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Protocol Title: Splanchnic Nerve Block for Therapy of Chronic Heart Failure (Splanchnic HF II)

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1. Protocol Title:

Splanchnic Nerve Block for Therapy of Chronic Heart Failure (Splanchnic HF II)

2. Purpose of the Study:

Splanchnic vasoconstriction may contribute to decompensation of chronic heart failure via volume redistribution from the splanchnic vascular bed to the central compartment. This is a sympathetically mediated reflex and can be interrupted through a splanchnic nerve block. Therefore, we hypothesize that interruption of the efferent/afferent innervation of the splanchnic vasculature will decrease cardiac congestion and improve renal function in subjects presenting with heart failure.

Objectives:

1. We will determine if splanchnic nerve blockade decreases cardiac preload as measured by invasive hemodynamics.
2. We will determine if splanchnic nerve blockade will improve invasive hemodynamics during exercise.
3. We will determine if splanchnic nerve blockade improves symptoms of shortness of breath.

3. Background & Significance:

Conventional wisdom dictates that heart failure (HF) exacerbations follow a period of fluid accumulation leading to volume overload. However, study of weight in HF shows that 54% of subjects have an exacerbation without antecedent weight gain. Invasive monitoring of hemodynamics showed that central venous pressure rises in the weeks prior to decompensation despite no weight change in both systolic and diastolic heart failure. The leading theory for explaining this phenomenon of increased central venous pressure in the absence of change in total body water is that subjects with heart failure (HF) have impaired ability to store blood in their splanchnic vascular compartment. In a healthy population, the splanchnic bed contains about 40% of the total blood volume, 80% of which is stored in capacitance veins, and serves as a buffer for the central vascular compartment. Fluid is normally mobilized from this compartment via increased sympathetic tone and circulating catecholamines in response to a variety of physiologic and pathologic stressors. Given the role that the splanchnic circulation plays in hemodynamic regulation, it is hypothesized that increased sympathetic tone in the splanchnic vasculature contributes to both acute and chronic heart failure decompensation by mobilizing fluid to the central vasculature (Fallick C, Circulation Heart Failure 2011).

Animal models provide direct evidence of this pathophysiological effect. In healthy animals, splanchnic nerve stimulation shifts blood into the central compartment, increasing preload and cardiac output. In dogs with cardiac pacing induced systolic heart failure, splanchnic vascular capacitance was decreased (Ogilvie RI, Circulation 1992). In these dogs, surgical transection of the splanchnic nerve,

terminating sympathetic tone, results in decreased preload as measured by systolic and diastolic filling pressures and increased compliance of the left ventricle. In humans splanchnic nerve blocks are commonly used for pain control in subjects with intractable visceral organ cancer pain. The nerve blocks are done temporarily using anesthetic agents or more commonly permanently using neurolytic agents. Interestingly, the most common "side-effect" of this therapy includes transient orthostatic hypotension due an increase in splanchnic vascular storage capacity, which typically is prevented by aggressive pre-procedural hydration (Eisenberg E, Anesthesia and analgesia 1995). In a pilot study using a short acting anesthetic agent (lidocaine) we have applied the splanchnic nerve block to acute heart failure subjects and found a reduction in resting cardiac filling pressures and an improved cardiac output (Figure 1 for the first 5 analyzed cases of total 10 subjects done by today). We found also found that the splanchnic nerve block improved shortness of breath and brain natriuretic peptide levels as an indication of cardiac decongestion.

