SPECIFIC AIMS: Association of arteriovenous fistula (AVF) access with clinical outcomes

Over 450,000 patients are dependent on maintenance hemodialysis (HD) in the United States alone and are reliant on vascular access for receipt of this life-preserving procedure. Since the “Fistula-first initiative” was implemented in 2003, the prevalent AVF use rate has increased from 33% to above 65% and continues to steadily increase. Although AVFs are beneficial, they are also associated with potential harms, including left ventricular hypertrophy, increased pulmonary flows, and changes in blood pressure, which are correlated with higher cardiovascular morbidity and mortality in HD patients. Currently, comprehensive data on hemodynamic assessment, including long-term effects of flow volume (Qa), is scarce. To date, there is no clear consensus on the optimal Qa either in National Kidney Foundation-Kidney disease Outcomes Quality Initiative guidelines or in the interventional nephrology literature. Therefore, there is a critical need to perform contemporary studies with the goal of determining the optimal range of Qa in relation to minimizing the risk of shorter- and longer-term adverse outcomes. Our following aims will test our central hypothesis that higher access Qa is associated with increased risk of shorter and longer-term complications.

AIM 1 - Association of AVF/Arteriovenous graft (AVG) flow volume with all-cause and cardiovascular mortality

Prior studies assessing the association of AVF/AVG Qa with cardiovascular outcomes are mostly short-term (2 weeks – 1 year). These studies reported a higher frequency of left ventricular dilation, increase in stroke volume and cardiac output (CO) following AVF/AVG creation, without changes in the right ventricle function and size. However, longer-term data, published by Reddy et al, showed that right ventricular remodeling and dysfunction develops after AVF/AVG creation and dialysis initiation. Unfortunately, AVF/AVG Qa was not measured in these analyses, precluding the ability to determine if Qa is associated with these observed risks. As such, there is limited data exploring the association of AVF/AVG Qa with longer-term ‘hard’ clinical outcomes, including hospitalization, cardiovascular outcomes, and mortality. We propose to leverage the unique dataset and long-term follow up of the Interventional Nephrology service at Brigham and Women’s Hospital (BWH) which has records of >2000 unique patients undergoing access procedure, which includes AVF/AVG Qa and clinical outcomes. This dataset will allow us to test the following hypotheses:

1) Higher AVF/AVG flow volume is associated with greater all-cause and cardiovascular mortality
2) Higher AVF/AVG flow volume is associated with development of hospitalization for heart failure (HF) or volume overload

AIM 2 - Association of AVF declotting procedures with cardiovascular events, a prospective cohort study

Previous data from the AURORA trial demonstrated that AVF thrombosis is strongly associated with higher all-cause and cardiovascular mortality in patients on maintenance HD. Interestingly, AVF thrombosis was associated with all-cause mortality when AVF restoration occurred within 7 days of the event. The main immediate complications after AVF declotting include peripheral arterial embolization, vein rupture, and pulmonary embolism (PE). However, the reported rates of these complications are low; thus, such immediate complications are less likely to be responsible for the higher risk of 7-day mortality observed in the AURORA trial after vascular access restoration. Given the acute changes in cardiac hemodynamics that occur following a declot procedure, on a frequent background of structural heart disease, we hypothesize that HD patients are at higher risk of cardiac arrhythmia in the days following a declot procedure. We will conduct a prospective cohort study in thirty patients undergoing an AVF declotting procedure to determine the association of AVF restoration with cardiac arrhythmia. We will use 7-day wearable Holter monitoring patches to continuously record cardiac rhythms, and will measure AVF Qa prior, immediately after, and 7 days after the declot procedure. We hypothesize that:

1) After immediate vascular restoration (AVF declotting), higher post-procedural blood flows are associated with greater frequency of clinically significant arrhythmias (atrial fibrillation, sustained ventricular tachycardia, asystole, bradycardia, or symptomatic arrhythmias)
2) Abrupt AVF flow changes after declotting procedures are associated with higher risk of adverse cardiovascular events in the 30-day period following these events (myocardial infarction, stroke, HF, PE, death).

The proposed work will advance the field of vascular access research, as defining the optimal Qa that is associated with better outcomes in HD patients, is essential. These studies will identify the short- and long-term adverse effects of AVF/AVG, leading to more effective treatment and management to reduce its related morbidity and mortality.
Significance
Although a life-preserving procedure, HD is related with increased mortality, and morbidity worldwide. The vascular access is the lifeline for the patient on HD. Since the “Fistula-First” initiative implementation in 2003, there has been a steady increase in prevalent AV fistula use. However, despite the increased prevalence of AVFs rates, quantitative associations between AVFs and various clinical outcomes is scarce. AVFs have known complications that increase morbidity and mortality. These include arterial emboli, fluid overload, pulmonary edema, infection and even death. Death is thought to be mostly caused by cardiac arrhythmia. In addition, all-cause mortality is clearly higher after a declotting procedure, leading us to explore potential mechanism by which the AVF restoration may lead to adverse outcomes. In particular, we have focused on AVF Qa, a surgically modifiable risk factor for cardiovascular morbidity and all-cause mortality in HD patients. AVF/AVG Qa To date, there is no clear consensus on the definition of the optimal Qa, and the Qa level above which a high-Qa fistula should be considered. This makes it difficult to determine the prevalence of high Qa fistulas. Several publications use a Qa >2.0 L/min as the cut-off value to define a high-Qa fistula. However, this cut-off is based on case reports and the analysis of ten patients with stage C heart failure (HF). Conversely, Pasquale et al, observed that when AVF Qa was indexed for height, a Qa >603 ml/min/m² was associated with high-output cardiac failure in a prospective cohort of 29 patients. Thus, more extensive data with larger patient size are needed to define a high-Qa fistula.

Cardiac Structural Abnormalities High Qa is postulated to increase CO and cause high-output HF and greater increases in left ventricular end-diastolic volume. In a 1-year retrospective study patients with a higher Qa (>2.0 L/min) had severe volume overload more frequently and higher left ventricular mass index. Other studies showed regression of left ventricular dilation following AVF closure in renal transplant patients. Conversely, Reddy et al, found that right ventricular (RV) remodeling and dysfunction developed after AVF creation and HD initiation in the long-term (median 2.6 years). RV dilation was strongly associated with increased risk of death. Interestingly, the development of LVD and dysfunction was uncommon. In their study access Qa was not measured. Therefore, further long-term studies, using Qa measurements, are needed to identify if there is an association between higher Qa and greater cardiac structural abnormalities.

AVF Thrombosis Data from the AURORA trial demonstrated higher all-cause mortality after declotting procedure within 7 days of AVF thrombosis, despite the lower rate of the main known immediate adverse effects (PE, arterial embolization). We hypothesize that patients are at higher risk of cardiac arrhythmia in the days following a declot procedure given the acute changes in cardiac hemodynamics. To date, to the best of our knowledge, there is no prospective data available studying the cardiac events after a declot procedure.

Access Qa and N-terminal prohormone of B type natriuretic peptide (NTproBNP) Currently, there are limited data examining the relationship between the temporal changes of NTproBNP with AVF/AVG Qa. Wärjä et al reported a case of a patient with NT-pro-BNP levels above the upper detection level of 70 ng/L. Echocardiography revealed a LV cardiac insufficiency. AVF Qa was at 3034 ml/min. The upper arm AVF was closed, and it was replaced by a lower arm AVF leading to a reduced Qa of 1344 ml/min. The patient recovered and NT-proBNP decreased to 7000 ng/L. Further evaluation is needed to determine if there is a relationship between Qa and NT-proBNP levels.

Summary: Based on the available evidence, we therefore postulate that higher AVF Qa is associated with all-cause and cardiovascular mortality in patients on HD. Definition of the optimal Qa is crucial to decrease the risk of short- and long-term complications. Our ultimate aim is to translate our findings to preventive interventions and therapies that result in improved patient care and reduce morbidity and mortality.

