8.0)% respectively ($r=0.57$, $p<0.013$). A paired t-test showed no significant difference between the StO₂ and ScvO₂ with a mean(SD) difference of 4(10.3)% ($95\%CI = [-1.3, 9]$, $p = 0.13$). Receiver Operator Characteristic (ROC) curves for predicting ScvO₂ at thresholds of ScvO₂ above and below 65, and 70% demonstrated the high predictive power of StO₂ with areas under the curve of 0.74 and 0.83 respectively. Improvements to the clip are currently underway to allow the sensor to penetrate deeper into the tissue of the buccal mucosa.

Conclusions: RSS is showing promise as a non-invasive alternative to ScvO₂. StO₂ measurements taken using RSS are highly correlated with ScvO₂, which is an important measure of tissue oxygenation. Because of its non-invasive nature, RSS 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.



Novel Monitoring of Tissue Microvasculature Oxygenation Using Resonance Raman Spectroscopy

Amanda Pennington, MS^{1,2}; Hakam Tiba, MD, MS^{1,2}; Brandon Cummings^{1,2}; Varisha Essani^{1,2}; Abdelrahman Awad, MD^{1,2}; Claire Roberge^{1,2}; Kyle Gunnerson, MD^{1,2}; Kevin Ward, MD^{1,2}

¹ Department of Emergency Medicine, ²Michigan Center for Integrative Research in Critical Care (MCIRCC) University of Michigan, Ann Arbor, MI

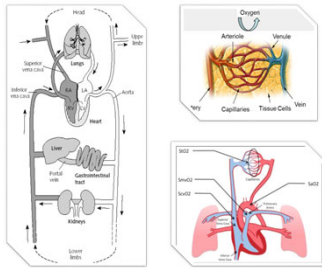


INTRODUCTION

- Using non-invasive methods to monitor tissue oxygenation status would be advantageous in the management of the critically ill patient.
 - *Early diagnosis*
 - *Accelerated decision making process*
 - *Enhanced management plan*
 - *Reduces oxygen debt and better utilization of treatment resources.*
- Various spectroscopy techniques has been investigated and used to monitor tissue hemoglobin oxygen saturation (StO₂)
 - Early diagnosis
 - Disorders associated with decreases in tissue perfusion and oxygenation

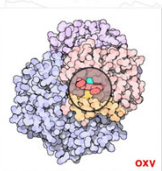
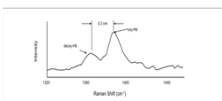
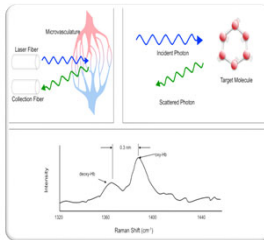
Principals of Tissue Monitoring

- 70-80% of the blood in any volume of tissue resides in the venous compartment.
- 20-30% residing in the arteriole and capillary.
- Spectroscopic techniques produce hemoglobin signals that are heavily dominated by venous blood.
- StO₂ is thus reflective of the post-extraction compartment similar to ScvO₂
- The choice of a tissue site that will change its oxygenation characteristics in a similar time domain as a central measure of oxygenation.



Principals Of Resonance Raman Spectroscopy (RRS)

- RRS provides information on the unique vibrational and electronic properties of compounds.
- Based on the well-defined and narrow Resonance Raman spectral fingerprint of oxy and deoxy-hemoglobin and direct measurement of hemoglobin concentration in the illuminated volume.
- Single wavelength (405nm) and short penetration depth (1-2mm).
- Spectral peaks are sharp and 0.3nm apart.
- Interfering chemicals such as melanin, tissue composition or myoglobin will not affect the signal.



AIM

Use Resonance Raman Spectroscopy (RRS) to evaluate StO₂ as a non-invasive and viable alternative and surrogate measure to central venous oxygen saturation (ScvO₂)

METHODS

- This study is approved for human subjects research by the University of Michigan IRB HUM00067675
- Critically ill patients with a central venous catheter in place were recruited from the cardiovascular ICU as well as the catheterization lab.
- Informed consent was obtained prior to any testing.
- The RRS sensor was placed on the buccal mucosa and StO₂ measurements were obtained and collected for 15 minutes.
- At the conclusion of testing, a blood sample was collected from the distal port of the central catheter and the RRS measurement at that time was recorded.
- An algorithm that utilizes the spectral peaks was used in GraphPad Prism8 statistical software to calculate the StO₂ which were compared to ScvO₂.



