AWARD NUMBER: **W81XWH-15-1-0669**

TITLE: **The Use of Quantitative SPECT/CT Imaging to Assess Residual Limb Health**

PRINCIPAL INVESTIGATOR: **Christopher L. Dearth, PhD**

CONTRACTING ORGANIZATION: **The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.**

REPORT DATE: **October 2018**

TYPE OF REPORT: **Annual**

PREPARED FOR: **U.S. Army Medical Research and Materiel Command**
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2018	Annual	09/30/2017 – 09/29/2018

4. TITLE AND SUBTITLE

The Use of Quantitative SPECT/CT Imaging to Assess Residual Limb Health

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-1-0669

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Christopher L. Dearth, PhD

E-Mail: Christopher.L.Dearth.civ@mail.mil

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.
6720-A Rockledge Drive, Suite 100 Bethesda, MD 20817

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The objective of the proposed study is to translate SPECT/CT imaging to patients with lower extremity amputation and subsequently evaluate the utility of non-invasive imaging for evaluating the impact of next-generation socket technologies on the health of the residual limb. It is hypothesized that SPECT/CT imaging will provide a highly sensitive, non-invasive tool for clinicians to assess changes in microvascular perfusion elicited by next-generation prosthetic socket technologies and that acute changes in microvascular perfusion will be predictive of long term residual limb health outcomes. While the project timeline is currently slightly behind / delayed from our initial projection, the study team has taken significant actions towards remedying these issues and is very confident that we can get the project back on track in short order and drive towards a successful end point – which will greatly benefit our patients.

15. SUBJECT TERMS
Prosthetics, residual limb health, imaging, extremity trauma, amputation

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U Unclassified	U Unclassified	U Unclassified	U Unclassified	11	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

INTRODUCTION:

Prosthetic devices aim to restore the appearance and/or function of the affected extremity for patients with amputations. The socket is a critical feature of a prosthetic device as it acts as the interface between the prosthesis and residual limb. Numerous residual limb health issues have been associated with traditional socket technologies. Accordingly, the DoD has invested significant effort and funding in recent years to facilitate the development of improved socket technology to aid in the maintenance of tissue health in the residual limb. While these efforts are beginning to yield exciting next-generation socket technologies (e.g., 'smart' sockets), limited technologies are available to assess the impact of these sockets on the underlying physiological response in the residual limb.

The health of residual limb tissue in persons with lower-limb amputation is of critical importance. Breakdown of tissue viability of the residual limb can negatively impact the progress of the patient's rehabilitation and/or lead to prosthesis abandonment, thus reducing their mobility, function, and overall quality of life. To date, the ability to accurately assess tissue viability within the residual limb of individuals with amputations while the socket is on has been challenging. Therefore, a non-invasive, sensitive, and quantitative imaging modality that could provide an objective assessment of the overall health of the residual limb would advance the standard of care for affected patients, as well as improve selection of the most effective socket technologies at promoting overall limb health.

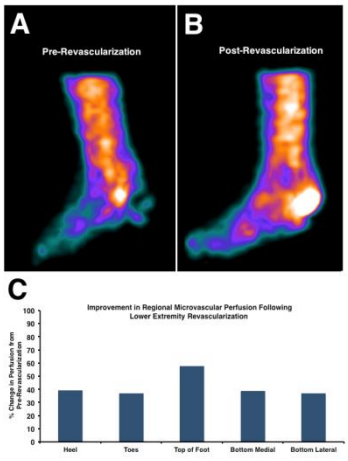


Figure 1. SPECT imaging of a patient with a non-healing heel ulcer before (A) & after (B) revascularization reveals increased microvascular perfusion to the ulcer region & distal foot. Further regional quantification of radiotracer uptake confirmed an improvement in microvascular perfusion in all of the segmented vascular territories of the foot (C).