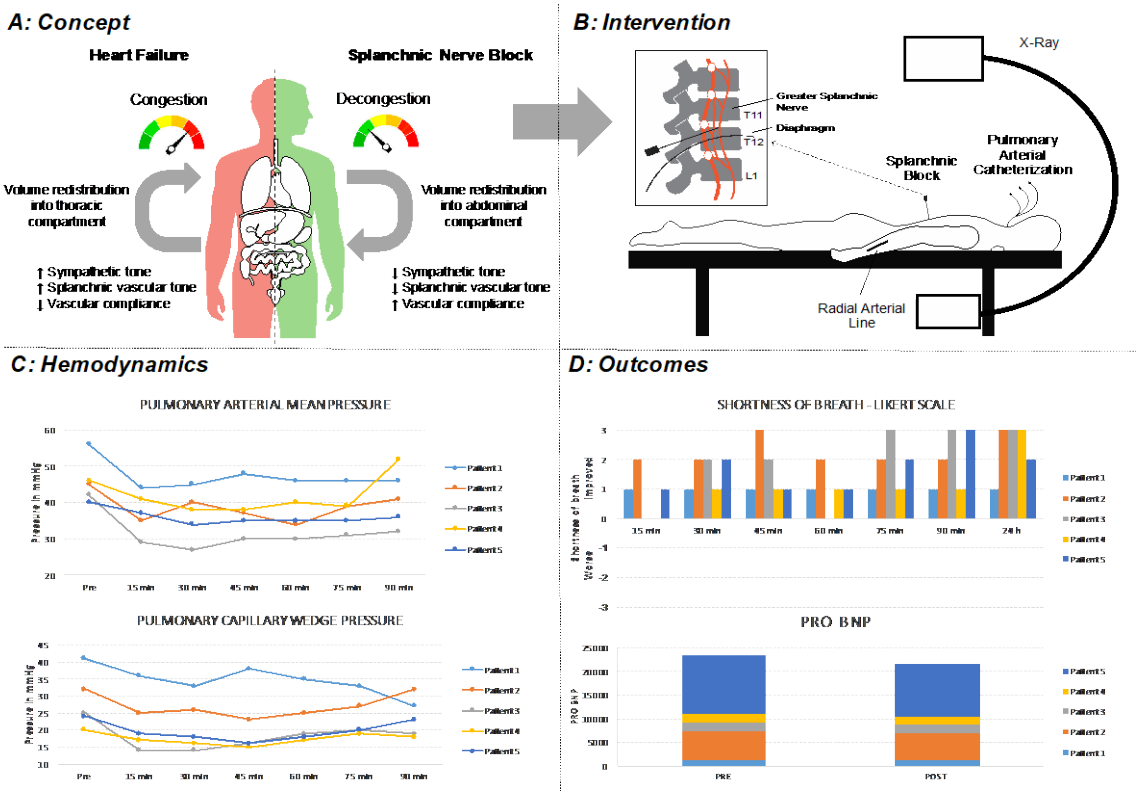


Figure 1:
Panel A: Role of volume redistribution in the congestion of heart failure.
Panel B: Procedural aspects of the splanchnic nerve block intervention.
Panel C: Effects of the splanchnic nerve block on intra-cardiac pressures.
Panel D: Effects on the splanchnic nerve block on symptoms and biomarker.

In addition to the strong evidence supporting splanchnic nerve blockade as treatment of volume overload, it is possible it will also treat cardiorenal syndrome. The autonomic nervous system plays a critical role in the regulation of the kidney. Though this system is not fully understood, preclinical and clinical studies indicate the presence of a hepatorenal reflex that inhibits the renal function and causes fluid retention. This reflex has its origin in the portal vein and is stimulated by portal congestion. The splanchnic nerves represent the afferent and partially the efferent arm of the reflex arch. Inhibition of this reflex pathway in animals and a small human pilot study was shown to improve renal function and urine production.

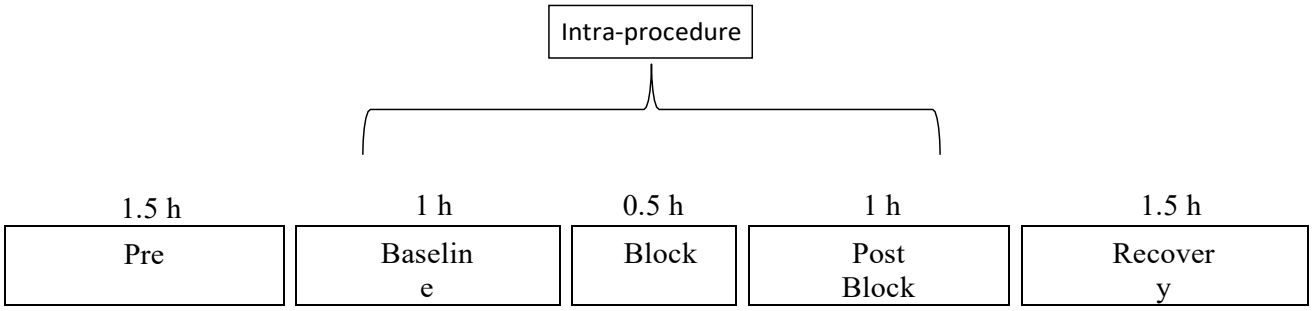
4. Design & Procedures:

This study will be a prospective, uncontrolled clinical trial. The study will not be controlled as invasive monitoring of hemodynamics will be performed, allowing clear demonstration of a cause-effect relationship.