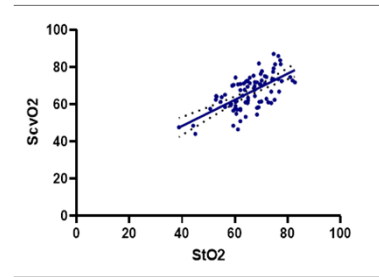
RESULTS

Eighty six patients
 • Average (SD) age of 62(14.5) y/o. Average (SD) Weight 83(35) kg
 All StO₂ values are multiplied by 0.9
 Table 1 lists descriptive statistics for both StO₂ and ScvO₂

	StO ₂	ScvO ₂
Minimum	38.8	44.2
25% Percentile	60.38	60.68
Median	65	66.9
75% Percentile	71.55	72.83
Maximum	82.8	87.2
Range	44	43
Mean	65.6	66.44
Std. Deviation	8.406	9.197
Std. Error of Mean	0.9064	0.9918
Lower 95% CI of mean	63.79	64.47
Upper 95% CI of mean	67.4	68.41

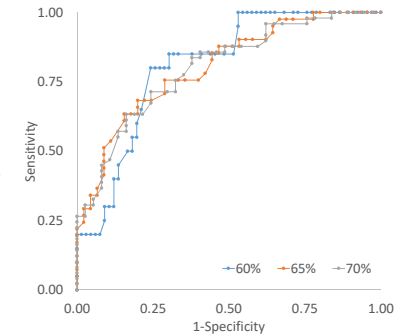
RESULTS

- The scatter plot demonstrates the significant correlation between StO₂ and ScvO₂. r = 0.643, p < 0.0001



- A paired t-test showed no significant difference between StO₂ and ScvO₂. Average(SD) difference of -0.84(7.4)% (95%CI: -2.4% - 0.5%, p=0.29)

- Receiver operating characteristic (ROC) curve for StO₂ at thresholds of ScvO₂ between 66% and 70% have demonstrated high predictive power of StO₂ with area under the curve above 0.8 (p < 0.0001).



CONCLUSIONS

- RRS is showing promise as a non-invasive alternative to ScvO₂.
- StO₂ measurements taken using RRS are highly correlated with ScvO₂, which is an important measure of tissue oxygenation.
- 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.

ACKNOWLEDGEMENT

- Supported by the Department of Defense – Combat Casualty Care grant award W81XWH-18-1-0078
- The authors would like to thank the Michigan Center for Integrative Research in Critical Care and Pendar Medical



Dear Faculty and Research Staff,

The continued health and wellbeing of our entire University of Michigan community remains paramount. In an effort to minimize the risk of contracting or spreading COVID-19 in human participant research interactions and to preserve personal protective equipment for clinical care, the university is placing temporary restrictions on human subjects research effective Saturday, March 14, and continuing through Friday, May 1. We will continue to reevaluate this timeframe.

1. All research studies that currently require direct person-person interactions, but do not offer direct therapeutic (drug and device) benefit to subjects must immediately pause new enrollment and discontinue in-person interactions unless study procedures can be modified to use alternative methods of gathering study data (e.g., telephone interviews, email, etc.). Studies involving no direct person-person interactions with participants may continue (e.g., secondary data analysis, remote or online contact, etc.).
2. Studies that involve the administration of drugs or monitoring of devices that provide therapeutic benefit to study participants may continue, but study teams should consider alternatives to having the participant be on-site for all study visits (e.g., electronic monitoring and/or data collection, as possible). Study teams also should evaluate how illness and absences, drug shortages, facility closures, or lack of required personal protective equipment may impact treatment delivery or monitoring.
3. IRB review of new studies that are not essential for managing COVID-19 circumstances may be delayed.

Principal investigators, schools, colleges and units will partner with their research staff, students and graduate student research assistants who are impacted by this pause in work to identify an appropriate plan moving forward, including any financial ramifications this may pose. Faculty principal investigators should actively work to communicate this change to the teams.

Thank you again for your continued support of the U-M research enterprise. I encourage you to visit our [COVID-19: Research Operations at U-M page](#), which includes the latest information and resources so that our campus community can best manage their research and scholarship activities. This webpage will be updated regularly and will be the source of ongoing guidance in this evolving situation.

Sincerely,

Rebecca Cunningham, M.D.

Interim Vice President for Research

William G. Barsan Collegiate Professor of Emergency Medicine

Research Reactivation

Campus-wide Guidance

Agenda

- U-M Guidance on Research Ramp Up
- Medical School Process

Information contained within is considered PRELIMINARY and ADVISORY in nature.



Public Health Informed Research Phased Re-engagement

PRELIMINARY and ADVISORY

(final guidelines will have to align with governor's orders when issued)

Research Ramp up Subcommittee:

UMOR VPR Rebecca Cunningham

UMOR AVP Brad Orr

UMOR AVP Srijan Sen

Rackham/Provost Office Mike Solomon

RAD MED Steve Kunkel

RAD CoE Steve Ceccio

RAD LSA NS Chris Poulsen

RAD ISR Rich Gonzalez

Chief Health Officer- Preeti Malani

EHS- Danielle Sheen



Information contained within is considered PRELIMINARY and ADVISORY in nature and is not for public reference

U-M Research Reactivation Framework

Phase 0 Shelter in place, only essential and maintenance lab work occurring (current state)

Phase 1 Only research work that can be low risk with mitigation (as defined by state) can occur

(Stabilizing)

- **WHEN STATE SAYS WE CAN**

- No public interaction for work (impacts human subjects, which will stay at Phase 0 status)
- Allowed density 1 person / 144-288 sq. ft. (lab space, not total building space)
- Need to work 6 feet apart
- No gatherings of more than 10 people
- Strict disinfection of shared equipment
- No inter-regional travel (regions defined by the state)
- All work that can happen remotely required to stay remote, including lab-related activities

Phase 2

- Remote work where possible
- Social distancing still required but not as restrictive
- Modest groups gather, size ~50(?)

Phase 3 TBD – informed by Phases 1 & 2

Phase 4 Fully functional, no longer remote, large groups can gather

Information contained within is considered PRELIMINARY and ADVISORY in nature.



Stabilization Phase 1 – Status of Research Categories

1. **Laboratories/Wet Bench/Studio Research:** can open when signal given by state and central campus
2. **Office-based/Dry Research:** no change, remains remote due to public health restrictions
3. **Clinical Research (Human Subjects):** remains in Phase 0 (current state) due to state public health restrictions

Timing of Stabilization Phase 1

- Mid- to end of May (optimistically) – could be June or later
 - Goal is to be ready to act when able to do so
- Phase 1 could last for weeks to months
- Transitions between phases and what is allowable will be determined by the state based on COVID cases
 - Medical School will follow campus-wide guidance
- If not re-opened correctly, may need to return to Phase 0 (today!)
 - Risk clinical research & fall semester if not done thoughtfully and well

Phase 1 Guidelines – Building Access

- Each building will have single point of entrance and exit
- Name and U-M ID cross checked against list of approved personnel
- Upon entering: check in, temperature check, and answer daily questions:
 - Do you have symptoms of fever (>100.4 °F), chills, cough, loss of sense of smell and/or taste, shortness of breath, sore throat?
 - Have you had household contact in the last 14 days with someone diagnosed with COVID-19?
 - Have you been maintaining the State of Michigan’s social distancing guidelines outside of work?
- Occupational Health will handle “positives” from entrance screens

Phase 1 Guidelines - Individuals Return to Lab

- Approval required from department & school to return to laboratory
- Completion of training module on safe return to work/laboratory
- Employees who are not feeling well reminded to stay home
- Individuals at high risk are not required to return to work and should be encouraged not to return (contact their doctor or Occupational Health Services)
- Occupational Health will perform initial triage for positive question screens and employees who present symptoms during work day
 - Established process for employee testing (off-site testing or UHS)
- Undergraduates and visiting researchers are not permitted in labs in Phase 1

Phase 1 Guidelines – Laboratory Workspace

- Each approved employee will be provided a cloth mask (or mask from home) and instructions on cleaning and maintenance
- Each laboratory should plan to return at fractional work force & will:
 - Provide a laboratory schedule & safety/hygiene plan that must be closely adhered to
 - Minimize people in each room — 1 person per 144 sq. ft. and at least 6-foot social distancing (rooms \leq 288 sq. ft. limited to 1 person only)
 - Limit interactions with others outside of the lab
- All non-laboratory related activities (e.g., lab meetings, journal club, supervisor meeting, etc.) are required to continue remotely
- Office and dry lab research will continue remotely
- ULAM & Medical School cores will be at reduced capacity — seek consultation prior to planning experiments

Information contained within is considered PRELIMINARY and ADVISORY in nature.



Phase 1 – ULAM Guidance

- ULAM will remain on “split-shift” staffing model (reducing available staff)
- Support for full volume of animal-related work is not feasible
 - Studies may only be performed on animals already in house
 - New orders for COVID-19-specific studies only
 - Breeding colonies must remain in maintenance mode (no new studies initiated on animals produced by breeding colonies)
 - Exceptions require Executive Vice Dean for Research approval
- Procurement of all non-critical supplies will be temporarily on hold
 - Ensure adequate supplies of anesthetics, analgesics, or any other pharmaceuticals that are not expired prior to initiating experiments
- Careful coordination of animal-use rooms will be required to ensure adherence to mandated social distancing and space density directives
- In-person training classes and workshops offered through the ULAM Training Core have been canceled until further notice

Information contained within is considered PRELIMINARY and ADVISORY in nature.



Phase 1 Guidelines – Monitoring & Continuous Improvement

- Sign on each room with maximum & approved occupancies
- Departments will need to help ensure compliance
- Environment, Health & Safety (EHS) will perform walkthroughs to help maintain public health standards so labs can remain open
- Personnel can report laboratory safety issues, including personnel who are ill or not following safety protocols, via the U-M compliance hotline
- Medical School Office of Research will monitor building access and reports of non-compliance
- Non-compliance may result in termination of building/laboratory access

Medical School Process



Process to Fulfill U-M Requirements

- Phased building openings & staggered start times
- Faculty complete Space Usage Request Form & safety plan
- Research personnel (faculty & staff) complete training module
- Department critical review and oversight role
 - Manage expectations of faculty
 - Pre-populate form, especially person per sq. ft. lab occupancy allowed
 - Approve safe laboratory schedule/plan
 - Confirm personnel access list
 - Prioritize access/research capacity issues, as needed

Process to Fulfill U-M Requirements

- Medical School review and approval
 - Verify person per sq. ft. lab occupancy and personnel access list
 - Confirm building maximum capacity; resolve as needed
 - Confirm safe laboratory schedule/plan submitted
 - Confirm training module completed
 - Provide PI and department with laboratory signs
 - Submit approved personnel list to facilities

Timing of Work Ahead

Week of May 4

- Develop school-level Ramp Up Plan that is compliant with UMOR guidelines and principles (DAC, Associate Chairs, CDAs, Facilities)
- OVPR communications at high level to broad research community (around May 7)

Week of May 11

- Medical School Office of Research provides instructions and forms to Departments
- School communicates to faculty on process for reactivation of laboratories
- Departments engage faculty to complete information
- Review of information

Mid May – on

- Be prepared to begin to open upon state and campus approval

Phase 1 Key Takeaways

- Must think differently – likely running at 30-40% research capacity.
 - Investigators:
 - ❖ Prioritize research projects/experiments (extremely rare case that the entire lab will return to work in Phase 1)
 - ❖ May need to change out some personnel access during Phase 1 depending on projects/experiments
 - Departments & School:
 - ❖ Must be rigorous in evaluating Space Usage Request Forms
 - ❖ Likely will have to make tough choices about labs & research
 - ❖ Active enforcement of guidelines & remediation, as needed
- Must act judiciously and prudently to increase likelihood of moving to Phase 2 and beyond.
- Research will look and feel different for months, so we will need to be patient.

How can we help?

- What will you need from us?
- How can we emerge even stronger from this?



Research Re-engagement

The University of Michigan, with guidance from public health experts, has developed guidelines for how to safely re-engage limited research activity across its three campuses when permissible by the State of Michigan.

The first re-engagement phase will apply only to individuals involved in experimental laboratory research and studio-based research, along with some locally based, non-human subjects field research. Office and dry lab research, including all lab meetings and supervisor meetings, will continue to occur remotely and will be in violation of the guidelines below if they occur in labs.

U-M is actively preparing, but will not ramp up research until the State authorizes this activity. It is important to note that research and scholarship that can occur remotely will continue to do so.

- Buildings that are not open for laboratory/studio-based research remain restricted to critical approved personnel only.*
- Buildings that will open to laboratory/studio-based research will not yet be open to other activities beyond the approved research and critical approved activities in the buildings.*

The COVID-19 pandemic has impacted nearly every facet of the U-M research enterprise, and so the university plans to implement a phased approach to ramp up research activity. This approach aims to protect the health and safety of the U-M community and the broader public, while following applicable State and other guidelines.

Accordingly, please refer to the important re-engagement guidelines below to prepare U-M to be in compliance with applicable State and other guidelines to reopen. The planning you do now will support the long-term success of the U-M research enterprise.

RESEARCH RE-ENGAGEMENT REQUESTS

Research leadership developed a sample Laboratory Space Usage Request Form and a sample Field Research Request Form to aid U-M schools/colleges/units in their research re-engagement planning. Please refer to the specific safety plan developed by your school/college/unit for more information as it relates to protocols and procedures for research re-engagement.

Sample Laboratory Space Usage Request Form

Sample Field Research Request Form

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These guidelines do not supersede any more stringent or heightened lab or other safety requirements – including any related to the use of specific personal protective equipment (PPE) – applicable to a given research project, which must continue to be followed at all times.

The information below applies to all buildings with allowable re-engaged research activities, and all employees and staff of the university entering and exiting those buildings, regardless of whether they are involved with re-engaged research activities.

LABORATORY AND STUDIO RESEARCH

- **Guiding principles for ramping up laboratory and studio research**

1. The safety of the workforce and everyone associated with its return, including members of surrounding communities, is the leading priority.
2. Planning recognizes the diversity of types of research across campus is a strength and critical to our research enterprise and mission.
3. Planning recognizes that for safety and feasibility, all laboratory and studio research will not reopen at the same time and we will need a stepped approach to reopening.
4. A required component of planning will be reversibility, in case a recurrence of COVID-19 forces another contraction of research activity.
5. Laboratories, including shared facilities, must carefully prepare equipment and materials for occupancy after a long period of dormancy and may require additional time or planning.
6. Planning will be as transparent as possible, to permit individual faculty to make plans that conserve their time and effort.
7. Graduate students may not be compelled to conduct research activities on campus as a condition of assistantship or postdoctoral research associate support, while public health orders governing individual activity remain in effect.
8. OVPR administrative review of school/college/unit staging plans in concurrence with their approvals of PI safety plans will occur to ensure coordination, effectiveness and compliance in health and safety.

- **Guidelines for entrance into any U-M laboratory building with research operations**

1. For all non-emergency situations, all buildings will have a wheelchair-accessible single point for entrance and exit, which everyone will be required to use.
2. Prior to entering

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1. Your name and U-M ID will be verified against a list of approved labs and names of allowed personnel; and
3. You will be required to indicate which room you are working in and participate in a screening that asks:
 1. Do you have symptoms of: fever (>100.4 °F), chills, cough, loss of sense of smell and/or taste, shortness of breath, sore throat, diarrhea?
 2. Have you had household contact in the last 14 days with someone diagnosed with COVID-19?
 3. Have you been maintaining the State of Michigan's social distancing guidelines outside of work?
 4. Have you travelled internationally or outside of Michigan in the last 14 days, excluding commuting from a home location outside of Michigan?
4. If your answers to the screening disallow you from being present at work (pursuant to an applicable Executive Order, University policy, or otherwise) or you are not listed among the approved personnel, you will not be allowed access into the building.
5. Any employee who has a positive intake screen will be referred for follow-up with the Occupational Health Services Hotline. (734-764-8021).
 1. Occupational Health Services (OHS) will conduct the initial triage for employees with a positive screen
 2. OHS employees are trained to determine the need for a COVID-19 test, etc.
 3. There is a process in place for employee testing, either with off-site testing or at University Health Service.
 4. Employees will not be allowed to work until cleared by OHS.

