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14. ABSTRACT The main purpose is to develop the prototype of a portable diffuse correlation spectroscopy (DCS) and near infrared spectroscopy (NIRS) based optical system with multiple capabilities to monitor: cerebral and somatic oximetry; cerebral and somatic blood flow and volume; and cerebral edema. The proposed system will include multi-distance multi-wavelength NIRS-based sensors and DCS-based optical fibers. The proof of concept and system test studies include design and study of phantom and animal models, tests in hemorrhage assessment during pre-shock, shock, after fluid resuscitation; and during hypoxia and edema development. Final proof of concept study will be conducted using a real-life clinical scenario with adult pig model (uncontrolled hemorrhagic shock). A fully operational DCS optical system with all the components including the sensor array, data acquisition box and software was developed in Year 1. The novel head phantoms and dynamic microvasculature model (mimicking adult human head with extracerebral layers) were also designed and implemented to model varying cerebral blood volume and cerebral blood flows. Animal models and test plans are also developed for graded hemorrhage. The data collection with intralipids and blood is completed, and the results validate that the prototype system is capable of measuring microvascular blood flow rate, volume and oxygenation changes.					
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1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The ability to combine local microcirculatory blood flow measures (which is the critical physiological biomarker for various injuries, in particular, hemorrhagic shock) and local tissue oxygen saturation via hemoglobin oxygenation and deoxygenation lends itself to an advanced approach and accelerated medical device development, specifically for a point-of-care monitoring in prolonged field care. The main purpose is to develop the prototype of a portable diffuse correlation spectroscopy (DCS) and near infrared spectroscopy (NIRS) based optical system with multiple capabilities to monitor: cerebral and somatic oximetry; cerebral and somatic blood flow and volume; and cerebral edema. The proof of concept and system test studies include design and study of dynamic phantom models mimicking brain tissue and animal models for the tests in hemorrhage assessment during pre-shock, shock, after fluid resuscitation as well as during hypoxia and edema development. Final proof of concept study will be conducted using a real-life clinical scenario with adult pig model for the uncontrolled hemorrhagic shock.

2. KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

Prolonged field care, diffuse correlation spectroscopy, DCS, near infrared spectroscopy, NIRS, TBI, hemorrhagic shock, local tissue oxygenation, blood flow index.

3. ACCOMPLISHMENTS: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Major Goals & SOW Tasks	Timeline (Month)	Progress
Aim 1 - Develop and test the prototype of the integrated diffuse correlation spectroscopy (DCS) - near infrared spectroscopy (NIRS) DCS-NIRS system		
Major Task 1. Develop & Test Prototype	<u>1-12 Month</u>	<u>In Progress</u>
Subtask 1.1: Develop the sensors and control box unit of the DCS system.	1-3 Month	100% (Complete)
Subtask 1.2: Re-design and develop an oximetry/edema board (NIRS system) by implementing new digital lock-in amplifiers.	2-6 Month	100% (Complete)

Subtask 1.3: Integrate DCS hardware components into NIRS system.	3-12 Month	100% (Complete)
Subtask 1.4: Perform initial prototype testing with phantoms, including but not limited to: <i>a. initial system tests on linearity, drift, depth of penetration, and noise analysis</i> <i>b. device performance evaluation in terms of repeatability and accuracy under hypoxia, ischemia, varying blood flow and edema development conditions.</i>	6-12 Month	100% (Complete) <i>a. 100% (Complete)</i> <i>b. 100% (Complete)</i>
Aim 2 - Perform animal tests for feasibility and validation		
Major Task 2. Test prototype in piglet model	<u>1-15 Month</u>	<u>In Progress</u>
Subtask 2.1 Prepare and submit the research protocol with animals for the review and approvals by IACUC and ACURO.	1-6 Month	100% (Complete)
Subtask 2.2 Test prototype in piglet model of graded hemorrhage: <i>a. Measure physiological data, including but not limited to heart rate (HR), blood pressure (BP), pulse oximetry; and DCS-NIRS somatic and cerebral signals for the tissue oximetry, blood flow and blood volume.</i> <i>b. Analyze physiological data and DCS-NIRS signal synchrony in response to change in the phase of hemorrhagic shock.</i>	9-15 Month	100% (Complete) <i>a. 100% (Complete)</i> <i>b. 100% (Complete)</i>
Subtask 2.3 Test the prototype for changes in cerebral and somatic signals following cerebral edema development in a piglet model of	9-15 Month	25% (In progress)

<p>hypoxia-induced cerebral edema:</p> <p>a. <i>Measure intracranial pressure (ICP), and physiological data including but not limited to HR, BP, pulse oximetry, and DCS-NIRS signals for the tissue oximetry, blood flow, blood volume and water content.</i></p> <p>b. <i>Analyze to determine the relationship between changes in DCS-NIRS signals of cerebral and somatic tissue oxygen saturation, cerebral edema, cerebral blood flow and changes in intracranial pressure (ICP) and pulse oximetry.</i></p> <p>c. <i>Analyze physiological data and DCS-NIRS signal synchrony in response to edema development.</i></p> <p>Subtask 2.4: Modify the prototype based on the piglet model tests.</p>	12-15 Month	<p>a. 25% (In Progress)</p> <p>b. 25% (In Progress)</p> <p>c. 10% (In Progress)</p> <p>100% (Completed)</p>
Aim 3 - Perform validation tests with adult pig models mimicking real-life clinical scenario		
Major Task 3. Test prototype in adult pig model of controlled and uncontrolled hemorrhagic shock	<u>12-24 Month</u>	<u>Not Yet Initiated</u>
Subtask 3.1: Test the prototype in an adult pig model of controlled hemorrhagic shock.	12-16 Month	5% (In Progress)
Subtask 3.2: Test the prototype in an adult pig model of uncontrolled hemorrhage by liver laceration.	17-20 Month	0% (Not Yet Initiated)
Subtask 3.3: System fine-tuning and final validation analysis.	21-24 Month	0% (Not Yet Initiated)
Aim 4 - Provide technical progress reports for the findings and system prototypes and disseminate research findings.		
Major Task 4. Reporting	<u>3-24 Month</u>	<u>In Progress</u>

Subtask 4.1 Technical progress reports (Quarterly).	3-24 Month	100% (Completed)
Subtask 4.2 Annual technical report.	12 Month	100% (Completed)
Subtask 4.3 Prepare and disseminate findings by attending a DoD-sponsored meeting.	16-24 Month	10% (In progress)
Subtask 4.4 Final technical report	24 Month	0% (Not Yet Initiated)

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Before discussing all the major findings, key outcomes and significant results with pertinent data and graphs in details, a summary for major tasks, objectives and a brief discussion are provided below for Year 2.

Summary of the major activities during Year 2, objectives, and brief discussion:

1. The first major activity was to complete simultaneous DCS and NIRS measures in phantom/head models for hypoxia, ischemia, and edema development.

Objective: Primary objective for this activity was to demonstrate the ability of system, algorithms, and associated index/biomarkers in measuring changes of cerebral blood flow and oximetry in response to microvascular blockage, varying speed and Hematocrit (HCT) levels.

Discussion of stated goal: The main goal for this major activity was met during this reporting period. We demonstrated the proposed system's ability to detect changes in cerebral flow rate and local oxygenation. We applied microvascular blockage tests and used varying Hematocrit percentage values for ischemia, hypoxia and hemorrhage models. Despite delays due to material availability, these blood tests were conducted, and the results for cerebral blood flow and local oximetry changes were very significant revealing that biomarkers from the proposed system, particularly **cerebral blood flow index (BFI) can serve as a biomarker to assess the changes associated with not only different flow rates, but also different HCT levels. Reduction in HCT levels caused decreases in total blood volume (BV) and the related oxygenated hemoglobin (HbO₂) and deoxygenated hemoglobin (Hb) measures, yet flow rate changes did not result in alterations in any NIRS measures as expected.** All these major findings, key outcomes and significant results are explained below including pertinent data and graphs.

2. Following lab/phantom studies, another major activity was to kick off and conduct animal studies using piglet model of graded hemorrhage and a piglet model of hypoxia-induced cerebral edema.

Objective: Primary objective for this activity was to test and demonstrate the proposed system's ability in detecting changes with cerebral flow rate and local oxygenation during graded hemorrhage and even before and during hemorrhagic shock.

