Title: Adjustable banding for arteriovenous fistula (AVF) to promote maturation and reduce high-flow complications.

Specific aims:
Patients with end-stage renal disease (ESRD) undergoing hemodialysis (HD) require a functional vascular access, which may include arteriovenous fistula (AVF), arteriovenous graft, or central venous catheter. AVF is the preferred access type because of its superior longevity, lower infection rate resulting in improved patient survival and lower cost when compared to other types of access(1). Despite these advantages, more than a third of AVFs fail to mature after creation (2, 3). Intimal hyperplasia of vessels and limited blood flow after fistula creation are significant causes for AVF maturation failure.

Surgical creation of AVF with higher blood flow might help with increasing the maturation rate. AVFs made from larger arteries and veins (such as brachio-cephalic and brachio-basilic AVFs) tend to have higher maturation rates when compared with AVFs made from smaller vessels (such as radio-cephalic AVFs). However, high uncontrollable blood flow rates may develop and can result in steal-syndrome, high output heart failure (HF), pulmonary hypertension, and cephalic arch stenosis (CAS).

We have created an innovative device design that would allow for remotely adjusting the AVF diameter and thus control the flow within the AVF. This will be done through a band that is wrapped around the AVF and has the ability to increase or decrease in diameter. This would function as a “faucet” control on the AVF to adjust the flow depending on the circumstances.

Our research proposal has the following specific aims:

Aim 1: To produce a work-like proof-of-concept prototype.
Aim 2: Bench-top system testing of the prototype.
Aim 3: Based on the information from bench-top testing, redesign the prototype in preparation for producing an alpha-prototype for animal studies.

Significance and Innovation:
Each year, about 100,000 patients are initiated on HD in the US. AVF remains the dialysis access of choice. However, two unmet clinical needs remain regarding AVF: improving maturation rates and eliminating cardiovascular complications related to the uncontrollable flow of AVF. Addressing these needs will result in a marked improvement in morbidity and mortality in HD patients as well as in significant savings in access-related costs.

Our proposed invention, namely the adjustable AVF band, will fill the gap in current clinical care by improving AVFs primary maturation rates while simultaneously reducing complications from high-flow. Although banding of AVF’s has been used for years(4-9), the ability to remotely adjust the band diameter has not been tested prior. If proven efficacious, the adjustable band may result in a shift in the current clinical practice paradigm.
The mechanism of the proposed benefits of the adjustable band is 2-fold: **First**, the device allows the safe utilization of larger arteriotomy and/or arteries and veins for AVF without fearing excessive flow through the fistula, as the band will be able to be tightened to reduce the high-flow should it occur. **Second**, the majority of patients with mature AVF develop flow rates of 1000-1700ml/min (10)(11), and it is not uncommon to have a blood flow >2000ml/min (7, 12-14). This is much higher than the needed 600ml/min to deliver HD. Those patients are then at a considerable risk of developing pulmonary hypertension, HF symptoms, steal-syndrome, and cephalic arch stenosis (5-7). Indeed, surgical AVF banding has been successfully used as a method to treat some of these complications (6, 8, 9). The adjustable band could be placed at the time of AVF creation-or at a later stage-, and can be adjusted at any point of time, reducing the rates of high-flow related complications. Furthermore, the band can be adjusted depending on the specific circumstances to accommodate for changes in the blood flow, thereby providing more accurate control. A potential overarching goal of the adjustable band project to test whether adjusting AVF flow during and between HD sessions will result in favorable hemodynamics, cardiac remodeling, and fistula patency rates.

**Device Design:**

In collaboration with the Center for Design and Manufacturing Excellence (CDME) at The Ohio State University, we have already created a preliminary design of the Adjustable AVF Band (Figures 1 & 2). This constitutes two parts; external and internal. The internal part has a magnetic screw, which when turned loosens or tightens a band that is wrapped around the AVF (similar to a traditional hose clamp). The outer part would be placed only when the device is to be activated and consists of a large magnet that corresponds to the inner magnetic screw. It would be used to turn the internal screw in the direction needed.

