
Protocol Title:	Hemodynamic effects of blood flow variation in continuous renal replacement therapy
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* * * Background, Purpose, Study Procedures * * *

Title

Hemodynamic effects of blood flow variation in continuous renal replacement therapy

Complete Sections 1 - 16. In sections that allow reference to sponsor protocol or grant, clearly state section and page numbers. Any information that is different or specific to the local site should be in the SLU application. Specify N/A as appropriate.

1. Background

Page numbers from a sponsor's protocol/grant may be referenced in 1a and 1b.

a) **Provide an introduction and background information. Describe past experimental and/or clinical findings leading to the formulation of the study, if applicable. Investigator Initiated studies must cite references in the response provided or attach a bibliography. *?HELP?***

Critically ill patients in the intensive care unit (ICU) with renal failure requiring renal replacement therapy (RRT) are frequently started on continuous renal replacement therapy (CRRT) as the renal replacement modality of choice. At Saint. Louis University Hospital (SLUH), CRRT is provided using the NxStage System One device, which is FDA-approved for this indication. The dialysis cartridge used at SLUH is approved for blood flow rates (BFR) ranging from 50 to 600 ml / minute for CRRT, and the choice of blood flow is determined by the prescribing physician. Lower BFRs in a CRRT circuit has been linked to the frequency of clotting of the CRRT circuit in some (Dunn 2014) but not all (Castillo 2008, Prasad 2000) studies. Importantly, in the prior studies that did not show a benefit of increasing blood flow rate, most patients received anticoagulation with CRRT. However, many patients are not candidates for anticoagulation due to coagulopathy or bleeding. In these patients, if BFR can be safely increased, CRRT circuit clotting leading to interruptions of therapy might be avoided. There is paucity of data to guide adjusting BFR on CRRT and the clinical impacts of such adjustments.

Please save frequently

b) **Describe any animal experimentation and findings leading to the formulation of the study, if there is no supporting human data.**

NA

2. Purpose of the study

a) **Provide a brief lay summary of the project in <200 words. The lay summary should be readily understandable to the general public.**

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Continuous renal replacement therapy (CRRT) is often prescribed as a supportive therapy in patients with renal failure in the intensive care unit. At Saint Louis Univeristy Hospital, the NxStage System One dialysis machine, along with the Nxstage Cartridge Express dialysis cartridge, is used for CRRT. Blood flow rate (BFR) is a parameter on a CRRT machine that has a range of acceptable values, and is determined by the prescribing physician. The purpose of this study is to study effects of changing blood flow from 150ml per minute to 350ml per minute in continuous dialysis on patients' hemodynamic parameters.

Page numbers from a sponsor's protocol/grant may be referenced in 2b and 2c.

b) List your research objectives (specific aims & hypotheses of the study).

Hypothesis:
We hypothesize that within the range of BFR currently used, and at a fixed dialysate flow rate, the impact of BFR in the CRRT machine on patient's hemodynamics will be clinically insignificant, as defined as a change in systolic blood pressure of less than 6mm mercury (see section 3d).

Specific Aims:
The goal of the study is to estimate the change hemodynamic parameters that occurs (if any) when blood flow is varied in the range specified above.

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c) Describe the study design (e.g., single/double blind, parallel, crossover, control, experimental, observational, etc.). If the study is investigator-initiated, a timeline for individual subject recruitment, follow-up, and analysis for the study is required. Also, indicate if the subjects will be randomized.

Prospective, cross-over, non-randomized study.

Timeline:
Recruitment: 18 months

Follow-up: subjects will be monitored for the 30 minutes during study protocol and for an additional 10 minutes. As this is a physiological study using an FDA-approved device being used in an FDA-approved manner after the clinical decision has already been made to institute therapy, long-term followup will not be required.

Analysis: Data analysis and publication will take one year after study is completed.

d) If subjects will be given placebo, please justify placebo use. *?HELP?*

NA

3. Study Procedures

a) N Is this project a multicenter study (i.e., same project is conducted elsewhere by a different investigator) OR does this study involve conduct of research at multiple sites?

Is SLU acting as a coordinating center for other sites OR is the SLU PI a direct recipient of a federal grant for this research? If yes, complete and attach the Supplemental

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Application for Coordinating Center Activities.

Will the SLU site be participating in all parts/procedures/arms of the study?

If No, explain what SLU will NOT participate in:

Please save frequently

Page numbers from a sponsor's protocol/grant may be referenced in 3b, 3c, and 3d.

b) Describe all the procedures, from screening through end-of-study, that the human subject must undergo in the research project, including study visits, drug treatments, randomization and the procedures that are part of standard of care. Specify which procedures are for research and which are standard of care. Please note: The box below is for text only. If you would like to add tables, charts, etc., attach those files in the Attachment section (#16).

Screening: subjects on CRRT who are on the medical ICU service will be screened for inclusion and exclusion criteria.

Informed consent: Consent will be obtained from patients or a health care proxy (in cases where patient does not have capacity to give consent) in a private room. The consent process is detailed in section 8d of this submission and attached consent form.

The study procedure and enrollment of patients receiving CRRT through the division of Nephrology at Saint Louis University has been approved by division chief Dr. Kevin Martin. Dr. Zafar Jamkhana, director of the medical ICU, is a coinvestigator and has approved the protocol and enrollment of eligible patients on the MICU service. When a patient is enrolled in the study, Dr. Dany Issa, a coinvestigator and faculty member with the division of Nephrology, will ensure that CRRT orders reflect the study protocol. The ICU physician conducting the study protocol will ensure that if the patient is prescribed vasopressors, titration orders are modified to reflect the study protocol; vasopressor dose will remain constant as long as blood pressure remains within the protocol-specified parameters, but may be titrated if patients develop any pre-specified safety endpoints, adverse reactions or at physician discretion if clinically indicated. if When a patient is enrolled, this will be communicated to the physicians on nephrology consult and the medical intensive care unit teams caring for the patient. All study procedures are consistent with FDA-approved uses of the dialysis device and are within established standards of care.