Discussion of stated goal: The main goal for this major activity was met. The results significantly support that the developed prototype system can detect changes in cerebral flow rate and local oxygenation during graded hemorrhage and even before and during hemorrhagic shock. The statistical analysis revealed significant difference between no shock versus hemorrhagic shock ($p < 0.01$). Importantly, **the results strongly support that this optical system can probe the hemodynamic status of local cerebral cortical tissue, and gain insight into the underlying changes of cerebral tissue perfusion at the microvascular level.**

Another critical accomplishment is that the sensor prototype was modified based on these piglet studies as the team had detected a major error (excessive heat and data acquisition software crash) in the system and software. All these major findings, key outcomes and significant results are explained below including pertinent data and graphs in details.

Major Activity 1 (SOW Task # 1.4). Simultaneous DCS and NIRS measures in phantom/head models for hypoxia, ischemia, and edema development:

This major task included evaluation of the DCS-NIRS system performances using hemorrhage models. We investigated and simulated another potential injury mechanism, namely acute anemia (e.g., due to blood loss or ischemia). This injury mechanism can result in changes in blood flow rate and oxygenation and lead to hypoxia [1-4]. It can also affect the biomarker estimations extracted from DCS measurements (the blood flow index – BFI values calculated by nonlinearly fitting the analytical and measured autocorrelation functions [5-9]) and the NIRS recordings (oxygenated hemoglobin – HbO₂, deoxygenated hemoglobin – Hb, total hemoglobin or blood volume – BV=HbO₂+Hb and water signals calculated by solving modified Beer-Lambert law [10]).

Study Design and Measurement Protocol: To test acute anemia, we have used the following phantom structure and experimental design. We used a previously designed and developed cube shaped container with a measurement window on one side having a circular opening covered with Mylar sheet to prepare a liquid phantom mimicking an adult human head (Figure 1a)). Appropriate mixtures of intralipid, ink and water in a total of 2500 ml liquid were used to provide the scattering and absorption coefficients of $\mu_s^l = 8\text{cm}^{-1}$ and $\mu_a = 0.1\text{cm}^{-1}$, respectively. Inside the phantom container, we placed microvasculature model (thin transparent tube bent and arranged on a circular support made of iron wire designed and developed for this project) at 12mm depth from the measurement window.

Both DCS and NIRS sensors (*see Appendix A for the achievement and improvement of the DCS-NIRS simultaneous data acquisition*) are placed on the outside of the measurement window of the head phantom and simultaneously collected data from the phantom during the experimental protocols (Figure 1(b)). Note that we have used the source detector separations (SDS) in the DCS sensor to 10, 18, 25, 30 mm distances to allow different depths of penetration into the tissue. The SDS in the NIRS sensor are 25 and 36 mm.

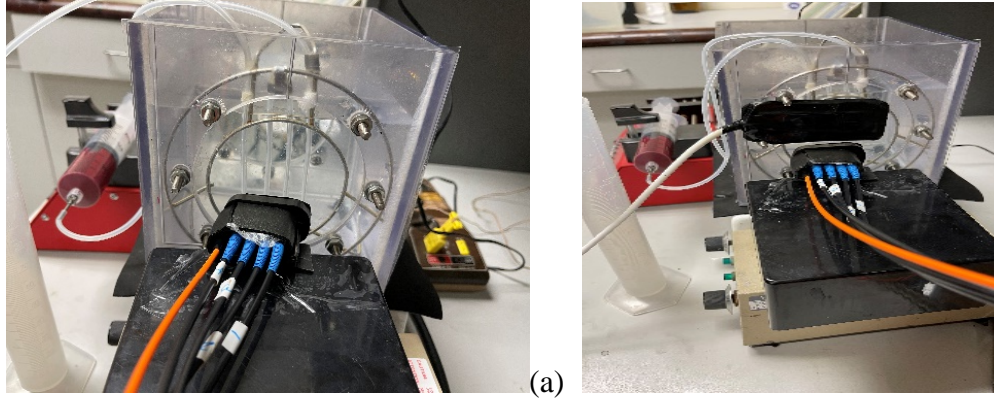


Figure 1. (a) Phantom model with its measurement window and microvasculature structure; (b) DCS and NIRS sensors placed on the phantom with electronic syringe pump.

Acute anemia can occur due to hemorrhage where the number of red blood cells (and their subsequent oxygen-carrying capacity) can become insufficient to meet the body's physiological needs, resulting in low oxygen saturation and ischemia. For anemia tests, we prepared and used three blood samples of different hematocrit (HCT) levels in the microvasculature model obtained by diluting whole blood with phosphate buffered saline to achieve hematocrit levels ranging from 20%, 30 % and normal levels of 40% in increments of 10%. Simultaneous DCS and NIRS measurements are collected using the blood samples at each of the 3 HCT levels while they are flowing within the microvasculature model either at a rate of 100 ml/hr speed (adjusted using an electronic syringe) or not flowing, i.e., 0 ml/hr speed. We evaluated the effects of different HCT levels in the estimation of DCS and NIRS parameters at different flow rates and SDS.

Results and Key Findings: The simultaneous DCS and NIRS results are reported here for anemia tests. In Figure 2 reveals estimated BF_I for all SDS and measurement frames, respectively. Six consecutive intervals in these plots separated by vertical dashed lines represent the periods for the blood samples flowing at 0 and 100 ml/hr flow rates consecutively for 20%, 30% and 40% hematocrit (HCT) levels used inside the microvasculature model.

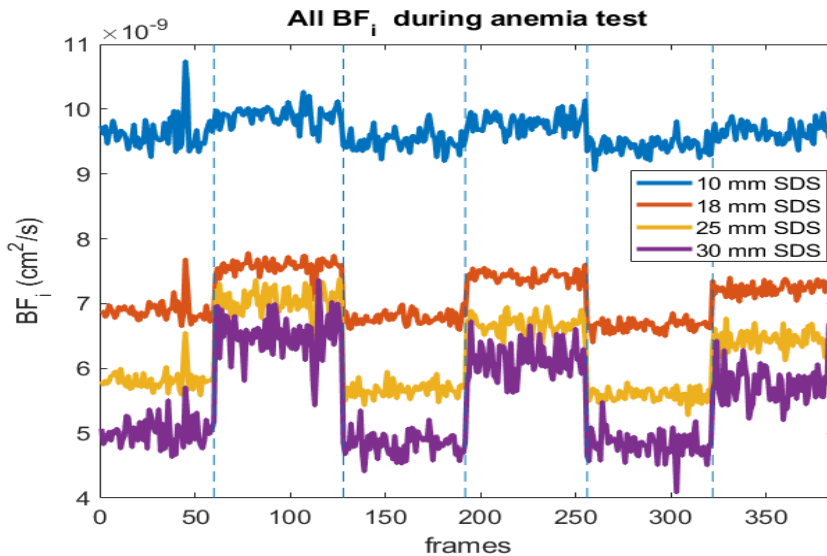


Figure 2. Estimated BF_I values in all frames of DCS data throughout the anemia test where flow rate is changed from 0 to 100 mL/hr within each of the HCT levels of 20%, 30% and 40% represented by the vertical dashed lines for detectors at SDS=10, 18, 25 and 33 mm.

The observations and critical results are:

- i. When the flow rate increased in each HCT level, there was an increase in **BFI** in all depths of penetrations, determined by SDS, but the SDS=10 mm: This could be due to the fact that at this SDS=10mm, the optical signals did not reach the microvasculature tube, which was located at 12 mm depth. As expected, the best resolution of flow rate changes was reached at SDS=30 mm providing the largest depth of penetration but with the compromise of increased noise levels due to the reduction of received signal/photon levels.
- ii. Within the period where the flow rate is kept constant (between each of the vertical dashed line intervals), the **BFI** did not change much as this is expected.
- iii. Another critical result is that for fixed flow rates at either 0 or 100ml/hr, there was an increase in the estimated **BFI** values as the HCT levels decreased. These increases can be related to the change in optical properties, such as scattering of the diluted blood. As provided in our annual report, the scattering titration test results have shown that when scattering decreased the estimated **BFI** had increased (Annual Report, Figure 7). Hence, the results here suggest that the **BFI** values can serve as a biomarker to assess the changes associated with not only different flow rates, but also different HCT levels.