In accordance with the intent of the OPORP award mechanism, the goal of the current research study is to provide outcomes data to inform and improve the care of military service members with lower extremity amputation(s). This will be accomplished by utilizing a validated SPECT/CT imaging technique to assess which prosthetic socket technologies will generate the best patient outcomes (i.e., residual limb health) for service members with limb loss. Successful completion of this study would significantly improve our understanding and advance the implementation of the prosthetic socket devices most effective at promoting the overall health of the residual limb, thereby greatly benefiting patient care.

KEYWORDS: Prosthetics, residual limb health, imaging, extremity trauma, amputation

ACCOMPLISHMENTS:

What were the major goals of the project?

The objective of the proposed study is to translate SPECT/CT imaging to patients with lower extremity amputation and subsequently evaluate the utility of non-invasive imaging for evaluating the impact of next-generation socket technologies on the health of the residual limb. It is hypothesized that SPECT/CT imaging will provide a highly sensitive, non-invasive tool for clinicians to assess changes in microvascular perfusion elicited by next-generation prosthetic socket technologies and that acute changes in microvascular perfusion will be predictive of long term residual limb health outcomes.

Specific Aim 1 **- To quantify basal microvascular perfusion and perfusion reserve of the residual limb in patients with lower extremity amputation using SPECT/CT imaging.**	**Percentage Completion**
Major Task 1: To evaluate SPECT/CT imaging as a means to assess limb health in patients with amputation.	
Subtask 1.1 – IRB Approval -- WRNMMC	95%
Subtask 1.2 – IRB Approval -- Yale University (ended upon departure)	100%
Subtask 1.2 – IRB Approval -- Research Institute at Nationwide Children's Hospital	75%
Subtask 1.3 – HRPO Approval	0%
Subtask 1.4 – Human subject testing of SPECT/CT imaging	0%
Subtask 1.5 – Image analysis and quantification	0%
Subtask 1.6 – Dissemination of results describing SPECT/CT imaging in an amputee population	0%
Specific Aim 2 **- To evaluate the efficacy of next-generation (e.g., breathable socket) prosthetic socket technologies at promoting tissue health of the residual limb of patients with lower extremity amputation using SPECT/CT imaging.**	**Percentage Completion**
Major Task 2: To use SPECT/CT imaging to evaluate new socket technologies on the long term limb health in patients with amputation.	
Subtask 2.1 – Long term follow up SPECT/CT imaging of 40 subjects	0%
Subtask 2.2 – Image analysis and quantification of long term follow up imaging	0%
Subtask 2.3 – Dissemination of results describing use SPECT/CT imaging to evaluate new socket technologies on the long term limb health in patients with amputation.	0%

What was accomplished under these goals?

During the current reporting period, considerable effort has been devoted towards completion the current project, specifically towards the establishment of the project specific infrastructure:

- The study team has received and responded to numerous rounds of stipulations related to the IRB protocol in both administrative and full IRB board review. The team anticipates receiving WRNMMC IRB approval imminently.

- The study team has conducted regular internal meetings to discuss the project and move it forward.
- A CRADA b/w HJF & WRNMMC has been developed and is nearing completion.
- A data sharing agreement has been developed and is nearing completion.
- Efforts to utilize the WIIR to create digital data collection forms and patient reported outcomes (PROs) are underway. (*note, this technology is being paid for with other leveraged funding (EACE) and thus is at no cost to this project).
- The study team has continued to advertise the position for the HJF research support staff position (which will devote 100% effort toward this project). Dr. Dearth has reviewed numerous applications and interviewed candidates. Several well qualified candidates have been identified, however, an offer has not yet been made due to timing considerations related to getting the IRB approved.

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

This project has provided training and professional development for several of our team members related to regulatory considerations for non-minimal risk studies.

How were the results disseminated to communities of interest?

The general concept of this study – i.e., utilizing next generation imaging technologies to generate novel, quantitative outcome assessments for the field of O&P – has previously been disseminated to our communities of interest (e.g., Military Medicine) via both manuscripts in peer reviewed, scientific journals and presentations at an internationally renowned conference.

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

Our main goal for the beginning of the next reporting period is to achieve full regulatory approval (IRB & HRPO) for the clinical protocol such that we can begin subject enrollment. Another goal is to hire the research support personnel for this project – as this individual will be assisting with recruitment, data collection & analysis, etc… we have been mindful to try to

synchronize the on-board and regulatory approval dates as closely as possible (i.e., we do not to hire this person ‘too soon’ [i.e., well before the protocol is approved] such that we do not ‘waste’ money by having the individual spending down money with nothing to do)

IMPACT:

We expect that this project will significantly improve our understanding and advance the implementation of the prosthetic socket devices most effective at promoting the overall health of the residual limb, thereby greatly benefiting patient care.

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

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report.

CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report.

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

The project timeline is currently behind our initial projection. This delay was initially due to the issues that were encountered with setting up the sub-award with Yale and subsequently have been due to numerous rounds of reviewer stipulations by the WRNMMC IRB.

Importantly, the study team has invested significant efforts towards remedying these issues with the goal of getting the project back on track. We are encouraged in that we have received comments back from the WRNMMC IRB which we addressed and resubmitted such that we can continue to push this effort forward ASAP. Taken together, the study team is very confident that we can get the project back on track during the approved NCE for this project to afford us the opportunity to drive towards a successful end point – which will greatly benefit our patients.

Changes that had a significant impact on expenditures

Due to the delays experienced, the overall project expenditures are significantly less than the original projection for this point in the study. However, importantly, the project is projected to come to a successful conclusion on budget (i.e., no additional funds are required)

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

Nothing to Report.

PRODUCTS:

Journal publications.

Nothing to Report.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers, and presentations.

Nothing to Report.

Website(s) or other Internet site(s)

Nothing to Report.

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

Nothing to Report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Christopher L. Dearth, PhD
Project Role:	Principle Investigator
Organization:	Extremity Trauma & Amputation Center of Excellence Walter Reed National Military Medical Center & Uniformed Services University of the Health Sciences
Name:	Mitchel R. Stacy, PhD
Project Role:	Co-Principle Investigator
Organization:	The Research Institute at Nationwide Children's Hospital
Name:	CDR Grant H. Bonavia, MD PhD
Project Role:	Associate Investigator
Organization:	Nuclear Medicine Service, Department of Radiology Walter Reed National Military Medical Center
Name:	Michael Valerio, PhD
Project Role:	Associate Investigator
Organization:	Extremity Trauma & Amputation Center of Excellence Walter Reed National Military Medical Center & Uniformed Services University of the Health Sciences
Name:	Elizabeth Husson, CCRC
Project Role:	Protocol Coordinator
Organization:	Extremity Trauma & Amputation Center of Excellence Walter Reed National Military Medical Center & Uniformed Services University of the Health Sciences
Name:	Heidi Mahatan, MA, LCPC
Project Role:	Protocol Coordinator
Organization:	Henry M. Jackson Foundation for the Adv. of Mil. Medicine Walter Reed National Military Medical Center

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. No changes have been made to efforts on this project.

What other organizations were involved as partners?

During the current reporting period, Dr. Stacy has relocated from Yale University to The Research Institute at Nationwide Children's Hospital / Ohio State University (Columbus, OH)

SPECIAL REPORTING REQUIREMENTS

QUAD CHART:

(See next page)

The Use of Quantitative SPECT/CT Imaging to Assess Residual Limb Health

Orthotics and Prosthetics Outcomes Research Award - W81XWH-15-1-0669

PI: Christopher L. Dearth, PhD **Org:** Walter Reed National Military Medical Center **Award Amount:** $484,210

Objective: The objective of the proposed proof of concept, pilot clinical study is to translate ^{99m}Tc-tetrofosmin SPECT/CT imaging to patients with lower extremity amputation and subsequently evaluate its effectiveness as a means to evaluate the impact of next generation socket technologies on the health of the residual limb. This objective will be evaluated by the following specific aims:

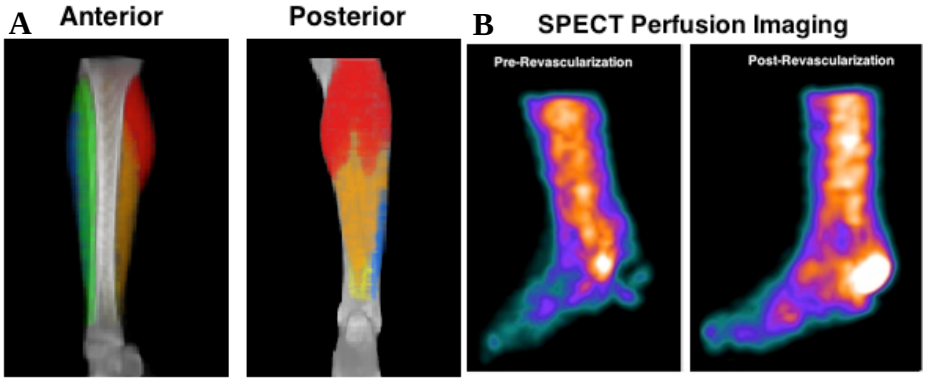
Specific Aim 1: To quantify basal microvascular perfusion and perfusion reserve of the residual limb in patients with lower extremity amputation using ^{99m}Tc-tetrofosmin SPECT/CT imaging.

Hypothesis: It is hypothesized that evaluation of microvascular perfusion via ^{99m}Tc-tetrofosmin SPECT/CT imaging will provide a highly sensitive, non-invasive tool for clinicians to use during the assessment of residual limb tissue health beyond traditional limb health outcome measures.

Specific Aim 2: To evaluate the efficacy of current (e.g., VASS) and next-generation (e.g., breathable socket) prosthetic socket technologies at promoting tissue health of the residual limb of patients with lower extremity amputation using ^{99m}Tc-tetrofosmin SPECT/CT imaging.

Sub Aim 2.1 - To determine if acute changes in microvascular perfusion are predictive of long term residual limb health outcomes.

Hypothesis: It is hypothesized that ^{99m}Tc-tetrofosmin SPECT/CT imaging will provide a highly sensitive, non-invasive tool for clinicians to assess changes in microvascular perfusion elicited by next-generation prosthetic socket technologies and these acute changes in microvascular perfusion will be predictive of long term residual limb health outcomes.



A) Anterior & posterior views of 3-D calf muscle regions segmented from a CT attenuation scan. Gastrocnemius (red), soleus (orange), tibialis anterior (green), tibialis posterior (yellow), and fibularis longus (blue) muscles are displayed and overlaid on a bone only CT image. **B**) ^{99m}Tc-tetrofosmin SPECT perfusion imaging in a patient with a non-healing heel ulcer prior to and following lower extremity revascularization demonstrates increased radiotracer uptake in the site of the heel ulcer and distal foot following treatment.

Timeline and Cost

Activities / Calendar Year	2016	2017	2018	2019
IRB creation / submission / approval				
Begin subject recruitment / enrollment				
Specific Aim #1				
Specific Aim #2				
Study Completion / Data Dissemination				
Budget ($K)			**$244**	**$240**

Updated: 29Oct2018

Goals / Milestones

CY16-18 Goals – Initiation / IRB / Personnel

- ☑ Study kickoff meeting
- ☑ Generation & posting of position description for research personnel
- ☑ CRADA & DSA document creation & submission
- ☑ WRNMMC IRB SRC submission & approval
- ☑ Yale University IRB submission & approval
- ☑ WRNMMC IRB submission
- ☑ Initiation of knowledge dissemination

CY18-19 Goals – Study Initiation / Data Collection / Study Completion

- ☑ IRB submission at Nationwide Children's Hospital
- ☐ WRNMMC IRB Approval
- ☐ HRPO Approval
- ☐ Begin subject recruitment / enrollment
- ☐ Begin data collection for SA 1 & 2
- ☐ Complete data collection for SA 1 & 2
- ☐ Manuscript(s) submission / publication
- ☐ Conference abstract submission / presentation