The device will act like a faucet that is loosened and tightened depending on the circumstances, thus allowing the AVF to deliver high flow only when needed.
RESEARCH STRATEGY:

Rationale and Overview

- **Aim 1:** To produce a work-like proof-of-concept prototype that can be used in-vitro.
  - **Rationale:** The proof-of-concept prototype is the required first step in order to be able to test the concept and collect data. We will make this prototype at the Center for Design and Manufacturing Excellence (CDME) at The Ohio State University (OSU). As noted above, we have an established relationship with CDME and have finalized the design of the device and are ready to manufacture the prototype. The CDME includes engineers from various backgrounds. Collaborating with the CDME will allow us to produce different prototypes with different approaches and layouts. The availability of different disciplines under one roof allows for cross-talk and optimization of the device.

- **Aim 2:** Bench-top testing of the prototype in a simulated environment.
  - **Rationale:** We will conduct bench-top tests of the different iterations and versions of the prototype using different simulation models. These will include artificial limbs with simulated blood along with animal tissues. The main objective would be to ensure that the device functions as intended in different layouts delivering the torque needed to “squeeze” the vessel containing simulation-blood even when separated by layers of tissue and skin. This will be done by the Principal Investigator (KB) along with the engineering team. We will also involve some of the hemodialysis nurses at this stage to get their feedback on the actuation method.

- **Aim 3:** Refine the design in preparation for producing a prototype for animal studies.
  - **Rationale:** Using the information from the bench-top testing, we will refine the design of the device in preparing us for the next phase, which is animal studies.

Overall research strategy:

While the specific aims at this stage remain within Phase 1, our overall longer-term strategy includes moving forward to Phases 2 & 3.

In Phase 2, we plan to manufacture and test the prototype on animal models to ensure safety and efficacy. Our preliminary approach is to create bilateral femoral AVFs in a porcine model and place the device on one AVF while the other one would function as a control. At this stage, we will test the functionality of the device, ensuring that it operates as intended and controls the blood flow. Adjustment of the prototype might be needed following that. Afterward, we will conduct longer-term testing to validate clinical outcomes (one group of animals with an AVF and the device and another with AVF and a sham device as a control). We already have multiple interested collaborators who have expressed their enthusiasm and willingness to collaborate in testing the prototype. These include investigators with extensive expertise in AVF creation and
in animal models of AVF, such as Prof Lian-Wang Guo at the University of Virginia and Dr. Ross Milner at the University of Chicago.

Finally, Phase 3 will include refining and testing the device in human subjects confirming clinical outcomes.

An overview of the current intellectual property (IP) landscape and a freedom to operate search did not reveal any blocking patents. We then filed a provisional patent application through the Technology Commercialization Office at The Ohio State University. Once we reach Phase 2, we plan to start discussions with the Food and Drug Administration (FDA) to help facilitate clinical testing approval in the future. Our long-term plan is to file a Traditional 510(k) application.

My role as a principal investigator will include coordinating all the steps described above and ensuring that the clinical rationale is pursued all along. I will be designing and conducting the bench-top tests. In the future, I will also be involved in designing and conducting the animal studies along with the human studies.

**Conclusion**

AVFs are the best access type for HD patients. Unfortunately, their maturation failure rate is high, and the issues with low or excess flow through them frequently lead to adverse clinical outcomes. We present an innovative device design that can control the blood flow externally, thus limiting blood flow to the least amount needed. We anticipate that our device will improve clinical outcomes in the HD population by increasing rates of AVF primary maturation and by reducing rates of high-flow related complications.

**Facilities and Collaborators:**

**Dr. Anil K Agarwal: Collaborator and Mentor**
Chief of Medicine, VA Central California.  
Professor of Medicine UCSF  
President, ASDIN
Dr. Agarwal will serve as a mentor and supervisor of the whole project. He has been very supportive of the project since the beginning of the process. With his extensive expertise in dialysis vascular access and in clinical studies, he will provide valuable input, ensuring that the progression of the device is scientifically and clinically sound.

**CDME at OSU:**
https://cdme.osu.edu
The Center for Design and Manufacturing Excellence is the manufacturing port of entry into Ohio State. It is staffed with diverse professionals ranging from former business leaders and entrepreneurs to practicing engineers. CDME houses various industry manufacturing equipment which can be utilized to manufacture a host of different devices ranging from 3D printed
prototypes to medical devices that are sterilized and ready to be used in clinical trials. The availability of different engineering disciplines within the center allows for further collaboration to produce the perfect end-product.

CDME will be contracted to produce the prototypes. Contracting with them will include the use of their facilities, equipment and personnel. Bench-top testing will also be conducted within their facilities.

References: