NCT02669407

1. Protocol Title:

Splanchnic Nerve Block for Therapy of Acute Heart Failure (Splanchnic HF)

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 patients 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 increases urine output.
3. We will determine whether splanchnic nerve blockade produces rapid improvement in creatinine clearance.

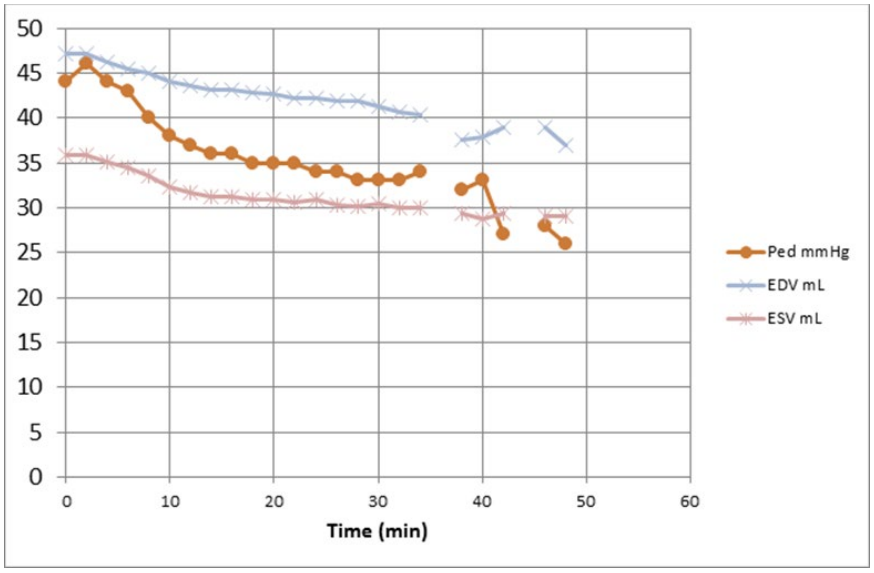
3. Background & Significance:

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 patients 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 patients 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 (Figure A). In humans splanchnic nerve blocks are commonly used for pain control in patients 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).

A



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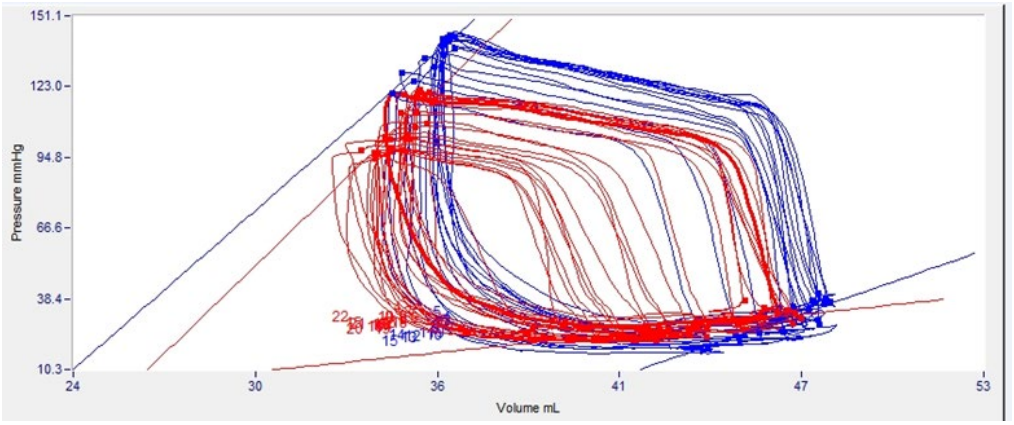


Figure A: Preliminary data from one paced HF dog model with transection unilateral splanchnic nerve. A: Left ventricular end systolic (ESV) and diastolic (EDV) volume following nerve transection at time point zero in mL. Ped = left ventricular end-diastolic pressure in mmHg.
Figure B: Pressure-volume recording in left ventricle in same animal. Blue curves are the baseline recordings and red indicate pressure-volume loops after nerve transection. Nerve transection caused flattening of the end-diastolic pressure-volume relationship indicating higher compliance. Unpublished pilot data.