This study aims to piggy-back on an elective right heart catheterization (RHC) in subjects with chronic heart failure. The right heart catheterization will be part of the subject's standard of clinical care (SOC). Subjects eligible for this study will be referred to the Duke cath lab for the evaluation of cardiac filling pressures because it is found to be necessary by the outpatient provider. This will occur in the cardiac catheterization lab. Subjects get scheduled for RHC days to weeks (2-3) ahead of their procedure. The eligible subject will be contacted before the study to be informed about the eligibility for the study and basic information about the study will be provided over the phone shortly after they have been scheduled. Subject will be consented in person in the morning of the procedure.

The subject will undergo pre procedural testing as demonstrated below in the flow chart (all part of the clinical study - CS). Besides the RHC (SOC) the subject will undergo an invasive cardiopulmonary exercise with the RHC in place. Baseline evaluation is followed by a regional nerve block (bilateral splanchnic nerves) while the subject is in the catheterization lab. This will be performed by an anesthesiologist experienced in splanchnic nerve blocks.

Figure 2: Study flow chart



Pre	Baseline	Block	Post Block	Recovery
- Exam/orthostatics/ bendopnea - Labs (BMP, BNP) - 6 min walk test - Pulse wave analysis - Heart rate variability - Lung volume (impedance) - SOB questionnaires - Urine output	1. Baseline RHC in supine 2. Labs (Angiotensin II), Plasma Metanephrines, Vasopressin, Plasma Catecholamines, Lactate) 3. RHC with feet up 4. Echo and abdominal US 5. Valsalva 6. Invasive CPX with leg raise - Clear-site	Splanchnic nerve block	1. Baseline RHC in supine 2. RHC with feet up 3. Echo and abdominal US 4. Valsalva 5. Invasive CPX with leg raise 6. Labs (Angiotensin II), Plasma Metanephrines, Vasopressin, Plasma Catecholamines, Lactate) - Clear-site	- Exam/orthostatics/ bendopnea - Labs (BMP, BNP) - 6 min walk test - Pulse wave analysis - Heart rate variability - Lung volume (impedance) - SOB questionnaires - Urine output

Table: Study events

Required Assessment	Pre procedure (day of)	Baseline (intra-procedure)	Block	Post Block Procedure	Recovery	24 h after procedure	48 h after procedure	6 Months after Procedure (±14 days)
Vitals (BP, HR, RR, SpO2)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)			
Weight	X (SOC)				X (SOC)			
Orthostatic vitals	X (CS)				X (CS)			
Urine output (continuous recording)	X (CS)	X (CS)	X (CS)	X (CS)	X (CS)			
Valsalva		X (CS)		X (CS)				
Labs: BMP, pro-BNP, urine sodium,	X (SOC/CS)				X (CS)			
Labs (Angiotensin II), Plasma Metanephrines, Vasopressin, Plasma Catecholamines, Lactate		X (CS)		X (CS)				
Dyspnea Questionnaire		X (CS)		X (CS)	X (CS)	X (CS)	X (CS)	
Six minute walk test	X (CS)				X (CS)			
Impedance and lung fluid content measurement		X (CS)		X (CS)				
Heart rate variability	X (CS)	X (CS)	X (CS)	X (CS)	X (CS)			
Echocardiogram		X (CS)		X (CS)				
Invasive CPX		X (SOC/CS)		X (CS)				
Splanchnic nerve block			X (CS)					
Phone Call						X (CS)	X (CS)	X (CS)

*Phone call will capture mortality status and number of subject admissions to the hospital since procedure

Following enrollment into the study the subject will undergo the following tests/measurements. A majority of the clinical testing occurs as part of the clinical study (CS) however the main procedure of RHC is standard of care (SOC).