Innovation
In this submission we propose to analyze a large dataset which includes >2000 patients at BWH to examine the association of AVG/AVF Qa and clinical outcomes. We also propose a prospective inpatient cohort study to determine the cardiovascular adverse events associated with AVF vascular restoration after a declotting procedure within 7 days of AVF thrombosis. Our innovative approaches include: 1) Use of a 7-day wearable Holter monitoring patches to continuously record cardiac rhythms after AVF vascular restoration, 2) Measurements of AVF Qa prior, immediately after, and 7 days after the declot procedure; 3) Measurement of NT-pro-BNP to determine if there is a relationship between this biomarker levels and access Qa; and 4) the research team expertise. The latter consist of Dr. Mc Causland (senior co-investigator) who has expertise in clinical trials, cardiac biomarker studies and cohort studies of HD patients; and Dr. Hentschel who has expertise in interventional nephrology research. In addition to providing unique expertise in the conduct, analyses, and interpretation of results, they will provide guidance on future preventive initiatives and therapeutic trials that may result from our observations.
Research Strategy for aims 1 and 2

Rationale and Overview
For aim 1 we will conduct an observational study including data from > 2,000 patients already collected and currently available at BWH. We will organize the data to test our hypothesis that higher AVG/AVF Qa is related with higher hospitalization rates and greater all-cause and cardiovascular mortality.

For aim 2 we will conduct a prospective cohort study in 30 patients who are undergoing an AVF declotting procedure within 7 days of AVF thrombosis to determine the association of AVF restoration with cardiac arrhythmia. In addition, we will measure AVF Qa prior, immediately after, and 7 days after the declot procedure to assess for changes in Qa and its relationship with outcomes.

Experimental Design

Aim 1
For aim one we will select patients with AVF/AVG followed for the last 10 years at BWH and BW Faulkner Hospital (BWFH).

Inclusion Criteria patients with AVF/AVG followed at BWH and BWFH, Qa measurements available overtime, age ≥18y; thrice-weekly HD.

Exclusion Criteria History of heart failure, previous myocardial infarction, pulmonary hypertension, sleep apnea, hyperthyroidism, significant valvular disease, constrictive pericarditis, heart transplant prior the AVG/AVF creation.

Data Collection Detailed data will be collected including date of AVF/AVG creation, location of AVF/AVG, AVF/AVG Qa measurements available overtime, AVF/AVG events (thrombosis, failure), cardiovascular events, hospitalization rates, causes of death, demographics, height, weight overtime, blood pressure measurements, information on co-morbid conditions, echocardiogram reports pre- and post AVF creation if available, and laboratory results from the electronic medical record.

Exposure & Outcomes The primary exposure is AVF/AVG Qa exposure over time, the baseline Qa will be the measurement at 6 weeks after access creation. Primary outcomes will be adverse events including heart failure, hospitalizations secondary to volume overload and/or HF, symptomatic arrhythmias, myocardial infarction, pulmonary hypertension, pulmonary embolism, stroke, and death. We will ascertain these data by using diagnosis and discharge codes available in the electronic medical record (EMR) and death records.

Analytic Approach We will inspect and plot the AVF Qa measurements overtime, and the significant events (hospitalizations for HF, volume overload, all-cause and cardiovascular mortality) and assess trends descriptively. Two-way comparisons will be reported with an alpha=0.05. Unadjusted and adjusted Cox regression models will be fit to assess the association of Qa with the outcomes of interest. Covariates for inclusion in adjusted models are age, gender, body mass index (BMI), smoking status, alcohol consumption, blood pressure, diabetes, peripheral vascular disease (PVD). Initially we will examine Qa as a continuous variable. We will also assess the association of categories of Qa and t flexible cubic splines, in order to determine if there is a threshold beyond which Qa is associated with adverse outcomes. Limitations Selection bias: we will attempt to minimize this by casting a wide net in terms of inclusion criteria, in order to maximize the generalizability of our results; Missing data: All the data was collected of patients undergoing AVF/AVG creation at BWH/BWFH with EMR data available. If missing data is an issue, we will consider approaches favored by the National Research Council, such as weighted estimating equations (16).