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. Furthermore, the goal of the study is to demonstrate proof of concept.

This study aims to piggy-back on an elective right heart catheterization (+/- left heart catheterization) in patients admitted for acute decompensated heart failure The right (+/- left heart catheterization) will be part of the subject's standard of clinical care (SOC). Subjects will undergo catheterization of the heart to obtain central cardiac pressure and other cardiac hemodynamic parameters found to be necessary by the primary team. This will occur in the cardiac catheterization lab. Once the SOC catheterization procedure is completed the subject will undergo, as part of this clinical study (CS), a regional nerve block (bilateral splanchnic nerves) while they are in the catheterization lab. This will be performed by an anesthesiologist experienced in splanchnic nerve blocks. Routinely, patient will remain in the catheterization lab for the duration of anesthetic block and will be continuously hemodynamically monitored. Also, prior to elective catheterization procedure and following splanchnic block patients will undergo a number of vital, laboratory and imaging tests, which will be in parts SOC or part of the CS (see Table of Assessments below).

Table of Assessments\

Required Assessment	<5 Days before procedure	Same day of procedure (<12h before procedure)	Procedure (1-1.5h)	Within 2 hours after Procedure	Day 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)	X (SOC)	
Weight	X (SOC)	X (SOC)		X (SOC)	X (SOC)	X (SOC)	
Orthostatic vitals	X (CS)			X (CS)	X (CS)		
Urine output (continuous recording)	X (SOC)	X (SOC+CS)	X (SOC)	X (CS) 3 and 8 hours post procedure	X (SOC+CS)	X (SOC+CS)	
Labs: BMP, pro-BNP, urine sodium,		X (SOC/CS)		X (CS) for pro-BNP and urine sodium	X (SOC) for BMP	X (BMP are SOC, no pro BNP needed)	
Labs (Angiotensin II), Plasma Metanephrines, Vasopressin, Plasma Catecholamines		X (CS)		X (CS)			
Dyspnea Questionnaire		X (CS)	X (CS)	X (CS)	X (CS)	X (CS)	
Six minute walk test	X (CS)			X (CS)	X (CS)	X (CS)	
Impedance and lung fluid content measurement			X (CS)	X (CS)			
Positional Change: Bending Over		X (CS)		X (CS)			
Positional Change: Leg Raise			X (CS)				
Heart rate variability	X (CS)	X (CS)	X (CS)	X (CS)	X (CS)	X (CS)	
Echocardiogram	X (SOC)			X (CS)			
Splanchnic nerve block			X (CS)				
Phone Call**							X (CS)

*Plasma Metanephrines will be performed only if subject is on inotropes

**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 routine clinical care and will be marked as SOC (like in the above table). Tests required only for the purpose of the study are marked with CS.

Pre-procedure: Following information will be collected from the patient charts that will 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). Additionally, subjects will be asked to void 3 hours prior to their procedure. They will be asked to void again immediately prior to the start of the procedure. 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)
- Labs: Basic metabolic panel (BMP) (SOC), brain natriuretic peptide (BNP) (SOC/CS), plasma angiotensin II (CS), plasma arginine vasopressin (CS), plasma catecholamines. Plasma metanephrines (CS) will be performed if subject is on inotropes. 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 during the admission and no longer than 5 days prior to study (SOC). If no up-to-date echocardiogram is present, a study related Echocardiogram will be obtained (CS).
- If the patient is on diuretics medications the scheduling of the medication will be adjusted to minimize interference with the study intervention.
    1. If the patient is scheduled to be an early morning case in the catheterization laboratory then the morning dose of the diuretic (typically given at 8-9 am) will be given 3 hours after the procedure (CS).
    2. If the patient is scheduled to be an afternoon case in the laboratory then the morning dose will be given as planned or earlier to guarantee at least 5-6 hours between last diuretic dose and the procedure (CS).