Pre-procedure: Following information will be collected from the subject's charts thatwill be done as standard of care (SOC). Study specific tests/recordings are also listed below:

- If the subject is female and childbearing potential and has not had a pregnancy test since the arrival to the hospital, a blood pregnancy test will be done (CS). If positive the subject will be excluded from the study.
- Subjects will have strict measurement of urine output (SOC). A urine sample will be sent to the laboratory to check for the sodium concentration (CS). Subjects requiring a foley catheter will have measurements taken at comparable time intervals (SOC).
- Recorded vitals including weight, BP, HR, RR, SPO2 on the day before procedure and within 1h before procedure (SOC) and record heart rate variability using a non-invasive wrist monitor for 5 minutes (CS).
- Orthostatic vitals (5 minutes supine, 1+5 minutes sitting and 1+5 minutes standing) on the day before procedure and within 1h before procedure (CS). Also we will document whether s has symptoms bending over for 10 seconds (bendopnea).
- Labs: Basic metabolic panel (BMP) (SOC), brain natriuretic peptide (BNP) (CS), urine sodium (CS) plasma angiotensin II (CS), plasma arginine vasopressin (CS), plasma catecholamines. This will not require an extra lab draw. Total expected blood loss is <20ml.
- Dyspnea questionnaire using a 7-point Likert scale and Visual Analog Scale (CS)
- Six minute walk test (CS)
- Echocardiogram at baseline and after the block will be performed while the subject is on the cath table (CS). This is considered one continuous echo. This ultrasound test will also be used to look at liver blood flow.
- If the subject is on diuretics medications the scheduling of the medication will be adjusted to minimize interference with the study intervention.
    - The subject will be asked to hold the morning diuretic medication and the morning dose will be given 3 hours after the procedure (CS). This is not expected to provide any risk to the stable chronic heart failure subject, especially since the diuretic medication will be resumed after completion of study that same day.

- Other medications can be continued, unless otherwise specified in the exclusion criteria.

Procedure:

1. Subjects will undergo elective right heart catheterization in the Duke catheterization laboratory lab as ordered by the primary team. A

cardiopulmonary exercise test will be added if not already ordered by the primary provider. Central hemodynamics will be recorded (baseline, prior to nerve block) (SOC). The access site for the right heart catheterization will be radial, brachial or cervical (SOC) to allow a prone positioning of the subject for the splanchnic nerve block described in the next paragraph. Additional baseline RHC numbers will be recorded with legs elevated, which is done to simulate a fluid bolus.

If the subject's hemodynamics provide any other concern for complications related to the splanchnic nerve block (such as underfilling or severe pulmonary hypertension, not related to left heart failure) as determined by the study personnel, the splanchnic nerve block and associated monitoring will not be performed. The subject will be considered a screen failure. Any information and samples collected prior to this will be discarded/destroyed per institutional policies.

Before cardiopulmonary exercise begins, the subject will perform the Valsalva maneuver. The subject will sit up on the catheterization lab table, after the intravenous lines have been placed. The subject will have an empty syringe placed in their mouth. He/she will blow into the syringe for 30 seconds. This is the standardized method for performing the Valsalva maneuver (Saxena, M, Journal of American Heart Association, 2018). The intracardiac pressures will be measured continuously during the 30 seconds. Following the Valsalva maneuver, the subject will be placed supine on the stationary bike for cardiopulmonary exercise. Cardiopulmonary exercise testing will include a 20 W initial steady phase during which RHC numbers will be recorded and echocardiogram with liver blood flow will be obtained. This will take up to 7 minutes followed by quick (every 1 minute increase in 20W) ramp to peak exercise. At peak exercise repeat hemodynamics and echocardiography will be obtained.

Subjects will further be monitored with:

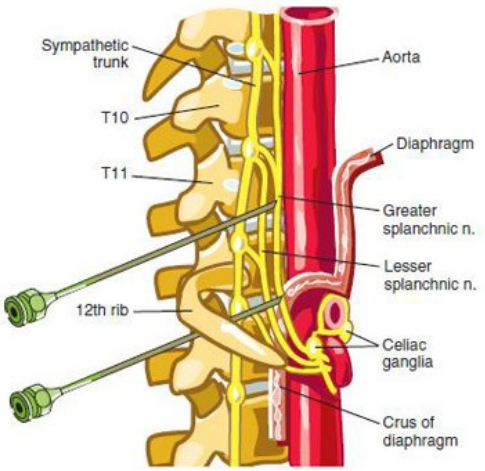
- Telemetry (SOC)
- ClearSite/CheetahMedical/Sphygmocor/ReDS for continuous non-invasive hemodynamic/lung fluid content recording (CS)
- Continuous urine output (ml/hour) recording if foley is present (SOC)
- A non-invasive wrist monitor/chest band to monitor the heart rate variability