Residual confounding: we will attempt to minimize this by performing multivariable adjustment.

Aim 2
For aim 2 we will recruit 30 out of >300 patients that typically undergo AVF declotting procedures over eight months at BWH and BWFH

Inclusion Criteria Declotting procedure within 7 days of AVF/AVG thrombosis diagnosis; age ≥18y; thrice-weekly HD; informed consent.

Exclusion Criteria Declotting procedure >7 days of AVF thrombosis diagnosis; history of HF, recent myocardial infarction, pulmonary hypertension, atrial fibrillation, sustained ventricular tachycardia, asystole, bradycardia, or symptomatic arrhythmias prior the declotting procedure.

Study Procedures Measurements of AVF Qa will be obtained prior to AVF declotting procedure; subsequently, after the declotting procedure, we will measure AVF Qa again. Then, we will place a 7 days wearable Holter monitoring patch. The patients will come back to the BWH clinic after 7 days, we will measure AVF Qa and NT-pro-BNP levels in that visit.
For the measurements of AVF Qa we will use a bedside doppler ultrasound (FUJIFILM SonoSite X-Porte ultrasound), available at BWH and BWFH facilities. We will perform two consecutive longitudinal measurements; the result will be the average between these two measurements. All measurements will be performed by interventional nephrologists and medical doctors trained on Qa measurements using an ultrasound. For the Holter monitor we will use a Zio Patch which is a peel and stick device that is worn for an extended monitoring period of up to 14 days. Plasma samples will be drawn 7 days after the declotting procedure. All samples will be time-stamped, labeled, kept on ice, and transported to the renal research laboratory at BWH for processing. A dedicated research assistant will be available to help with all blood collections and to ensure that patients get the Holter wearable patches after the declotting procedure.

**Data Collection** Detailed data will be collected including the AVF Qa measurements pre and post the declotting procedure, day of thrombosis diagnosis, blood pressure prior and after the declotting procedure, type of declotting procedure and fistula location. In addition, we will collect demographic details, information on co-morbid conditions, weight, height, adverse events within 7 days after the procedure, and non-study laboratory results from the EMR. Data from the wearable device (ZioPatch) will be obtained from the company iRhythm (provider of ZioPatch). The data will be securely stored per Partners protocols. All other data will be entered on case report forms and recorded on a study-specific secure dataset.

**Exposure & Outcomes** The primary exposures are the AVF Qa values post-declotting procedure. The primary outcomes will be cardiovascular events within 7 days of declotting procedure.

**Analytic Approach** Unadjusted and adjusted negative binomial regression models will be fit to assess the association of Qa with the rates of arrhythmia. Covariates for inclusion in adjusted models are age, gender, BMI, smoking status, alcohol consumption, blood pressure, diabetes, PVD. Initially we will examine Qa as a continuous variable. We will also assess the association of categories of Qa and fit flexible cubic splines, in order to determine if there is a threshold beyond which Qa is associated with adverse outcomes. In sensitivity analyses, we will fit logistic regression models with yes/no arrhythmia outcomes. We will inspect and plot the AVF Qa measurements prior, immediately after, and 7 days after the declot procedure and the cardiovascular events captured by the ZioPatch and assess trends descriptively. We will also plot and assess other adverse events within the 7 days of the declot procedure and AVF Qa measurements. Two-way comparisons will be reported with an alpha=0.05.

**Limitations** Recruitment: we will recruit patients undergoing AVF declotting procedure at BWH or BWFH. Based on clinical data, there will be >300 eligible patients/year for possible inclusion. Follow-up visit: Participants will need to come 7 days after the procedure for blood work and AVF Qa measurement to the BWH clinic, this can be challenging for some patients. In this case we will provide a $25 incentive for patients to come for the second visit.

**Expected Results**
For aim 1 we hypothesize that higher AVF/AVG Qa is associated with greater adverse events, all-cause and cardiovascular mortality in the short- and long-term. In case our results are different that our hypothesis, we will examine other potential metrics within our database and/or will examine other datasets to confirm our findings.
For aim 2 we hypothesize that higher AVF Qa after the declotting procedure within 7 days of AVF thrombosis diagnosis, is associated with worse cardiovascular outcomes. Similarly, we hypothesize that higher NT-pro-BNP levels is associated with higher AVF Qa.

