

SPECIFIC AIMS

Over 400,000 people currently receive hemodialysis treatment in the United States¹. Each year more than 100,000 additional people develop end stage kidney disease and most will require hemodialysis. Every patient receiving hemodialysis treatment requires a well-functioning vascular access.

Once established, an autogenous arteriovenous fistula (AVF) has the longest survival and lowest cost when compared to other types of vascular access² like an arteriovenous graft (AVG) or central venous catheter (CVC)³. Moreover, patient survival is longer with an AVF⁶. Recent efforts such as the Fistula First initiative have been successful at increasing the rate of AVF placements; yet, AV fistulae still constitute only about 55% of prevalent accesses.

The major problem limiting increased use of an AVF is impaired fistula maturation, the failure of a new AVF to develop into a usable vascular access. Based on numerous single center studies, impaired maturation occurs in 20-60% of new fistulas⁷. This leads directly to prolonged reliance on CVCs for dialysis. Yet, CVCs are the most expensive type of access³ associated with the highest patient morbidity and mortality⁴. Currently over 80% of patients initiate hemodialysis with a central catheter while only 16% starting with a mature fistula¹¹. Starting dialysis with a mature fistula substantially reduces overall costs¹². It has been estimated that if we could improve the percent of fistulas that are mature at initiation of dialysis from 16% to 50%, it would save Centers for Medicare and Medicaid Services (CMS) 500 million dollars per year¹² and significantly improve patient survival¹⁰.

We seek to address this significant problem in our study and attempt to improve the fistula maturation through vascular conditioning by the use of our innovative device. The vascular conditioning is achieved by applying constrictive pressure and heat before and after the AVF placement.

Applying heat to the arm increases blood flow often by 10 fold or more. This leads to an increase in vein size¹⁵. Applying constrictive pressure to the upper arm (like a blood pressure cuff) increases in venous compliance and medial vein thickening as long as the pressure does not exceed arterial pressure¹⁶. We have combined both these methods into one innovative device named Thermovasc, which will apply controlled heat and pressure to the arm to accomplish these benefits.

In order to perform a larger study, we need to demonstrate that this study design is feasible. This pilot study will help us determine not only the parameters of heat and pressure to be used, but also the compliance of the patients with the protocol. It will help us develop co-ordination among the surgeons, the vascular lab, the clinic, and help us identify any potential problems that would need to be addressed prior to a larger trial. The following are our specific aims for this pilot study.

- **Aim 1:** To determine optimum parameters of heat and constrictive pressure for vascular pre-conditioning
- **Aim 2:** To determine whether 6 weeks of pre-operative vascular pre-conditioning with Thermovasc will improve vein size and compliance
- **Aim 3:** To determine whether pre-operative and post-operative vascular conditioning will improve AVF maturation

If we can establish the effectiveness of this simple and cost-effective device, this could significantly improve clinical practice, patient outcomes, and hemodialysis health care costs.

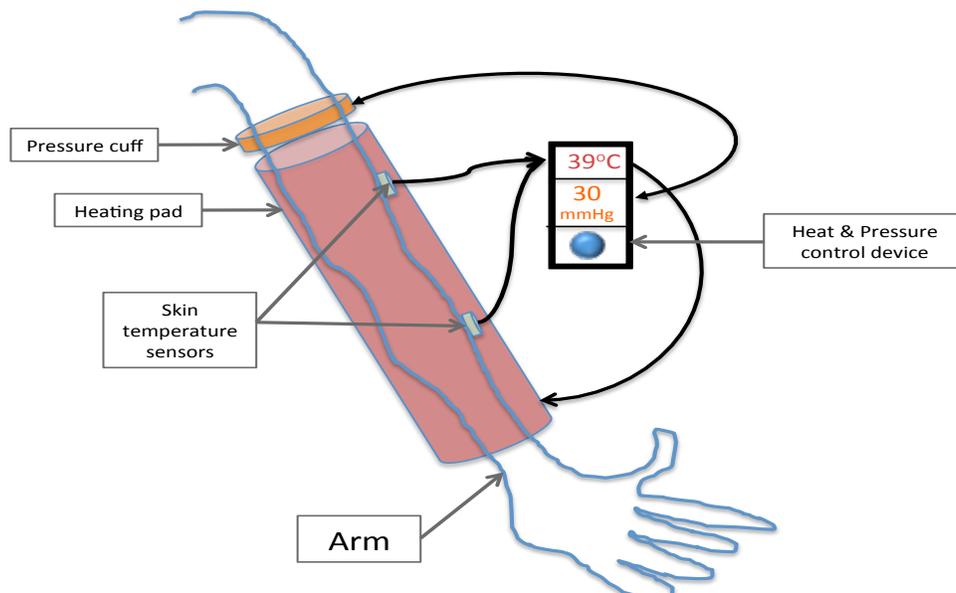
SIGNIFICANCE

About half a million people will receive hemodialysis this year for end stage renal disease. The accepted gold standard for hemodialysis access is an AVF due to the improved outcomes for the patients in terms of mortality and morbidity. However failure of AVFs to mature remains a vexing problem. This leads to dependence on CVCs for dialysis, thus increasing not only the costs, but also morbidity and mortality of the patients. Through our study, we seek to address this significant problem and hope to find a way to improve the maturation of the AVFs.

INNOVATION

Successful fistula maturation requires an increase in blood flow, vein dilation and wall thickening to be suitable for repetitive cannulation for hemodialysis⁶. This requires a fistula blood flow of at least 500 ml/min and a vein diameter greater than 4 mm, ideally achieved within 4-6 weeks after fistula surgery¹³. Forearm exercise and infra-red therapy have been shown to increase the diameter and compliance of the blood vessels due to increased blood flow. However many patients cannot perform sufficient exercise, and there were no practical and cost-effective ways to deliver infra-red therapy.

To address these limitations, we propose to test a novel portable, cost-effective device consisting of a circumferential controlled heating element with a regulated upper arm pressure cuff (see Figure) to determine whether intermittent application of heat in the presence of increased venous pressure to the arm before fistula surgery (i.e. vascular preconditioning) will improve fistula maturation.



The device consists of a circumferential controlled heating element applied around the extremity. It contains sensors to measure skin temperature coupled to a control mechanism to regulate the heating element. This feedback system maintains the specified skin temperature. The device also has a regulated pressure cuff applied around the proximal arm. The pressure cuff is connected to the control unit that controls the pressure in the cuff. The major innovation is the assembly of these components into a complete cost-effective and portable device that provides for regulated heating and pressure to optimize preconditioning of veins for use in the arterial circulation.

RESEARCH STRATEGY:

Rationale and Overview

The repetitive application of controlled heat and upper arm constrictive pressure will lead to vein dilatation, improved compliance and wall thickening necessary to precondition the vein for improved use as an AVF. We have combined both these methods into a single device called Thermovasc, which is expected to improve the fistula maturation rate if it is used pre-operatively and post-operatively.