We also present simultaneous NIRS chromophores in terms of HbO₂, Hb, BV, and water in Figure 3 for 25 and 36 mm SDS, respectively.

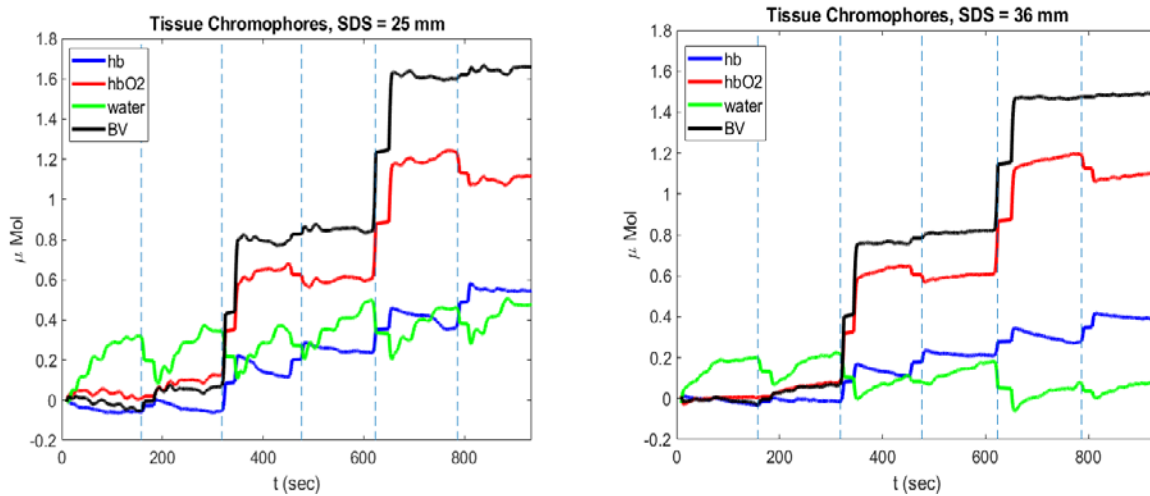


Figure 3. NIRS measurements for blood volume ('BV' in black), oxygenated hemoglobin ('hbO₂' in red) and deoxygenated hemoglobin measures ('hb' in blue) and water ('water' in green) signals measured from detectors at 25 and 36 mm SDS during different HCT values.

The observations and critical results for the NIRS are:

- i. The flow rate changes did not result in alterations in any NIRS measures as expected.
- ii. Reduction in HCT levels caused reductions in blood volume and the related oxygenated hemoglobin and deoxygenated hemoglobin measures, accordingly as expected.

Further analyses include:

- i. Descriptive statistical values (mean± standard deviation) of **BFI** values, measured by DCS, and blood volume values measured via NIRS at different SDS, flow rates and HCT levels are provided in Tables 1 and 2, respectively.

- ii. We conducted a 3-way ANOVA analysis for the main effects including all the interactions between HCT levels, flow rates and SDS factors to evaluate whether the observed differences in the estimated **BFI** values are statistically significant. The results (F, p values) are summarized in Table 3.
- a. The main effects across all channels, hematocrit levels and flow rates, and all two- and three-way interactions were found to be significantly different ($p < 0.05$). These results prove that that the **BFI** values at different flow rates and hematocrit levels were significantly different.

Table 1: Mean \pm standard deviation of **BFI** values at different SDS (Figure 2), flow rates and HCT levels

SDS	Flow Rate	HCT=20%	HCT=30%	HCT=40%
10mm	Flow Rate =0 mL/h	(9.62 \pm 0.24) 10^{-9}	(9.51 \pm 0.14) 10^{-9}	(9.43 \pm 0.12) 10^{-9}
	Flow Rate =100 mL/h	(9.90 \pm 0.14) 10^{-9}	(9.78 \pm 0.13) 10^{-9}	(9.65 \pm 0.13) 10^{-9}
18mm	Flow Rate =0 mL/h	(6.89 \pm 0.15) 10^{-9}	(6.77 \pm 0.09) 10^{-9}	(6.66 \pm 0.08) 10^{-9}
	Flow Rate =100 mL/h	(7.58 \pm 0.12) 10^{-9}	(7.41 \pm 0.08) 10^{-9}	(7.22 \pm 0.09) 10^{-9}
25mm	Flow Rate =0 mL/h	(5.82 \pm 0.14) 10^{-9}	(5.66 \pm 0.10) 10^{-9}	(5.58 \pm 0.09) 10^{-9}
	Flow Rate =100 mL/h	(7.02 \pm 0.23) 10^{-9}	(6.67 \pm 0.14) 10^{-9}	(6.44 \pm 0.14) 10^{-9}
30mm	Flow Rate =0 mL/h	(5.02 \pm 0.21) 10^{-9}	(4.84 \pm 0.18) 10^{-9}	(4.82 \pm 0.20) 10^{-9}
	Flow Rate =100 mL/h	(6.50 \pm 0.32) 10^{-9}	(6.15 \pm 0.26) 10^{-9}	(5.74 \pm 0.27) 10^{-9}

Table 2: Mean \pm standard deviation of blood volume ('BV' depicted in black in Figure 3) signal at different SDS, flow rates and HCT levels

SDS	Flow Rate	HCT=20%	HCT=30%	HCT=40%
25mm	Flow Rate =0 mL/h	-0.012 \pm 0.017	0.79 \pm 0.015	1.61 \pm 0.012
	Flow Rate =100 mL/h	0.053 \pm 0.009	0.85 \pm 0.008	1.65 \pm 0.012
36mm	Flow Rate =0 mL/h	-0.006 \pm 0.006	0.76 \pm 0.003	1.47 \pm 0.003
	Flow Rate =100 mL/h	0.051 \pm 0.017	0.81 \pm 0.004	1.48 \pm 0.004

Table 3: 3-Way ANOVA results for channel, hematocrit levels and flow rate and their interactions

	Sum. Squares	df	F	P
Channel	3.78 x 10^{-15}	3	42125.39	<0.0001
Hematocrit (HCT)	3.16 x 10^{-17}	2	529	<0.0001
Flow Rate	2.41 x 10^{-16}	1	8053.29	<0.0001
Channel x HCT	2.85 x 10^{-18}	6	15.86	<0.0001
Channel x Flow Rate	5.45 x 10^{-17}	3	606.6	<0.0001
Hematocrit x Flow Rate	4.87 x 10^{-18}	2	81.4	<0.0001
Channel x HCT x Flow Rate	2.87 x 10^{-18}	6	15.99	<0.0001

Major Activity 2 (SOW Tasks # 2.1-2.4). Animal studies using piglet model of graded hemorrhage and a piglet model of hypoxia-induced cerebral edema:

This major task included animal data collection and data analysis. We collected data from total of 13 animals, including n=11 animals in a clinical setting with varying phases of hemorrhagic shock and n=2 animals for hypoxia induced cerebral edema/brain injury. We analyzed the data and conducted preliminary statistical analysis to investigate the main effect between the measures and hemorrhagic shock. The results significantly support that the developed prototype system can detect

changes in cerebral flow rate and local oxygenation during graded hemorrhage and even before and during hemorrhagic shock.

Study Design and Measurement Protocol (graded hemorrhage): The following experimental protocol was followed for graded hemorrhage: Blood was withdrawn manually 7 times over a two-hour period (Figure 4). A total of ~66% of the animal's total blood volume, estimated to be 90 mL/kg [11], was removed. All the sensor measurements were collected at baseline and throughout each hemorrhagic epoch.

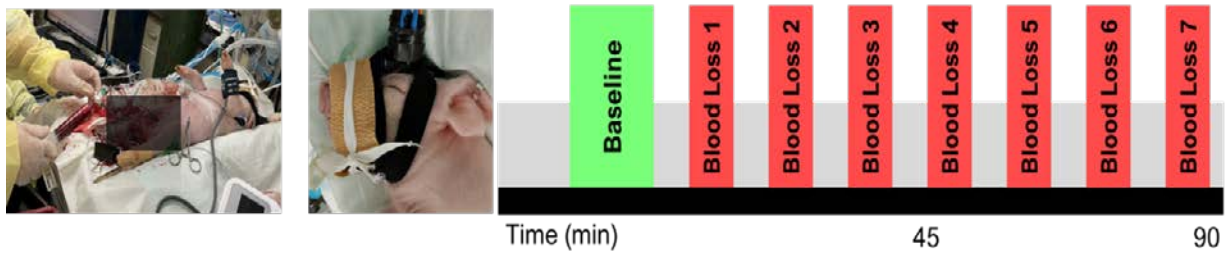


Figure 4. Experimental protocol for graded hemorrhage: Hemorrhagic shock was induced through controlled hemorrhaging via syringe from a femoral artery cannula.

Results and Key Findings (graded hemorrhage): We first performed the data analysis to investigate the relationship between progression of hemorrhagic shock and the measured cerebral blood flow (CBF). Figure 5 shows each episode of blood loss and corresponding averaged blood flow measures with standard error of mean.

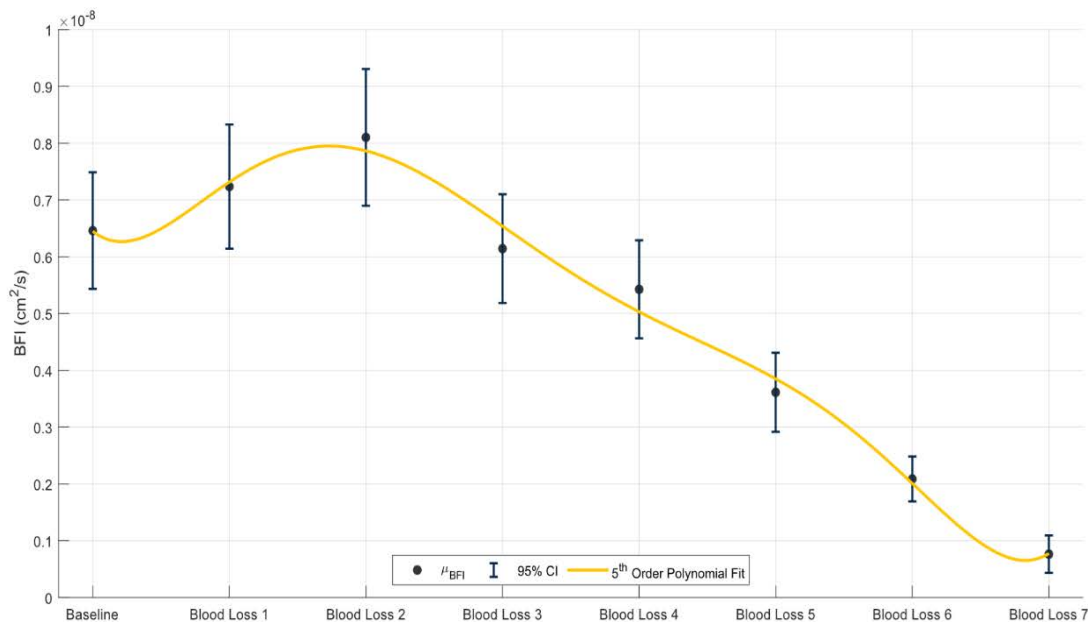


Figure 5. Progression of hemorrhagic shock by relative blood flow index (BFI). Note the compensatory response up to 2nd episode, followed by significant decrease of CBF which is indication of decompensated shock.

The key finding here is that early CBF acceleration consistent with initial compensatory homeostatic response though cerebral vasodilation (up to second blood loss in the graph), followed by severe deceleration of CBF, indicative of decompensated circulatory shock.

Another accomplishment is that we were able to model this trend with a polynomial fit (colored in 'yellow') that can *facilitate development of an index for warning/early detection of shock.*

Following the analysis and aforementioned model in Figure 5, the statistical analysis revealed significant difference between no shock versus shock ($p < 0.01$). Figure 6 shows the shock condition (6th blood drawn) versus no shock conditions (1st and 2nd blood drawn in which animal was not in the hemorrhagic shock).

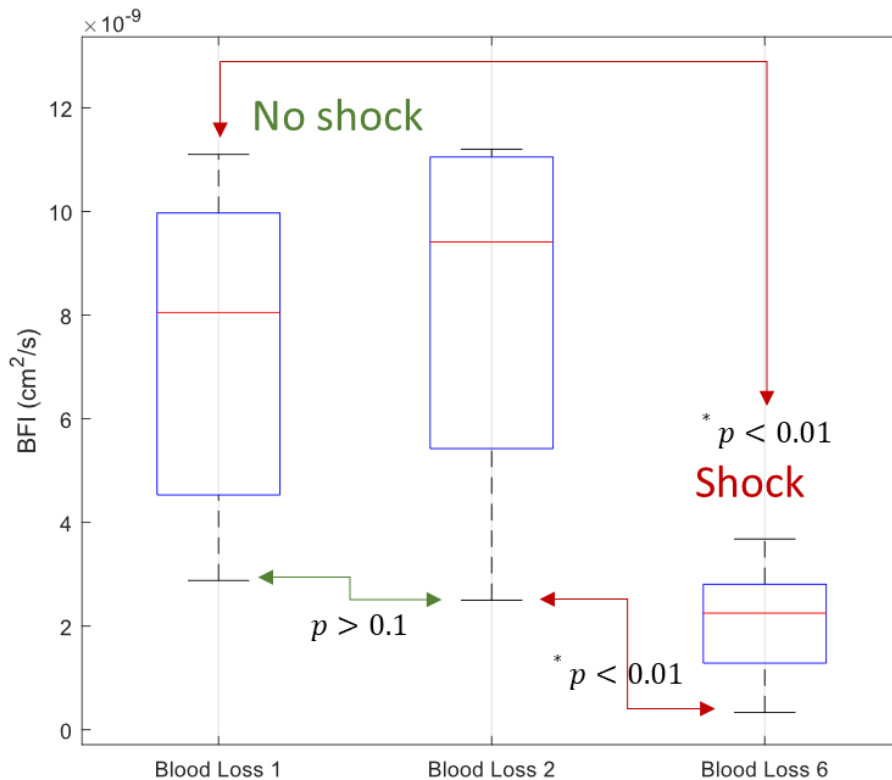


Figure 6. Statistical analysis of the measures between no-shock (initial blood drawn) and hemorrhagic shock (severe blood drawn) shows significant differences ($p < 0.01$) in the CBF.

The key findings are:

- The team modelled early compensatory response to blood loss and later shock response to severe blood loss (see Figure 5). Early cerebral blood flow (CBF) acceleration consistent with initial compensatory homeostatic response though cerebral vasodilation, followed by severe deceleration of CBF, indicative of decompensated circulatory shock.
- The statistical analysis revealed significant difference between no shock versus hemorrhagic shock ($p < 0.01$). That is, the first blood draw versus sixth ($p < 0.01$) and the second blood draw

versus sixth ($p < 0.01$) revealed significant differences, whereas no significant differences were observed between the first blood draw versus second one ($p > 0.1$). (See Figure 6)

- These results strongly support that this optical system can probe the hemodynamic status of local cerebral cortical tissue, and gain insight into the underlying changes of cerebral tissue perfusion at the microvascular level.

The observations and critical results for the NIRS are:

- In addition to cerebral blood flow measures in response to progression of hemorrhagic shock, the developed DCS-NIRS system also provided measures for cerebral hemodynamics with NIRS. By using these measures, the team analyzed the data and calculated the biomarkers, including total hemoglobin (HbTotal), oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR). Figure 7 shows each episode of blood loss and corresponding averaged total hemoglobin changes with standard error of mean. The HbTotal decreased with each blood withdrawn as expected.

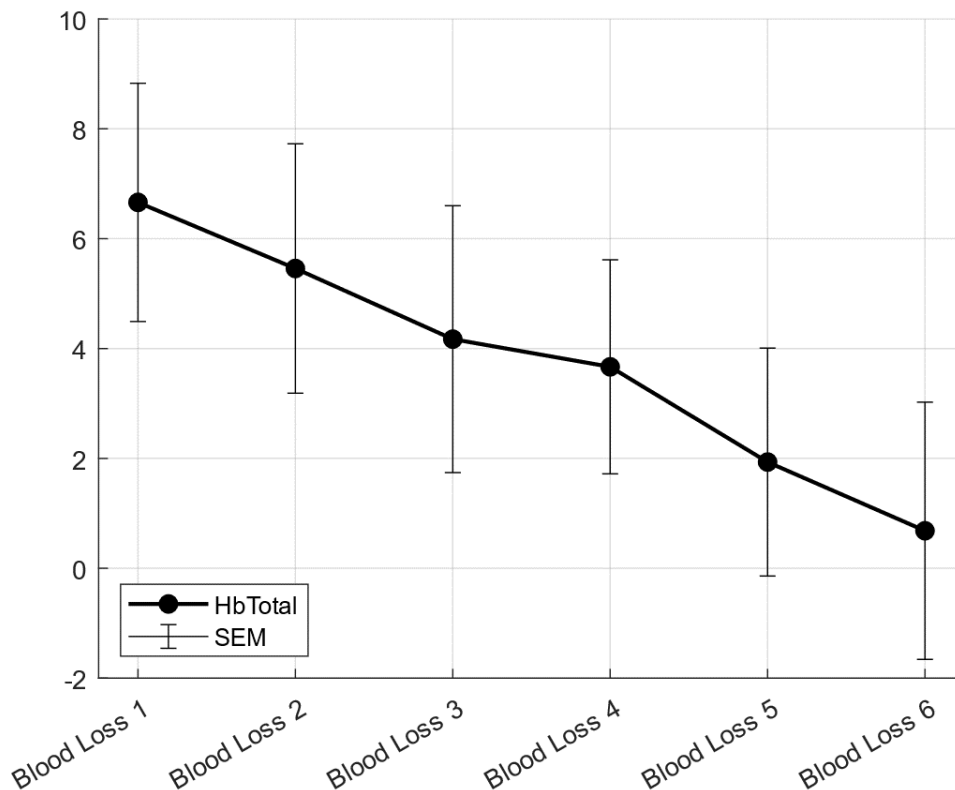


Figure 7. HbTotal Changes: Progression of hemorrhagic shock by relative total hemoglobin changes (HbTotal). Note the decrease after each blood withdrawn.

- Like previous study and analysis for HbTotal, we also performed data measurement and analysis for the biomarkers, namely oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) in response to graded hemorrhage again. Figure 8 shows each episode of

blood loss and corresponding averaged cerebral HbO and HbR changes with standard error of mean. The HbO decreased with each blood withdrawn as expected, yet HbR slightly changed.

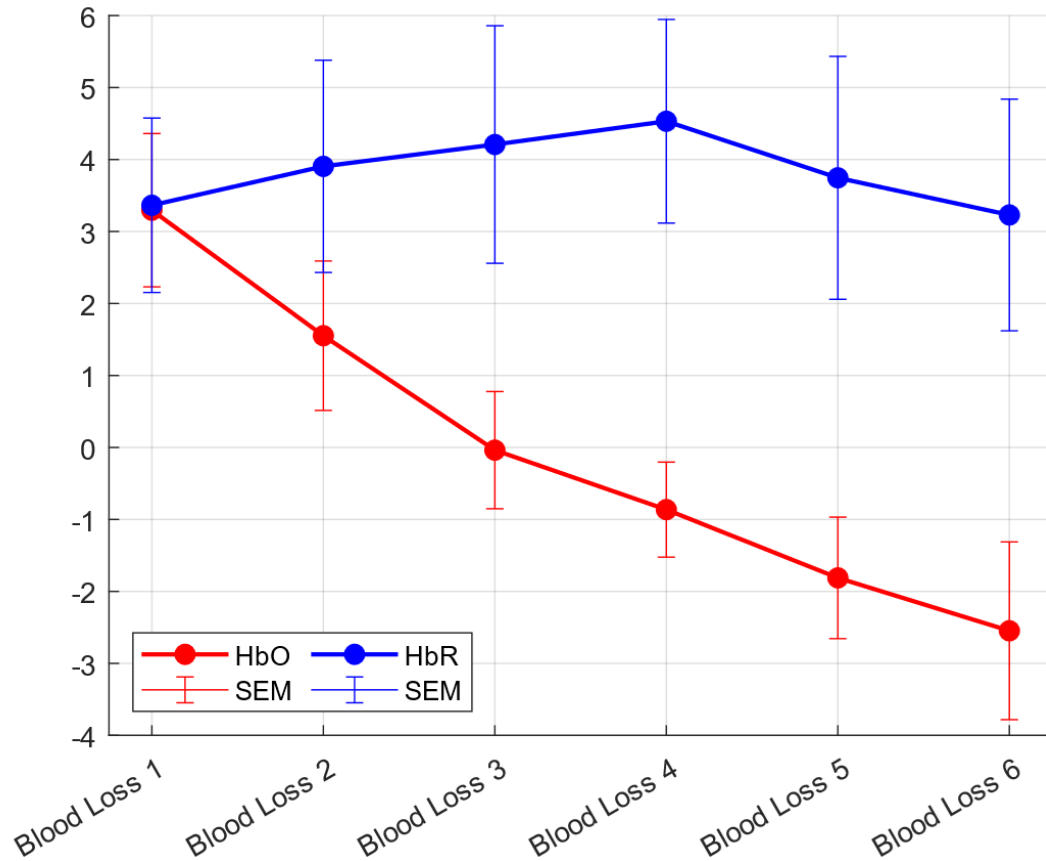


Figure 8. Progression of hemorrhagic shock by changes in HbO (Red) and HbR (Blue). Note the decrease in HbO and slight changes in HbR after each blood withdrawn.

Study Design and Measurement Protocol (hypoxia- induced cerebral edema): We used a piglet model of hypoxic-induced ischemic injury and cerebral edema to investigate the biomarkers measured via developed DCS-NIRS sensors, i.e., cerebral blood flow (CBF), oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) in response to different injury mechanisms. Anesthetized and ventilated piglets were subjected to approximately 3 hours of hypoxic fraction of inspired oxygen (FiO_2), i.e., fraction of inspired oxygen (FiO_2) was lower than ~15%), then re-oxygenation by subjecting them to ~50% FiO_2 , and compared cerebral blood flow, cerebral oxygenation and deoxygenation. The study protocol is shown below (Figure 9).



Figure 9. Hypoxic-induced ischemic injury and cerebral edema study protocol. Anesthetized and ventilated piglets were subjected to *hypoxic* fraction of inspired oxygen (FiO_2), i.e., fraction of inspired oxygen (FiO_2) was lower than ~15%)

Results and Key Findings (hypoxia-induced cerebral edema): We are currently conducting data analysis to determine the relationship between changes in FiO₂ administered for hypoxic ischemic injury and cerebral edema and the changes in each biomarker CBF, HbO and HbR. The initial results will be reported in next Quarterly report for each episode of FiO₂ value changes and corresponding biomarkers calculated with standard error of mean. The team will also conduct invasive measurements with intracranial pressure (ICP) and will run studies without hypoxia (sham control animals) for further validation.

Modify the prototype based on the piglet model tests (Subtask 2.4): Following the animal tests in Year 2, we modified the DCS-NIRS system to ensure reliable measures (see Appendix A for improvement in the system) and detected system errors during the animal studies. The data acquisition program for the new integrated system stopped functioning properly and terminated the data collection in the middle of measurements. The data acquisition program was first updated, and a new code was developed to fix the software error part.

As for the hardware, we detected overheating. During this last quarter, we did some temperature readings from some of the electronic components and mounted a heatsink on the FPGA component and enhanced the airflow with a dust filter screen to the hardware box. This design modification was not enough for the overheat. Then, we installed another fan into main box in order to exhaust heated air, and this major overheat problem is fully fixed now.

Describe the Regulatory Protocol and Activity Status as applicable.