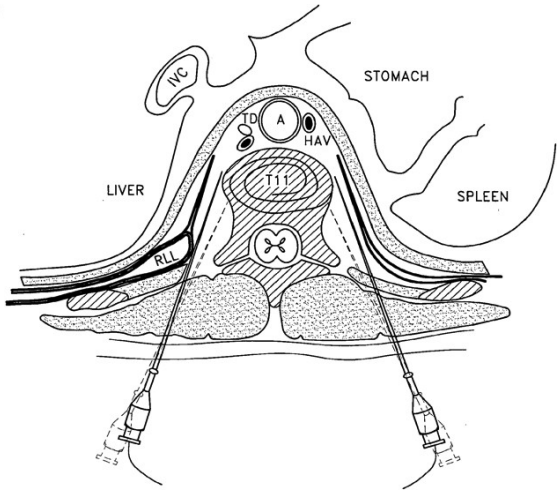
Baseline hemodynamics and exercise CPX will be performed before and after the nerve block detailed below.

2. Unilateral splanchnic nerve block performed by an anesthesiologist (see images below) (CS). The anesthesiologist will perform a unilateral block to the splanchnic nerve. The blood pressure will be checked, after 15 minutes, post-block. If the systolic blood pressure is reduced by > 20mmHg, the contralateral splanchnic nerve will not be blocked. Following the right heart catheterization procedure the subject will be prone on the abdomen. Central venous access remains in place. Needle will be placed under fluoroscopic guidance in the posterior chest wall. Anesthetic solution (1.5% lidocaine with 1:200.000 epinephrine and of 0.5% ropivacaine) will be injected. Lidocaine 1.5% with Epinephrine 1:200.000 will be used initially to confirm extravascular administration. The subject with will then be placed back on his/her back. The subject will then undergo repeat hemodynamic measurement with the RHC catheter that was already in place. Then the subject proceeds with invasive cardiopulmonary testing after a 30 minute break. The central venous catheter will be removed after the hemodynamic monitoring/testing is completed in the catheterization laboratory.

Additional measurements include:

- Orthostatic vitals (CS).
- Dyspnea questionnaire (CS)
- Echocardiography and liver flow measurements (CS)





Follow up procedures:

Following right heart catheterization and lidocaine splanchnic nerve block the will be observed for monitored in the cath lab holding area for 3 hours following nerve block (SOC).

- Continuous recording of urine output for the procedure day (CS) will be achieved by recording urine output at the beginning of pre-testing, just before the cath lab procedure, just after the cath lab procedure and before the subject leaves home.
- Basic vitals (SOC) and orthostatic vitals (CS) following the cath lab procedure and record heart rate variability using a non-invasive wrist monitor (CS).
- Repeat labs after the procedure before the subject leaves. Pro-BNP, BMP, serum sodium (all CS)
- Labs: Angiotensin 2, plasma metanephrines (if on inotropes), plasma catecholamines, vasopressin, lactate, and urine sodium will be collected immediately before and after the procedure
- Dyspnea questionnaire after nerve block (CS) and again at 48 hours
- Six minute walk test (CS) after the block
- Weight after the procedure.

Phone Call

Subjects will be contacted by study team 24h, 48h and six months (± 14 days) following their nerve block procedure. The purpose of this call will be to obtain shortness of breath status, potential long term complications and mortality status and document the number of inpatient admissions since the procedure.

Blood samples processing:

Some blood samples collected before and after the nerve block (plasma metanephrines, plasma catecholamines, angiotensin II and arginine vasopressin, lactate) will be processed (centrifuged) and stored at -70 degrees Fahrenheit before sent out to an external lab. Storage

duration may vary between weeks to months. Samples will be stored in a research freezer located on the 7th floor of Duke North (cath lab research freezer). As part of the study, we will send blood for study-related laboratory tests to the Mayo clinic and Inter Science Institute. These would include laboratory tests such as metanephrines, vasopressin, catecholamines, and angiotensin. A data transfer agreement is already in place.

Safety endpoints:

- The duration of the anesthetic block is estimated for 12-24 hours. The subject will be monitored for up to 3 hours in the catheterization laboratory/holding area, if there is any concern or evidence of procedure related complications the will be kept overnight in the cath lab holding area. A potentially observed effect of the block to prevent discharge the day of procedure could be orthostatic hypotension. will also be contacted at 48 hours post procedure to ascertain any potentially missed complications. Further the subject's medical chart will be observed for 6 months following study enrollment to evaluate for admissions for heart failure.

  Incidence of major side effects has been reported to be <1:1000 and are expected to occur immediately post nerve block. They include:
  - Pneumothorax, possibly requiring a chest tube
  - Aortic puncture with retroperitoneal bleed or hematothorax
  - Spinal cord trauma with possibly paralysis

  Incidence of minor side effects like:
  - Orthostatic hypotension
  - Pain at puncture site and intercostal neuralgia
  - Gastrointestinal dysmotility including diarrhea, constipation and abdominal cramping
  - Bleeding at puncture site

Efficacy endpoints:

The following efficacy endpoints will be evaluated:

Primary:
- Improvement in 20 W and peak exercise PA mean and wedge pressure
- Reduction in central venous pressure and/or pulmonary artery pressure (diastolic) and/or pulmonary capillary wedge pressure at 30 minutes after nerve block

Secondary:
- Reduction in central venous pressure and/or pulmonary artery pressure (diastolic) and/or pulmonary capillary wedge pressure at 30 minutes after nerve block
- Increase in cardiac output at rest, improvement in echocardiographic parameters like ejection fraction (increase), central venous pressure (decrease), pulmonary artery systolic pressure (decrease), right ventricular diameter (decrease), left ventricular diameter (decrease)
- Reduction in pro brain natriuretic peptide (pro-BNP)
- Increase in UOP (output measured in ml/hour) and renal function (BUN and creatinine) in the hours following the procedure.

- Symptomatic improvement like a decrease in dyspnea (dyspnea questionnaire) and 6-minute walk test

Exploratory aims:

- Change in cardiac and autonomic markers after nerve block (i.e. angiotensin and catecholamines)

7. Selection of Subjects:

Subjects will be recruited from Duke University Medical Center outpatient environment. All potential study subjects will be scheduled electively by the cardiologist for a RHC +/- an invasive cardiopulmonary exercise. Subjects will be identified via a routine screen of the outpatient cath schedule weeks ahead of time.

The study will enroll subjects who meet the criteria as detailed below. Potentially eligible subjects will be contacted and informed about the possibility of the study. The actual consent process will occur on the morning of the procedure. The primary enrollment target is up to 30 subjects (15 HF with preserved ejection fraction and 15 HF with reduced ejection fraction).

Inclusion criteria:

- Age 18-90
- Followed at DUMC for known or suspected diagnosis of HF (NYHA stage 1-3, Class C-D), including subjects on inotropic medication
- Systolic blood pressure (SBP) > 100 mmHg
- Planned for elective diagnostic right heart catheterization

Exclusion criteria:

Contraindicated medications:

- Anticoagulation at the time the procedure or in case of recent warfarin use an INR >1.4. Anticoagulation includes: warfarin, or novel oral anticoagulants like dabigatran, rivaroxaban, apixaban, endoxaban or full dose intravenous heparin products or bivalirudin and fondaparinux). Antiplatelet agents besides aspirin such as ticagrelor, prasugrel, Plavix are also considered to be a contraindication if used at time point of procedure.
- Immunosuppressive medications for solid organ transplant

HF medication regimen:

- Initiation of HF medications (in the 48 hours preceding the study) such as beta blockers, ACEI, ARB, aldosterone receptor blockers, calcium channel blockers of any type, central sympatholytics like clonidine, moxonidine,
- **Recent acute MI or hemodynamic instability:**
  - Acute MI (STEMI or Type I NSTEMI) within 7 days?
  - Evidence of progressive cardiogenic shock within 48 hours
  - Repeat systolic blood pressure <90mmHg or >180mmHg

Certain forms of HF:

- Restrictive cardiomyopathy
- Constrictive pericarditis
- Pericardial effusion with evidence of tamponade
- Severe valvular stenosis

Severe bleeding risk:

- Known history of an increased bleeding risk
- Thrombocytopenia (<50,000)

Significant comorbidities:

- NYHA class symptoms
- End-stage renal disease CKD stage 5 due to primary renal pathology
- Any form of preceding acute or chronic use of ultrafiltration or hemodialysis
- History of thoracic spine surgery
- Severe scoliosis of the thoracic spine
- History of lung surgery or history of pneumothorax or chest tube placement during the current admission
- History of lung disease other than asthma and COPD (like interstitial fibrosis, cystic fibrosis, pneumonitis, lung cancer etc.)
- Respiratory instability (dependent on >4 L nasal cannula for a saturation >90% SpO2)
- Exclude severe pulmonary hypertension
- History of organ transplant (heart, lung, liver, pancreases, small bowel, kidney).

Pregnancy

Procedure

- Unable to tolerate procedure as determined by subject or investigator
- will be excluded if invasive hemodynamics on study date determine that the subject does not have elevated filling pressures at rest or stress. Following pressures/situations will exclude the subject: wedge pressure <15mmHg (<12mmHg on inotrope) at rest and <25mmHg with peak stress (<22 with inotropes) and greater than the central venous pressure or determined by study personnel to be at risk for nerve blockrelated complications.

8. Subject Recruitment & Compensation:

Potential subjects will be identified via two potential pathways. Research team will screen the outpatient scheduled RHC cases and send a recruitment letter to the subject once their primary care provider has agreed to this. The subject will be contacted over the phone if the subject has not replied to the letter in at least 10 days per policy. The subject will be provided with any additional information he/she wants. In a second scenario the primary provider approaches the study team with a potential cases. In both cases the subject will be given a heads up about being

approached on the day of the study about a second approach in person by a health care provider known to the patient for potential consent.

9. Consent Process

Candidate subjects will be informed of the risks and benefits of participation in the study. They will be informed of the study process and demands. They will be given a copy of the informed consent document to review and afforded adequate time to do so.

Informed consent will be obtained prior to the right heart catheterization. Consent will be obtained by Study PI, Duke Heart Center study coordinators who are trained on the study and who have been trained on Informed Consent Process and other key personnel as designated by the PI. Consent will be obtained in the catheterization laboratory holding area. A subject is considered enrolled in this clinical study at the time at which the subject and investigator or authorized designee have personally signed and dated the Informed Consent Form.

10. Subject's Capacity to Give Legally Effective Consent:

Subject has to be able to understand the English language and understand the study process including all potential risk and benefits to the subject. Any subject where the study personnel or treatment team has cause for concern regarding the subject's ability to understand the study process or follow the consent process capacity, will be excluded from

the study.

11. Study Interventions:

- Regional nerve block under fluoroscopic guidance
- Cardiopulmonary exercise
- Lab draws
- Vital signs
- Orthostatic vital signs
- 6-minute walk test
- Non-invasive imaging with ultrasound
- Non-invasive hemodynamic monitoring (heart rate variability, sphygmocor, ReDS, Cheetah Medical)
- Optional: Foley placement

12. Risk/Benefit Assessment:

Procedural risks of splanchnic nerve blocks have been extensively studied. Risks associated with this anesthetic nerve block are uncommon. Patients undergoing this procedure have a small risk (<1%) risk of developing local anesthetic systemic toxicity as a complication of regional anesthesia. Symptoms include non-specific central nervous system effects (altered mental status, agitation, seizures) and cardiac arrest. We have now completed 10 cases in the first pilot trial using lidocaine and found no acute or chronic complications.

Mild complications like local pain at injection site, orthostatic hypotension and gastrointestinal dysmotility are time limited and improve with resolution of the anesthetic block. Severe complications like pneumothorax possibly requiring a chest tube, aortic vessel puncture with retroperitoneal bleed or hematothorax and spinal cord injury with possible paralysis. These are very rare since placement of the needle occurs under fluoroscopic guidance.

Other minor risks can include (in order of report in literature and experience at Duke):

- Pain at puncture site and intercostal neuralgia
- Gastrointestinal dysmotility including diarrhea, constipation and abdominal cramping as well as nausea
- Bleeding at puncture site

We will perform the splanchnic block for chronic heart failure, which is a new indication. The splanchnic nerve block has now been studied by us for acute heart failure but not been studied in the setting of chronic disease. We do not expect unexpected side effects other than stated above but unexpected side effects cannot be excluded. For safety purposes subjects enrolled in this study will remain monitored for several hours after the SNB and re-contacted at 48h.