**Alternative Approach**
Alternatively, a long-term prospective cohort study would be ideal for aim one; however, it would take several years of research to accumulate significant events including hospitalizations for heart failure (HF) or volume overload, cardiovascular and all-cause mortality events. For this reason, a retrospective cohort study is more cost-effective at this stage.
For aim two, a prospective randomized study with a cardiac implantable device will be an alternative for the wearable patches. With the implantable devices the data would be captured for a longer period of time. This study would be larger and would take longer than the one we propose. Our study will serve as a preliminary study for more complex future study designs.
References


Resources and Facilities

Personnel
Dr. McCausland's laboratory currently has two research fellows, three dedicated research coordinators and one research trainee.

Equipment
All necessary equipment is located between the sites of the Harvard Institutes of Medicine (HIM), BWH and BWFH. Dr. McCausland and five other employees at BWH are on the telephone contact list for any freezer malfunctions on a 24/7 basis. Laboratory studies will be performed by collaborators in the Clinical Biochemistry department, located at Brigham and Women's Hospital. Two iPads with accessories and software are already available in our research group to facilitate patient enrollments.

Two FUJIFILM SonoSite X-Porte ultrasound (US) are available to use for the study; one is at BWH nephrology clinic and the second one is at BWFH interventional nephrology site. In addition, two portable Philips Lumify handheld US with probe are also available in Dr. McCausland's office.

We will buy 30 Zio AT monitors directly from iRhythm company.

Computer: All study data will reside on a secured desktop computer residing in Dr. McCausland's office. Available software includes PRISM, SAS and Stata. Image processing software is also supplied. The Electronics and Maintenance Department of BWH provide first-class technical support. Software packages to protect against viruses will be provided by BWH. Computer access is linked to Harvard School of Public Health, where, department computing resources include a state-of-the-art Linux computing cluster, modern desktop computers for members of the department, and a computing laboratory for students. The Linux cluster is a 32-node (64-CPU) shared computing cluster that provides high performance, parallel processing computing and is designed for future growth. The cluster is operated by the Department of Information Technology (IT) by professional systems administrators, who provide considerable user support to researchers with accounts on the cluster. Members of the Department of Biostatistics are the core users of the cluster and have a substantial say in the policies and operation of the cluster. Each cluster node is a Dell dual CPU 3.2 Ghz Xeon 64-bit machine with 6 Gb RAM. The cluster uses ROCKS cluster scheduling software to balance usage, has 1 Tb of disk space, and has weekly tape backup. Software includes R, Matlab, and Mathematica, as well as compilers for common programming languages.

Patient numbers if applicable
Brigham and Women's Hospital (BWH) is an 800+ bed major teaching hospitals of Harvard Medical School. We have a rich tradition of patient-oriented research. The primary units from which we will enroll patients to our study are the BWH dialysis unit and BWFH Interventional Nephrology center. Faulkner Hospital is in close proximity to Brigham and Women's Hospital. More than 400 patients have a declotting procedure within a year at BWFH.

Laboratory or clinical research space as applicable
Office: Dr. McCausland has a dedicated 200 sq ft research office, with computer, internet access, secure storage and telephone line. Statistical packages such as SAS and STATA are available for analyses. Other software will enable word processing, image analysis, and internet searches. BWH provides excellent technical backup.

Dedicated cubicle space is available for two research fellows, adjacent to Dr. McCausland's office. This space is supplied with personal desktop computer, broadband internet access, Microsoft office, secure storage and dedicated telephone line.

Laboratory: Located on the first floor of the Medical Research building at BWH. Equipment as mentioned above.

Research Coordinators office: Dedicated space for three research coordinators, with computer, internet access, secure storage, and telephone line. Statistical packages such as SAS and STATA are available for analyses. Other software will enable word processing, image analysis, and internet searches.