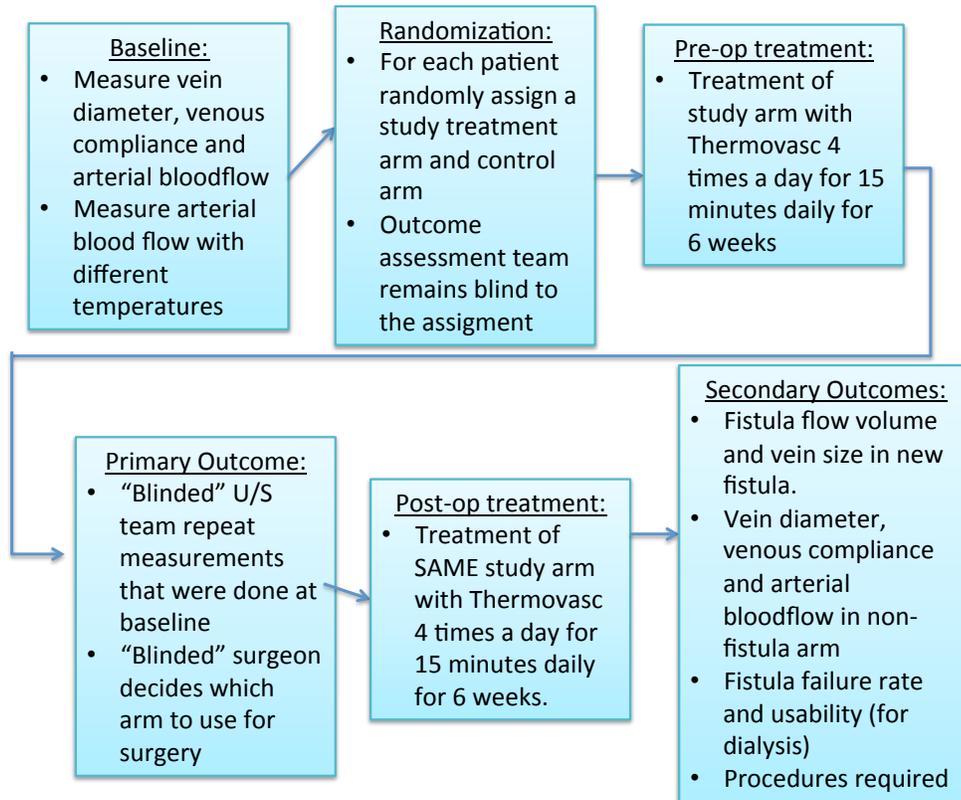
- **Aim 1:** To determine optimum parameters of heat and constrictive pressure for vascular pre-conditioning
- **Rationale:** Heat and constrictive pressure to the arm are expected to increase venous diameter and compliance of the veins. We aim to determine the optimum parameters to aid this pre-conditioning. These will provide guidelines for use of the protocol in a larger study and ultimately, in clinical practice.
- **Aim 2:** To determine whether 6 weeks of pre-operative vascular pre-conditioning with Thermovasc improves vein size and compliance
- **Rationale:** If vascular pre-conditioning can improve vein size and compliance, this would translate into improved AVF maturation, which would not only improve the mortality and morbidity of the patients, but also result in significant savings in health care costs.
- **Aim 3:** To determine whether pre-operative and post-operative vascular conditioning improves AVF maturation
- **Rationale:** The increased vein diameter and compliance that are expected from the vascular conditioning are only significant if they result in an improved maturation rate of the AVF. Although this would be more reliably tested in a larger trial, it is important to look at this outcome in this pilot study as this forms the crux of the study

Experimental Design

The study design will be as follows. Please see flow chart for schematic.

- **Baseline:** The patients will undergo a baseline measurement of cephalic vein diameter, blood flow in the brachial artery, and venous compliance (determined from pressure vs vein diameter curves) in both arms at the on-site ICAVL accredited ultrasound laboratory. The arterial flow measurements will be repeated with various temperatures (38°C, 39°C, 40°C, 41°C).
- **Randomization** will be done for each patient: one arm is randomly assigned as a study arm and the other as a control arm. The ultrasound team and the surgeons will be blinded to the assignment of the arm.
- **Pre-operatively:** The Thermovasc will be used on the study arm four times a day for 15 minutes at a time, for six weeks. An imbedded temperature sensor (e.g. iButton, Maxim, CA) sandwiched between the arm and the heating element will ascertain compliance. After six weeks, the above measurements will be repeated in both arms. The surgeon chooses the arm to be used for surgery. The ultrasound team and the surgeons will be blinded to the assignment of the arm
- **Post-operatively:** The treatment of the study arm with Thermovasc continues (irrespective of which arm was used for surgery) four times a day 15 minutes at a time for six weeks. Six weeks later, vein diameter and fistula flow volume (FFV) in the new fistula will be measured. The above mentioned measurements will be repeated on the arm that was NOT operated on.

- *Primary outcomes* (measured *pre-operatively* following the 6 week intervention)
 - Venous diameter (forearm cephalic vein) of both arms with and without 30 mmHg pressure
 - Venous compliance (forearm cephalic vein) of both arms (change in vein diameter with 0, 5, 10, 15, 20 & 30 mmHg upper arm pressure)
 - Brachial arterial flow at ambient temperature & 1°C increments from 37-41oC in both arms