Anticipated benefits to the subject include improvement in central vascular congestion with a reduction in cardiac preload and pulmonary arterial pressures as well as left sided filling pressures. A reduction in cardiac pressures is also likely to improve symptoms of congestion, including shortness of breath.

Further it is expected that a decongestion of the central veins and interruption of the cardiorenal reflex loop will result in an improvement in renal function as measured by urine output. This will further contribute to the decongestion of the subject's vasculature.

While both of those effects are only temporary (12-24h), the benefit provided by the brief episode of decongestion can provide lasting symptomatic improvement. Our intervention serves an additional diagnostic purpose by confirming an increased sympathetic tone in the abdominal innervation and could prompt the treatment team to adjust medical therapy to address the increased sympathetic tone and possible benefit on increased splanchnic capacitance.

13. Costs to the Subject:

The study will be at no additional cost to the subject on top of his regular hospitalization for heart failure and elective catheterization.

14. Data Analysis & Statistical Considerations:

Descriptive statistics of continuous outcomes will include sample size, mean, median, standard deviation, minimum and maximum. For categorical outcomes, the number and percentage of subjects in each category will be presented. Statistical comparisons will be made using t-tests for continuous outcomes and chi square or Fisher's exact test (depending on overall event rates) for categorical outcomes. Paired t-tests will be used to compare changes from baseline to post-intervention. All statistical analyses will be performed using SAS for Windows (version 8.2 or higher) or other widely accepted statistical or graphical software. Subject data listings and tabular and graphical presentations of results will be provided. Unless otherwise specified, a two-sided 0.05 level of significance will be used to declare change in pre- and post-procedure variables different.

For power analysis, our primary endpoint is decreased in central venous pressure following nerve blockade. Based on preliminary animal experiments, we anticipate a reduction of CVP of 25%. For a sample size of 16, If the true difference in the experimental and control means is 25%, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) .90. The Type I error probability associated with this test of this null hypothesis is 0.05.

There is no direct measure of technical success following attempted block of the splanchnic nerves. The location of the splanchnic nerves is estimated biased on human anatomy dissections and established nerve block protocols used by the anesthesiology department. Procedural success to block the splanchnic nerves will be assumed in 70% of the cases based on the experience in splanchnic nerve blocks in subjects with intractable cancer.

15. Data & Safety Monitoring:

Due to the experimental nature of this intervention, data will be recorded after each subject completes the intervention for signs of unintended negative effects. These include hypotension, worsening renal function, or clinical deterioration. Additionally, subject's electronic medical data will be screened for any traumatic complications from the nerve block at 48 hours post-procedure.

Unanticipated adverse events, which are severe (listed above), will be reported to the IRB within 24 hours. Any other adverse event will be reported to IRB within 10 working days or per IRB policy. The Principal Investigator will also provide an annual report of any side effects or problems to the IRB during the study renewal process.

Following discharge, the subject's medical record will be monitored for readmission to the Duke hospital for heart failure for 6 months.

No PHI is sent outside of Duke.

16. **Privacy, Data Storage & Confidentiality** – see Section 12 of the e-IRB submission form and complete the questions in that section.

1. Data will be obtained by approved study personnel. An enrollment log will also be maintained in Excel Spreadsheet on the Heart Center's S:drive. The subject ID will also be stored on the folder to track subject enrollment and collection of data. Data will be recorded in Excel. Only deidentified data will be available for statistical analysis. All subject identifiers will be removed for database storage, statistical analysis and data reporting. This data will be stored on a study specific folder on the Duke server behind the Duke firewall. The subject ID code will be destroyed after data analysis is completed. Protected health information will not be used for any other purposes than those described in this protocol without obtaining further IRB approval. This information will be used for research purposes only and subjects will never be contacted regarding information obtained through chart review. A designated statistician from the DCRI will provide support with statistical analysis.

   The adequacy of the Research Data Security Plan (RDSP) will be evaluated and approved by the Cardiology CRU prior to study conduct.

   Any publications or presentations that result from this research will not identify any subjects individually, and will present data in aggregate form only.

   Gathered data will be stored for at least 6 years.