- Guidelines for individuals returning to work

1. Approval is required from School/College/Unit to re-engage in laboratory work.
2. Before approved individuals may return to work, they must complete a training module that outlines practices for safely returning to lab work.
3. Employees who are not feeling well are required to stay home. Please refer to the following video from the U-M Chief Health Officer.
4. According to the U-M Chief Health Officer, individuals who are at high risk for complications of COVID-19 are not required to return to work. If an employee has a concern that they may be at high risk, they should contact their own doctor or Occupational Health Services. Some examples of high risk factors are:
 1. Age greater than 70,
 2. Persons with primary or acquired immunodeficiency,
 3. Persons on anti-rejection therapy following solid organ transplant or bone marrow transplant,

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4. Persons on biologic therapeutic agents, such as tumor necrosis factor inhibitors,
 5. Persons with malignancy and ongoing or recent chemotherapy, or
 6. Persons receiving system immunosuppressive therapy, including corticosteroids equivalent to 20 mg/day or prednisone for >2 weeks.
5. No undergraduate students, visitors, or visiting researchers are permitted in laboratories (regardless of whether the individual has an Mcard).
6. Graduate Student lab engagement should follow **Rackham Guidance**. Specifically the manner in which graduate students return to research in the laboratory or field should be mutually agreed upon by faculty mentor/PI and the graduate student. This agreement should be part of the work plans that faculty develop with their graduate students as part of the ramp up. Faculty should create pathways for graduate students to return to research that address both the priorities of the student and the priorities of the PIs research projects. If not fully aligned, the following factors can potentially provide flexibility: (1) Engage the research group as a team to complete high-priority lab tasks in ways that accommodate the individual situations of lab members; (2) Incorporate variable levels of on-campus (e.g. lab work) and remote (e.g. data analysis, experimental design) research activities into the work plans of graduate students during the initial ramp up in ways that accommodate their individual situations; (3) as needed, the student's department or program can work with the faculty and student to develop alternative methods for academic and research progress.
1. In addition, the Graduate student's department or academic program should review faculty/student work plans to ensure safety and equity. In the event that the manner in which a graduate student returns to laboratory or field research cannot be mutually agreed upon by the faculty member and student, the department or academic program should assist in developing such an agreement. The graduate student, faculty member, and department can also call upon available campus resources, including those in the student's school or college, the Rackham Resolution Office, or the Dean of Students Office of Conflict Resolution.
 2. Confidentiality of a graduate student's individual circumstances should be maintained by the faculty mentor.

- Guidelines for preparing the workspace and operating a safe laboratory/studio

1. Each laboratory/studio must provide all of the following items before reopening: safe laboratory schedule/plan, individual duty list, and occupancy list that, at all times, maximizes employee spacing and complies with social distancing and all relevant PPE. The plan must be approved by your school/college/unit. All of the described procedures must be followed and adhered to:
 1. This safe laboratory plan/schedule should minimize the number of people in each laboratory room and all associated spaces (for example, break rooms) at any one time. This **example form** will be used by several schools to guide obtaining and approvals for this information. Approvals of safety plans will be given by each school's research leadership, with concurrence from OVPR. Please follow guidance from your school or unit on the form and process for obtaining approval to return to the lab.

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2. Distribute a list of duties to be performed by personnel, indicating the location and designated time of day for such duties to be completed.
 3. Develop a means of signifying who is present in the lab/studio space at any given time, preferably through an online sign-in tool to minimize touching items such as a physical sign-in sheet, or other mechanism of controlling the number of people in the lab at the same time.
 4. Stagger break times to minimize contact between people in rooms. Conference rooms and cafeterias will be closed off and cannot not be used. Ensure eating and drinking is not occurring in labs.
 5. Post a map inside the lab/studio entryway with maximum room/bay occupancy to maintain social distancing.
 6. Each lab/studio room can only accommodate a maximum of 1 person per 144 square feet. If you cannot maintain at least 6 feet of social distance, or the person per square feet requirement, then the schedule will need to be revised and/or reconfigured to achieve these.
 7. Small, narrow laboratories/facilities smaller than 288 square feet can only accommodate one person at a time.
 8. Lab Benches are not 6 feet across, thus plan for work to occur only on one side of the lab bench in most instances.
 9. Note that, depending on the research area/experiment, safety guidelines for the specific research project may require more than one person to be present in the room at any one time. Even in this case, the individuals present must maintain a 6-foot separation at all times. If the appropriate physical separation cannot be maintained, this work cannot be started.
 10. Move equipment to create at least 6 feet between users.
 11. Tape will be used to mark out 6-foot spaces for high traffic areas or bottlenecks.
 12. PI safety plans should include attestation that buildings must not be used for social gatherings or group meetings, that conference rooms and other group spaces will be off limits,
2. Masks
1. Employees authorized to return to lab work must be provided a cloth face covering and instructions on cleaning and maintenance. Refer to EHS **Face Covering Usage for COVID-19**
 2. A new mask will not be provided daily, so you must retain this mask and bring it with you daily, after complying with all relevant and applicable cleaning and care requirements. Refer to EHS **Face Covering Usage for COVID-19**.
3. Create a safe space and maintain at least 6 feet between researchers at all times.