Procedure: An attending or fellow physician who is a member of the investigator team will supervise the entire protocol at the bedside. An ICU nurse will be present during the protocol. The study physician will ensure that patient's MAP is >=65 mm Hg prior to initiating protocol. to ensure The study protocol is divided into three periods, each lasting 10 minutes. During all three periods, dialysate flow rate will be as prescribed by the nephrology consult attending physician, and fluid removal will be set to minimal.

The pre-specified protocol BFR rates of 150 and 350 ml/min were chosen because these are values at the lower and higher end of standard of care, respectively, and the range outside of which circuit lifespan observational studies suggest circuit lifespan may decrease (Dunn 2014). The protocol consists of two separate periods of BFR set to 150 in order to account for the influence of time on hemodynamics, separate from the influence of BFR. To clarify, if hemodynamics change from period 1 to period 2, it will not be clear if this is due to change in blood flow or changes over time. Repeating measurements at low blood flow will permit estimation of time-dependent effects. Large randomized trials involving the use of CRRT have used blood flows similar to those being studied in this protocol (Vinsonneau 2006, Palevsky 2008).

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Hemodynamic data: blood pressure, heart rate, and vasopressor dose will be documented. If the patient's primary care team has prescribed a device for cardiac output monitoring, stroke volume will also be documented.

Period 1: CRRT will be administered with blood flow rate (BFR) of 150 ml per minute. Hemodynamic data will be documented every minute for 10 minutes

Period 2: BFR will be increased to 350 ml per minute. Hemodynamic data will be documented every minute for 10 minutes.

Period 3: BFR will be decreased back to 150 ml per minute. Hemodynamic data will be documented every minute for 10 minutes.

Blood flow rate changes will be made at approximately one minute intervals in increments of no more than 75 mL/min.

After the third study period, patients will be monitored with the ICU nurse at the bedside and the attending physician immediately available for additional 10 minutes.

After the completion of all three study periods, BFR will be returned to the level prescribed by the clinical nephrology team caring for the patient, determined by standard of care.

c) **If the proposed study is a clinical trial where a drug, vaccine, device or other treatment is compared to a placebo group or comparison treatment group, what are the guidelines or endpoints by which early decisions regarding efficacy or lack of efficacy can be made? For example, it may be reasonable to stop enrollment on a study when efficacy has already been clearly demonstrated, to avoid unnecessary enrollments of additional subjects. Alternatively, it may be reasonable to stop enrollment when it is clear that efficacy will never be demonstrated, given the statistical power of the study as designed. Describe the guidelines that are in place to assist in making these determinations, if relevant to the proposed study.**

NA

d) **Describe how data analysis will be performed (statistical tests, methods of evaluating data) and indicate the smallest group/unit for which separate reporting will occur. For studies involving a questionnaire, if data and reliability information are available, please describe or provide references. For full board, unfunded studies describe sample size determination and power analysis. If none, please justify.**

Changes in blood pressure, heart rate, stroke volume, and vasopressor dose will be studied with paired t-tests. Based on prior studies of patients with sepsis, short-term variability of systolic blood pressure is about 6% ± 4% (Tavernier 1998, Michard 2000) after patients have received volume expansion. Taking this difference in blood pressure as the minimum clinically important difference, a sample size of about 12-15 patients will be needed for a power of 0.9 and α of 0.05 to show a 6mm or greater difference in blood pressure.

Please save frequently

e) **State if deception (including incomplete disclosure of study purpose/procedures) will be used. If so, describe the nature of the deception and provide a rationale for its use. Also, describe debriefing procedures or justify a waiver of the requirement to debrief. NOTE: for studies using deception, an alteration of consent must be justified in the Informed Consent section of the protocol (#13) and the debriefing script/statement must be uploaded in the Attachments section**

(#16). See IRB Deception Guidelines.

f) Is there an accepted standard of care and/or standard practice at SLU for the condition/disease/situation being studied? This information will assist in comparing the risk/benefit ratio of study procedures relevant to usual care that would be received outside of the research context. *?HELP?* Y

If yes, please describe the standard of care and standard practice at SLU for the condition/disease/situation being studied.

All portions of the experimental protocol are within standards of care. The NxStage Cartridge Express device is approved for blood flows from 50-600 ml per minute. We will be studying blood flows within this range. The usual blood flow rate prescribed at Saint Louis University Hospital is 200-300 ml per minute. The dialysate flow rate and composition will be determined by standards of care and the judgment of the nephrology consult attending physician, and will not be altered in the study.

There are no studies or manufacturer guidelines establishing how quickly blood flow should be changed. When the prescribed blood flow rate is changed, standard nursing practice in Saint Louis University Hospital medical intensive are unit is to change blood flow settings in a single step. As a cautionary measure, blood flow rate changes will be made at approximately one minute intervals in increments of no more than 75 mL/min.

g) Does this study involve any diagnostic imaging, labwork or genetic testing that could result in clinical discovery (diagnoses, genetic mutations, etc.)? Note that this could include discovery that is expected (related to the research) or incidental (not related to research aims, but possible, like a mass/shadow found in imaging despite not looking for it). N

If yes, please describe and include whether there are plans to share findings with study participants.

h) Is this study subject to the NIH Genomic Data Sharing Policy? N

The NIH GDS policy applies to all NIH-funded research that generates large-scale human genomic data as well as the use of these data for subsequent research and includes: genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, metagenomics, epigenomic and gene expression data, irrespective of NIH funding mechanism. Click here for more specific examples.