- *Secondary outcomes* (measured *post-operatively* following the 6 week intervention)
 - Fistula flow volume (FFV) of the AVF
 - Vein diameter of the AVF
 - Venous compliance (forearm cephalic vein) of the non-fistula arm
 - Venous diameter (forearm cephalic vein) in the non-fistula arm
 - Primary AVF maturation rate (using criteria of Robbin; KDOQI rule of 6's).
 - Fistula usability for dialysis
 - Interventions required to assist with AVF maturation
 - AVF failure rate

Sample Size Calculation and Data Analysis

We estimate that we will need a minimum of 11 subjects to adequately power this pilot study, with venous diameter being the most important outcome that we would like to study. Some of the other outcomes like AVF maturation rate will require a

bigger sample size, which we hope to address in a larger trial. We will use a paired sample t-test for difference in vein diameter, brachial arterial flow and venous compliance before and after use of the Thermovasc device with a power of 90% and α of 0.05. Relative risk will be calculated for AVF graft survival and failure. Modified logistic regression useful for relative risk will be used for multivariate analysis to assess differences in AVF graft maturation and failure

Data Collection and Handling

Data will be collected by a research assistant and stored in the secured University of Iowa research electronic data capture system and only authorized investigators will have access to the data.

Human Subjects

All investigators involved in this study are familiar with the ethical guidelines for research involving human subjects as described in the Belmont Report and the Declaration of Helsinki. These guidelines were heeded in the study design. Potential risks to the patients are believed to be no different from the risk of using a blood pressure cuff and/or of using a heating pad. These include risk of a tourniquet effect on the arm resulting in decreased perfusion (which can be easily reversed by undoing the cuff) and the risk of a burn (which is extremely unlikely given the mild temperature of the device). Potential benefits include improved maturation of the AVF, avoidance of additional interventions to help with AVF maturation, and decreased likelihood of re-operation. IRB approval is pending

Expected Results

Arteries dilate in response to increased wall shear stress that results from an increase in blood flow (known as flow-mediated vasodilation, FMD)¹⁴. Repetitive or sustained increases in blood flow can lead to improvement in FMD and vessel size¹⁵. Higher FMD and venous compliance has been associated with improved fistula maturation⁶

It is expected that prescribed use of Thermovasc will improve the blood flow and venous diameter of the veins in the treated arms. This is expected to translate into an improved fistula maturation rate and decreased fistula failure rate as well as decreased number of interventions required for primary assisted patency.

Alternative Approaches

- Forearm exercise, with or without an upper arm tourniquet, has been reported to increase vein dilation and vein size in patients with chronic kidney disease (CKD)¹⁶ and has been recommended to improve fistula maturation. However it is difficult for many patients with late stage CKD to perform sufficient exercise to improve vein dilation (Dixon et al, unpublished).
- Forearm blood flow can also be increased with external heat¹⁷. Treatment with far-infrared therapy, which applies heat to the arm has been reported to improve access blood flow, fistula maturation and patency of newly created fistulas in patients with CKD¹⁸. However, the machine used to deliver this therapy is not particularly portable, cost-effective or practical for general use

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FACILITIES AND RESOURCES

Personnel

This project involves collaboration between the departments of Vascular Surgery, Nephrology and Bioengineering, and the Vascular Laboratory at the University of Iowa. The principal investigator, the key collaborators, and the support personnel belong to one of these departments.

- Principle investigator
- Key collaborators
- Vascular laboratory technicians of University of Iowa Hospitals and Clinics
- Seven total staff vascular surgeons performing AV fistula creation procedures
- Vascular surgery fellows and residents assisting
- Biomedical engineers
- Vascular surgery technicians and operating room nurses

Equipment

- Thermovasc devices
- Ultrasound machines
- Computers
- Database created by investigators, maintained by University of Iowa Institute for Clinical and Translational science
- University of Iowa Hospitals and Clinics Electronic Medical Record (Epic)
- Statistical analysis software (SPSS)

Patient numbers

Vascular surgeons in our tertiary referral center perform pre-operative vein assessment for most of the AVFs in the on-site vascular laboratory. We estimate that we will need a minimum of 11 patients for this pilot study. We expect that we should be easily able to enroll the needed number of patients while accounting for any possible attrition.

Clinical research space

University of Iowa Hospitals and Clinics vascular ultrasound laboratory, the vascular surgery clinic, and the offices of the involved personnel will comprise the research space