1. Always wear the cloth face covering provided to you unless your research procedures dictate heightened PPE requirements. When not wearing the safety PPE required for your laboratory work, reapply your provided face covering. Proper hand hygiene before and after using any face covering is critical.
2. Wash your hands with soap upon entering and before leaving the lab/studio, and wash them after touching shared accessory devices like phones (use speaker phone if possible).
3. Wear eye protection when there is a potential for splash or splatter to the face, or when surface contact is a possibility, e.g. microscopy work.
4. Minimize shared items (pens, notebooks, frequently used reagent bottles, etc.). As much as possible, each person should have their own.
5. All principal investigators must formally assign a daily in-lab sanitation role which includes daily decontamination of lab-space procedures including the cleaning of all work benches, door handles & lock keypads, keyboards/mice/desks for shared equipment computers, telephones, printer, cameras, microscopes, control panels, etc.
6. If it can be done safely, use paper towels or Kimwipes when handling common laboratory items, laboratory equipment and cabinet handles.
7. Wipe or spray door handles with 70% ethanol (or other EPA-registered disinfectant) after use. See **EHS guidelines**.
8. Lab coats, gowns or aprons are recommended to protect personal clothing. Follow **EHS guidelines** for cleaning and disinfecting hard, non-porous surfaces.
9. Remove lab coats and gloves when leaving the lab.
10. Consider footwear and clothing as a possible transmission source. You should have a pair of shoes that you use for external use (including working in a laboratory/facility) that you do not wear into your place of residence. Such shoes could be left just inside the door of your place of residence.
11. Be sure to disinfect surfaces, such as tables and chairs, before and after using such facilities.
 1. Cups, mugs, plates, and silverware must be washed with soap before and after use.
 2. Wash your hands after using a break room.
 3. Food and drink are not allowed in labs. (link coming here)
4. Create a plan for shared equipment. All shared equipment must be disinfected before and after each use.

1. Wear disposable gloves when cleaning and disinfecting equipment. Discard (where supplies allow) or disinfect gloves after each use with 70% ethanol or sanitizer.
 2. Special care should be taken to disinfect equipment that makes direct physical contact with skin, including eyepieces for microscopes, touch pads, etc.
 3. Use disposable tissues, Kimwipes, etc. to touch surfaces that cannot be disinfected, and/or when gloves are not available.
5. Create a plan for interacting with individuals outside the lab
1. Contact with other labs should be made via phone or electronic means, except in cases of extreme emergency.
 2. Those also working in the patient care setting should change clothes prior to lab entry.
 3. Transfer of items should be arranged by leaving them in the hallway or other designated area for a no-contact approach, as opposed to handing them over in person. The timing of these transfers should be closely coordinated to ensure the safety of all involved, as well as to eliminate the potential for lost or otherwise unattended items in these settings.
 4. Research studies must be carefully and thoughtfully planned given the likelihood that support services, such as animal facilities/ULAM, central stores, core laboratories, etc. will be operating at reduced levels.
 5. Use of shared facilities and other labs' equipment must be pre-arranged in order to avoid accidental contact. Be sure that all users understand lab sign-in procedures.
 6. Use precautions when entering a restroom, shared use facility, or other common areas. Call out to assess occupancy or create an "occupied" door sign. Use a disposable towel or Kimwipe to touch door handles and faucets, and wash your hands upon entering and leaving.
 7. Develop a safety protocol plan for deliveries.
6. Working safely with animals in the vivarium
1. The Unit for Laboratory Animal Medicine (ULAM) will maintain mechanisms for providing continued daily care to all animals housed on campus in the event of a natural disaster or other events that may interrupt normal business, including the COVID-19 situation. This includes continued veterinary medical care; assessment of animal health and well-being; provision of food, water, and clean cages; and maintenance of appropriate environmental conditions. Our top priority is to continue the provision of critical life support services that ensure animal welfare.
 2. IACUC approval processes remain intact and any changes to research protocols must be submitted to IACUC for review and approval prior to implementation, pursuant to normal processes.