Animal Use Regulatory Protocols

PROTOCOL(S): 2

			<u>Enter information regarding number of subjects</u>					
<u>ACURO Protocol Number</u>	<u>Protocol PI Name</u>	<u>Organization (Site)</u>	<u># Target</u>	<u># Screened</u>	<u># Recruited</u>	<u># Enrolled</u>	<u># Completed</u>	<u>Other</u>
RC190294.e001	Dr. Shadi Malaeb	Drexel University	30	15	15	13	13	
RC190294.e002	Dr. Dean Nachman	Hebrew University	20	0	0	0	0	
This annual reporting period			15	15	15	13	13	
Cumulative			50					

Protocol (1 of 2 total):

Protocol [ACURO Assigned Number]: RC190294.e001

Title: Portable Diffuse Optical Sensors for Point-of-Care Monitoring in Prolonged Field Care

Target required for statistical significance: 30

Target approved for statistical significance: 30

Submitted to and Approved by:

Provide bullet point list of protocol development, submission, amendments, and approvals (include IACUC in addition to ACURO).

Protocol Development: This protocol was developed to conduct proof of concept study and system tests in piglets. The experimental procedures and interventions, i.e., graded hemorrhage, fluid resuscitation, and induction of hypoxia ischemia are described in detail and reviewed.

Submission and Approvals: The protocol was first submitted to the Drexel University Institutional Animal Care & Use Committee and approved by the IACUC (*IACUC Protocol Number: 20889*) The protocol was reviewed and approved by the US Army Medical Research and Development Command (USAMRDC) Animal Care and Use Review Office (ACURO Protocol Number: RC190294.e001) on 10/15/2020.

Amendments: None

Status:

Progress Status: In progress.

Number of animals recruited/original planned target: 15 / 30

Number of animals enrolled/original planned target: 15 / 30

Number of animals completed/original planned target: 13 / 30

Protocol (2 of 2 total):

Protocol [ACURO Assigned Number]: RC190294.e002

Title: Portable Diffuse Optical Sensors for Point-of-Care Monitoring in Prolonged Field Care

Adult Pig Models for Real-life Clinical Scenario

Target required for statistical significance: 20

Target approved for statistical significance: 20

Submitted to and Approved by:

Provide bullet point list of protocol development, submission, amendments, and approvals (include IACUC in addition to ACURO).

Protocol Development: This protocol has been developed to conduct validation tests with adult pig models mimicking real-life clinical scenario. The experimental procedures including uncontrolled hemorrhage by liver laceration are described in detail and will be reviewed.

Submission and Approvals: The protocol was first submitted to the Hebrew University Institutional Animal Care & Use Committee and approved by the IACUC (*IACUC Protocol Number: MD-21-16440-3*). The protocol was reviewed and approved by the US Army Medical Research and Development Command (USAMRDC) Animal Care and Use Review Office (ACURO Protocol Number: RC190294.e002) on 11/24/2021.

Amendments: None

Status:

Progress Status: Not Yet Initiated.

Number of animals recruited/original planned target: 0 / 20

Number of animals enrolled/original planned target: 0 / 20

Number of animals completed/original planned target: 0 / 20

Administrative, Technical or Logistical issues: None.

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”

2 PhD level graduate students have participated in animal tests which help their training and degrees to conduct preclinical animal studies.

How were the results disseminated to communities of interest?

The team has disseminated these new development and test results by attending and presenting at one conference¹. We will also prepare a manuscript for a journal in this year to report these models, implementation of the algorithms and test results which are highly significant.

¹Sinahon, R., Polat, M.D., Malaeb, S., Izzetoglu, K. (2022, Apr 23-24). Monitoring Cerebral Blood Flow with Diffuse Correlation Spectroscopy During Hemorrhagic Shock. 48th Northeast Bioengineering Conference, New York City, NY.

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

If this is the final report, state “Nothing to Report.”

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We will accomplish following goals for the next annual reporting period:

Year 3 Quarter 1:

- Continue tests using a piglet model of hypoxia-induced cerebral edema
- Continue to analyze and report the initial data analysis results aiming to investigate the biomarkers measured via developed DCS-NIRS sensors in response to different injury mechanisms. The team will also run studies without hypoxia (*sham controls*).

Year 3 Quarter 2:

- Analyze to determine the relationship between changes in DCS and NIRS signals of cerebral and somatic tissue oxygen saturation, cerebral edema, cerebral blood flow and changes in intracranial pressure (ICP) and pulse oximetry. The team will conduct *invasive* measurements with ICP for further validation.
- Prepare and recruit pigs to conduct tests in adult pig model of graded hemorrhage

Year 3 Quarters 3 & 4:

- Test the prototype in an adult pig model of controlled hemorrhagic shock and uncontrolled hemorrhage by liver laceration.
- Analyze and report validation analysis using physiological data and DCS and NIRS signal synchrony in response to change in the phase of hemorrhagic shock during this clinical model

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

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

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Using same modality, i.e., optics, with implementation of two different techniques, namely near infrared spectroscopy (NIRS) and diffuse correlation spectroscopy (DCS) techniques, multiple biomarkers were extracted and tested via novel and dynamic phantom models as well as piglet animal models. The head models were custom designed, developed and enabled us to control and mimic various physiological and physical changes in medium (tissue). The critical accomplishment and key contribution here is that the new prototype DCS system developed with the support of this award revealed distinct changes in local cerebral blood flow (CBF) that followed each hemorrhagic epoch, more importantly, *the changes in the DCS system were more sensitive to hemorrhaging than measured changes in heart rate (HR)* (see Figure 10).

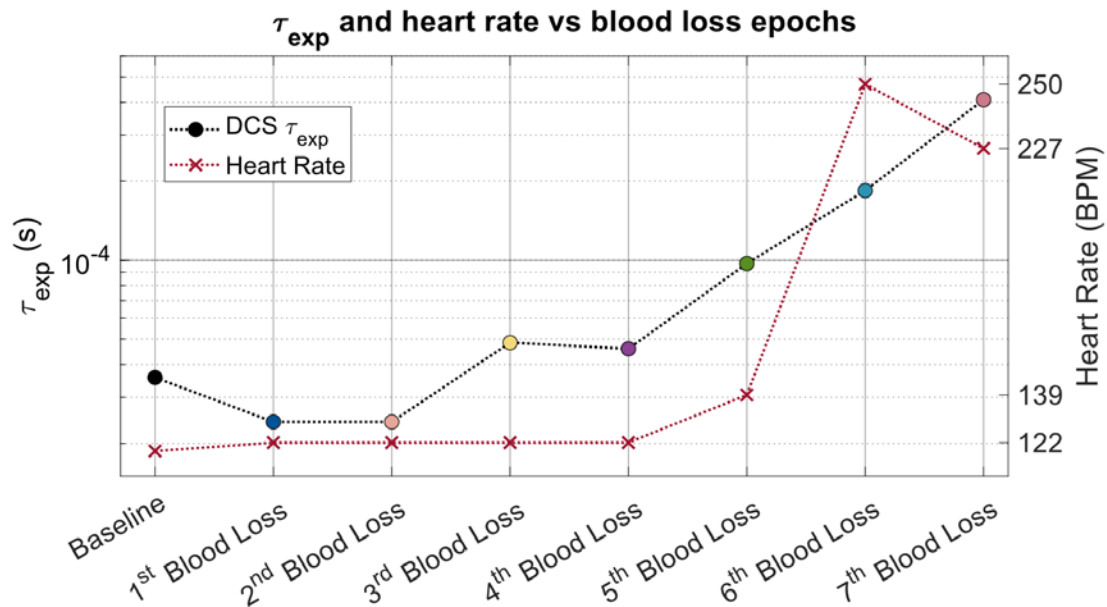


Figure 10. Measured blood flow changes and Heart Rate (HR) after each hemorrhagic epoch: **Our system shows changes after each epoch whereas HR did not change until 5th blood loss epoch.**

In summary, our results strongly support that this optical system can probe the hemodynamic status of local cerebral cortical tissue, and gain insight into the underlying changes of cerebral tissue perfusion at the microvascular level.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Specific to this period and previous period in this project, the head models we custom developed for this project can easily be used to test other clinical modalities or systems, such as efficacy and reliability of new local tissue oxygenation sensors which have been recently key sensory device in detecting some of COVID-19 symptoms. Decision making or regulatory agencies, such as the U.S. Food and Drug Administration can use these test models for independent evaluations. These models are modular, dynamic and can be easily tailored to mimic different tissue oxygenation, cerebral blood flow or water content changes for different injury types.

Use of the prototype system we are developing revealed the measures for cerebral tissue perfusion at the microvascular level which can also be extended to other clinical uses or field applications, such as depth of anesthesia and sedation monitoring for ambulatory anesthesia.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Nothing to report for this period.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

As previously mentioned, decision making or regulatory agencies, such as the U.S. Food and Drug Administration (FDA) can use these phantom/head models for independent evaluations.

This project helps two PhD level graduate students to improve their knowledge and training on pre-clinical studies by participating in animal tests.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:*

Nothing to report.

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

We experienced following delays throughout Year 2:

- During the first quarter of Year 2, there was again material availability issue and shipment delay for the supplies necessary to assemble printed circuit boards and main box hardware modification and to form further capillary-like tubes and head models.
- During animal studies, our new integrated system crashed and terminated the data collection in the middle of measurements. To resolve this issue and continue animal experiments, the data acquisition program was updated, and a new code was developed to fix the software. We troubleshooted the system later to find main source of the problem and to come up with a permanent solution. We found the overheating over some major components and modified the main box as aforementioned in Page 16 of this report.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Not applicable

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”*

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume; year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Apr 23-24, 2022. Poster at the 48th Northeast Bioengineering Conference, New York City, NY. Title: 'Monitoring Cerebral Blood Flow with Diffuse Correlation Spectroscopy During Hemorrhagic Shock.

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

- A complete fully functional diffuse correlation spectroscopy (DCS) with a multi-distance optical probe/sensor and data acquisition software.
- A novel algorithm is implemented to determine cerebral blood flow indices from experimental data recordings.
- Animal models of different brain injuries are developed and studied.

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*

- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and other.*

Custom developed dynamic phantom models, techniques and set ups to mimic the changes in blood flow and blood volume; and custom developed animal model to study different brain injuries.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Name: Kurtulus Izzetoglu
Organization: Drexel University
Project Role: PI
Researcher Identifier (ORCID ID): 0000-0001-5304-7361
Nearest person month worked: 3.0
Contribution to Project: Dr. Izzetoglu has been leading overall conduct of the project and ensure the successful completion of the SOW tasks, the efforts include but not limited to, tests and modification of the device, phantom models, animal tests, data analysis and modelling in Year 2, and led internal technical team meetings, and report preparation.

Name: Leonid Zubkov
Organization: Drexel University
Project Role: Co-Investigator
Researcher Identifier (ORCID ID): 0000-0001-6523-5984
Nearest person month worked: 4.2
Contribution to Project: Dr. Zubkov has designed and developed DCS control box and system, optical fibers, and multi-distance probes. He has provided technical support for system and sensor/probe setup during tests and troubleshooted the system during animal studies.

Name: Shadi Malaeb
Organization: Drexel University
Project Role: Co-Investigator

Researcher Identifier (ORCID ID): 0000-0001-6523-5984
Nearest person month worked: 0.6
Contribution to Project: Dr. Malaeb as a clinician has led the animal tests. This Year, he recruited 15 animals and developed the study for piglet model of graded hemorrhage and hypoxia-induced injuries.

Name: Sinan F. Tuzer
Organization: Drexel University
Project Role: Animal study coordinator
Researcher Identifier (ORCID ID): 0000-0001-8483-6339
Nearest person month worked: 1.0
Contribution to Project: This year, Dr. Tuzer supported animal recruitment and screening of 15 piglets (supervised by Dr. Malaeb). He also provided support with the animal tests.

Name: Juan Du
Organization: Drexel University
Project Role: Lab technician & manager
Researcher Identifier (ORCID ID): 0000-0002-7978-0665
Nearest person month worked: 12.0
Contribution to Project: This year, Ms. Juan Du guided all the animal studies at the clinical setting and worked on animal tests and system performance tests. She designed and developed new phantom (lab) models mimicking the cerebral blood flow. She has been coordinating the lab and clinical animal facility for the device setups and measurements.

Name: Deniz Polat
Organization: Drexel University
Project Role: Graduate student
Researcher Identifier (ORCID ID): 0000-0002-0980-1416
Nearest person month worked: 4.5
Contribution to Project: Mr. Polat actively participated in supporting clinical studies and worked on all the animal studies and data collection from 13 piglets.

Name: Pratusha Reddy
Organization: Drexel University
Project Role: Graduate student (PhD)
Researcher Identifier (ORCID ID): 0000-0002-6589-9075
Nearest person month worked: 9.0
Contribution to Project: Ms. Prat has been assisting the tests and working on development of signal processing algorithms for cerebral blood flow (DCS) and blood volume (NIRS) measures. She performed the data and statistical analyses included in this annual report.

Name: Baruch Ben Dor
Organization: InfraScan, Inc
Project Role: Subaward PI
Researcher Identifier (ORCID ID): 0000-0002-5531-8732
Nearest person month worked: 0.7
Contribution to Project: Dr. Ben Dor has been leading the subaward efforts for hardware development and modification.

Name: David Solt
Organization: InfraScan, Inc
Project Role: Subaward co-Investigator (co-I)
Researcher Identifier (ORCID ID):
Nearest person month worked: 1.0
Contribution to Project: Mr. David has been supervising and developing NIRS system with flat probes and FPGA; working on the mechanical system design, integration and NIRS system with flat probes.

Name: Gerald Mullin
Organization: InfraScan, Inc
Project Role: Subaward Electrical Engineer
Researcher Identifier (ORCID ID):
Nearest person month worked: 1.7
Contribution to Project: This year, Mr. Gerry has performed work in system integration, assembled new boards into the control unit as well as software development, specifically embedded coding of communication protocols, DCS-NIRS synchronous data collection and an FPGA module. He also modified the box to fix system crashes and overheating.

Name: Meltem Izzetoglu
Organization: Villanova University
Project Role: Subaward PI
Researcher Identifier (ORCID ID): 0000-0002-1768-3384
Nearest person month worked: 3.0
Contribution to Project: Dr. Meltem Izzetoglu has been working on algorithm development for the blood flow and cerebral volume indices using measures of the optical sensors developed in this project. She supported the data analysis with particular focus on modeling and statistical data analysis of NIRS data during this year.

Name: Luis Gomero
Organization: Villanova University
Project Role: Graduate student (MSc) (Subaward)
Researcher Identifier (ORCID ID): 0000-0001-6374-3096

Nearest person month worked: 6.0

Contribution to Project: Mr. Gomero, who is supervised by Subaward PI (Dr. Meltem), has worked on blood flow and oximetry data analysis and supported the animal studies.

<i>Name</i>	<i>Project Role</i>	<i>Organization</i>	<i>Calendar Months (Year 1)</i>	<i>Contribution to Project</i>
Kurtulus Izzetoglu	PI	Drexel University	3.0	Dr. Izzetoglu has been leading overall conduct of the project and ensure the successful completion of the SOW tasks, the efforts include but not limited to, tests and modification of the device, phantom models, animal tests, data analysis and modelling in Year 2, and led internal technical team meetings, and report preparation.
Shadi Malaeb	Co-Investigator	Drexel University	0.6	Dr. Malaeb as a clinician has led the animal tests. This Year, he recruited 15 animals and developed the study for piglet model of graded hemorrhage and hypoxia-induced injuries.
Leonid Zubkov	Co-Investigator	Drexel University	4.2	Dr. Zubkov has designed and developed DCS control box and system, optical fibers, and multi-distance probes. He has provided technical support for system and sensor/probe setup during tests and troubleshooted the system during animal studies.
Sinan F. Tuzer	Animal Study Coordinator	Drexel University	1.0	This year, Dr. Tuzer supported animal recruitment and screening of 15 piglets (supervised by Dr. Malaeb). He also provided support with the animal tests.
Juan Du	Lab Technician & Manager	Drexel University	12.0	This year, Ms. Juan Du guided all the animal studies at the clinical setting and worked on animal tests and system performance tests. She designed and developed new

				phantom (lab) models mimicking the cerebral blood flow. She has been coordinating the lab and clinical animal facility for the device setups and measurements.
Deniz Polat	Graduate Student (PhD)	Drexel University	4.5	Mr. Polat actively participated in supporting clinical studies and worked on all the animal studies and data collection from 13 piglets.
Pratasha Reddy	Graduate Student (PhD)	Drexel University	9.0	Ms. Prat has been assisting the tests and working on development of signal processing algorithms for cerebral blood flow (DCS) and blood volume (NIRS) measures. She performed the data and statistical analyses included in this annual report.
Baruch Ben-Dor	Subaward PI	InfraScan	0.7	Dr. Ben Dor has been leading the subaward efforts for hardware development and modification.
David Solt	Subaward Co-I	InfraScan	1.0	Mr. David has been supervising and developing NIRS system with flat probes and FPGA; working on the mechanical system design, integration and NIRS system with flat probes.
Gerald Mullin	Subaward Electrical Engineer	InfraScan	1.7	This year, Mr. Gerry has performed work in system integration, assembled new boards into the control unit as well as software development, specifically embedded coding of communication protocols, DCS-NIRS synchronous data collection and an FPGA module. He also modified the box to fix system crashes and overheating.
Meltem Izzetoglu	Subaward PI	Villanova University	3.0	Dr. Meltem Izzetoglu has been working on algorithm development for the blood flow and cerebral volume indices

				using measures of the optical sensors developed in this project. She supported the data analysis with particular focus on modeling and statistical data analysis of NIRS data during this year.
Luis Gomero	Graduate student	Villanova University	6.0	Mr. Gomero, who is supervised by Subaward PI (Dr. Meltem), has worked on blood flow and oximetry data analysis and supported the animal studies.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*
- *Collaboration (e.g., partner’s staff work with project staff on the project);*

- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Organization Name: InfraScan, Inc

Location of Organization: (if foreign location list country) Philadelphia, PA

Partner's contribution to the project (identify one or more)

- Collaboration/Subcontractor: InfraScan, Inc. is a subawardee and the engineers have troubleshooted and modified the system including hardware and software development in Year 2.

Organization Name: Hebrew University

Location of Organization: (if foreign location list country) Jerusalem, Israel

Partner's contribution to the project (identify one or more)

- Collaboration/Subcontractor: Hebrew University. is a subawardee and will develop adult pig animal models and experimental protocols and conduct these studies. Colleagues at the Hebrew University developed the research protocol during this Year 1 and secured the approvals in Year 2.

Organization Name: Villanova University

Location of Organization: (if foreign location list country) Villanova, PA

Partner's contribution to the project (identify one or more)

- Collaboration/Subcontractor: Villanova University. is a subawardee and collaborating with lead institute on analyzing animal tests reported during this year. They have also been supporting algorithm development for data analysis, particularly blood flow indices using measures of the optical sensors developed in this project.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ebrap.org/eBRAP/public/index.htm> for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil/Pages/Resources.aspx>) should be updated and submitted with attachments.*

Updated quad chart is submitted.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

APPENDIX A

DCS-NIRS Integrated Data Acquisition:

In Year 2, we performed DCS-NIRS simultaneous measurement tests with newly developed boards. Figure A.1 shows the system measures without new boards and software. Figure A.2 shows the proposed system with new boards. As shown in Figure A.2, once the DCS system is ON, the new system eliminated the interference and thus enabled simultaneous measures of blood flow and blood volume.

Discussion: The new system enables simultaneous measures of two key cerebral biomarkers for hemodynamic changes, blood flow and blood volume. This is a major accomplishment as it allows simultaneous measures of local cerebral hemodynamic changes.

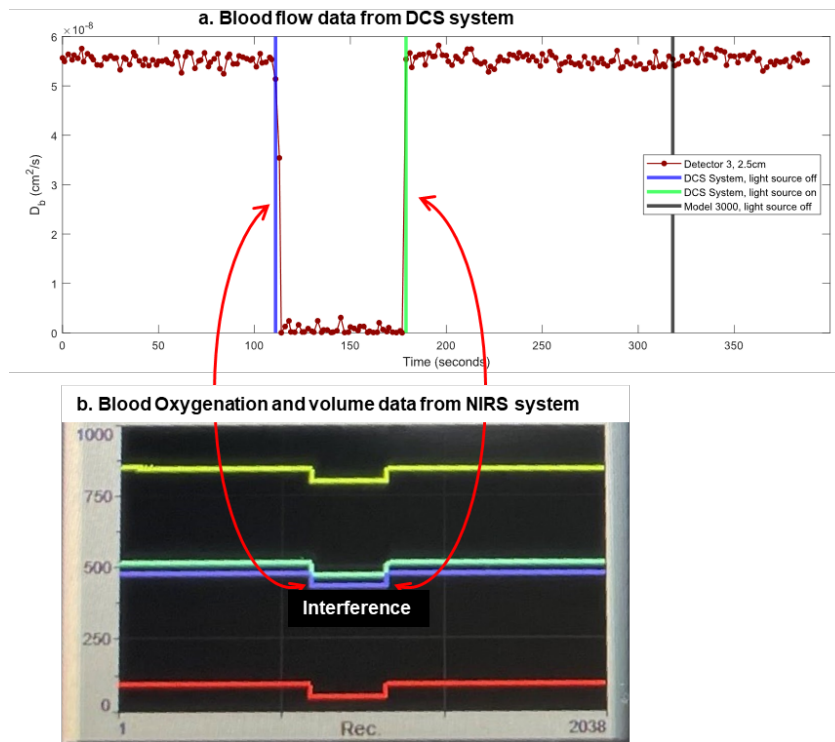


Figure A.1. When both systems are on, there is a significant interference (red arrows pointing the interference caused by DCS system-blood flow measures on the second graph – (b)) and does not allow simultaneous measures of blood flow and local cerebral oxygenation and volume.

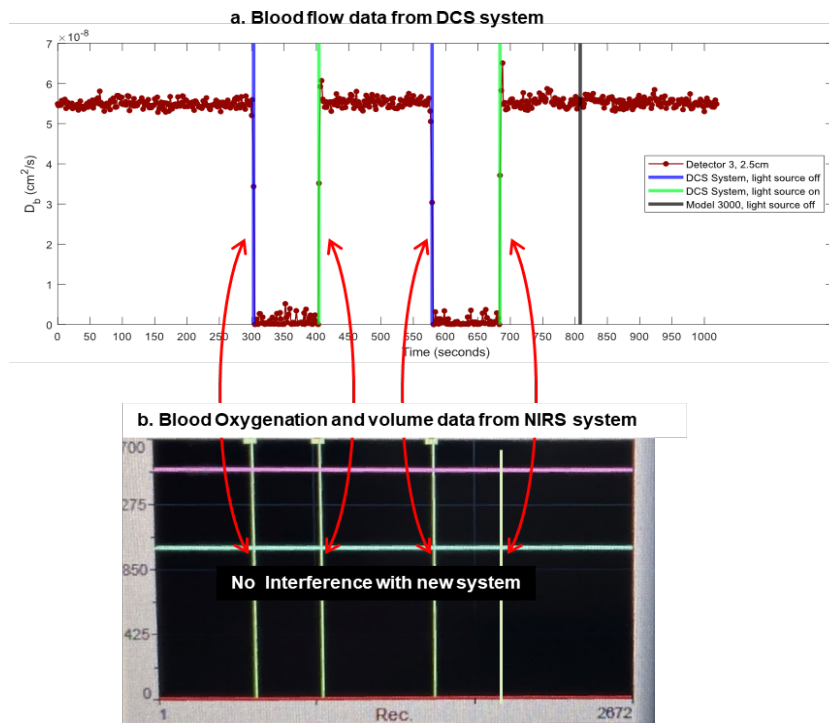


Figure A.2. Performance of new integrated DCS-NIRS system: There is no interference (red arrows pointing the time that both systems are ON). This is critical development as the new system enables simultaneous measures of cerebral blood flow, local cerebral oxygenation and volume.

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6. Verdecchia, K., Diop, M., Lee, A., Morrison, L. B., Lee, T. Y., & Lawrence, K. S. (2016). Assessment of a multi-layered diffuse correlation spectroscopy method for monitoring cerebral blood flow in adults. *Biomedical optics express*, 7(9), 3659-3674.
7. Gagnon, L., Desjardins, M., Jehanne-Lacasse, J., Bherer, L., & Lesage, F. (2008). Investigation of diffuse correlation spectroscopy in multi-layered media including the human head. *Optics express*, 16(20), 15514-15530.

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