3. ULAM will remain in “split-shift” mode, effectively reducing available staff. This augments the need to limit studies to those that could be relatively easily ramped-back-down should the need arise. Full ULAM staffing is not possible during this phase of re-engagement of laboratory work and thus support for a full volume of animal-related work cannot be expected.
 1. Studies may only be performed on animals already in-house; new animal orders will only be accepted for COVID-19-specific studies. Exceptions must be approved by the pertinent Research Associate Dean.
 2. Breeding colonies must remain on maintenance-mode only; no new studies may be initiated on animals produced by breeding colonies.
 3. Additional limits may be required based on ULAM staffing levels and/or as needed to maintain social distancing.
4. Subject to the restrictions and exceptions outlined above, researchers must generally consider animals already housed in the vivaria when planning for potential re-engagement in animal-related experiments. ULAM can assist in verifying the number and locations of animals assigned to a researcher’s protocol(s).
5. The ULAM Business Office will continue placing orders for the critical supplies needed to ensure animal health and well-being (e.g., feed, bedding, critical care veterinary supplies), but procurement of all non-critical supplies will be temporarily placed on hold. If your animal-related experiments require the use of anesthetics, analgesics or any other pharmaceuticals, ensure you have adequate supplies that are not expired prior to initiating those experiments.
6. Space within ULAM and animal-use rooms must be carefully coordinated to ensure mandated social distancing and space density directives. Animal holding and procedures rooms will be identified with the maximum allowable occupants at a given time. ULAM will post times needed for daily animal husbandry and any veterinary clinical care activities; initially, this will consist of morning vs. afternoon routines. Research interaction with animals must be scheduled to ensure mandated social distancing and space density directives. This may require interlaboratory coordination in rooms housing/used by more than one PI. Sign-up sheets for scheduling shared procedure rooms will be provided to allow for scheduling in advance. The sanitation procedures needed between users will also be provided.
7. All in-person training classes and workshops offered through the ULAM Training Core have been canceled until further notice. Animal-based research may only be performed by staff that have already completed all in-person training, including laboratory-specific training.

- Creating a culture and opportunity for continuous improvement of lab and health safety

1. Frequent communication from OVPR and EHS regarding lab safety, research re-engagement and important public health updates.
2. EHS will perform walkthroughs to help maintain public health standards so that labs can remain open.

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3. Report lab safety issues, including personnel who are ill or not following safety protocols, via the **U-M compliance hotline website**. You can also report concerns by calling 866-990-0111 or contacting EHS at 734-647-1143 or emailing **EHS**.
4. OVPR and Occupational Health Services will track aggregate data on COVID-19 illness in labs with weekly reports.

FIELD RESEARCH (LOCALLY BASED, NON-HUMAN SUBJECTS)

- Guiding principles for ramping up field research

1. The safety of the workforce and everyone associated with its return, including members of surrounding communities, is the leading priority.
2. Planning will be as transparent as possible to permit individual faculty to make plans that conserve their time and effort.
3. Graduate students may not be compelled to conduct field research activities as a condition of assistantship or postdoctoral research associate support, while public health orders governing individual activity remain in effect.
4. OVPR administrative review of school/college/unit field research plans in concurrence with their approvals of PI safety plans will occur to ensure coordination, effectiveness and compliance in health and safety.

+ Guidelines for performing field research

+ Guidelines for individuals returning to work




+ Guidelines for preparing the field research operation

+ Travel procedure

+ Creating a culture and opportunity for continuous improvement of field and health safety

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References and Resources

-  [Laboratory Space Usage Request Form \(Sample\)](#)
-  [Field Research Request Form \(Sample\)](#)
-  [Environment, Health & Safety: COVID-19 Resources](#)

Posted on: Thursday, May 7, 2020 - 16:56



CONTACT US

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