Subjects who receive also an evening dose of diuretics will receive their second dose of diuretic as scheduled in the evening after the procedure (SOC).

- Other medications can be continued, unless otherwise specified in the exclusion criteria.
- Positional change of bending over to evaluate 'bendopnea' (shortness of breath symptoms with bending over).

Procedure:

1. Patients will undergo elective right (+/- left) heart catheterization in the Duke catheterization laboratory lab as ordered by the primary team. 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 patient for the splanchnic nerve block described in the next paragraph.

If the patient's hemodynamics do not show evidence of cardiac decompensation or provide any other concern for complications related to the splanchnic nerve block as determined by the study personnel, the splanchnic nerve block and associated monitoring will not be performed. The patient will be considered a screen failure. Any patient information and samples collected prior to this will be discarded/destroyed per institutional policies. Cardiac decompensation is defined as a wedge pressure <15mmHg (<12mmHg on inotrope) and greater than central venous.

If invasive hemodynamics support decompensated heart failure the patient will proceed with the study procedure and monitoring outlined below.

Prior to the nerve block being performed, the subject will perform a positional change of a leg raise to observe if any shortness of breath symptoms occur.

Patient 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 to monitor the heart rate variability

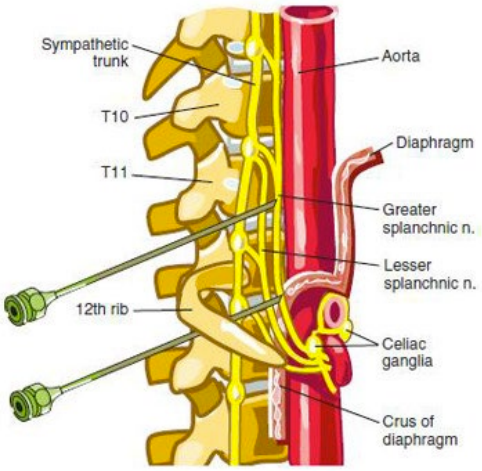
2. Bilateral splanchnic nerve block performed by an anesthesiologist (see images below) (CS). Following the right heart catheterization procedure the patient will be prone on the abdomen. Central venous access remains in place. Needle will be placed under fluoroscopic guidance in the posterior chest wall. Anesthetic solution (1% lidocaine with epinephrine) (1:200.000) will be injected (10-15 ml on each side). Patient will then be placed back on his/her back and central

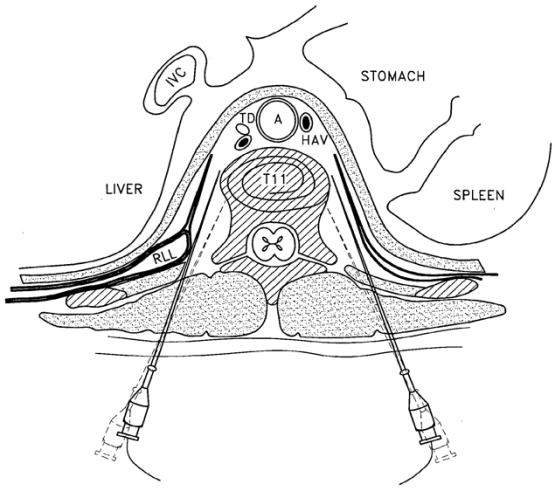
hemodynamics are recorded again for the next 1-1.5 hours, approximately every 15 minutes. The central venous catheter will be removed after the hemodynamic monitoring is completed in the catheterization laboratory. Unless the primary team requested the catheter to remain in place and the patient is moved to the intensive care unit.

Following the block, the subject will repeat the positional change of a leg raise at 30, 60, and 90 minutes post-block to observe any changes in shortness of breath symptoms.

Additional measurements include:

- Orthostatic vitals will be obtained at the end of the hour while in the catheterization lab (CS).
- Dyspnea questionnaire (CS)
- If medically indicated a Swan Ganz catheter will be left in place. This would enable continuous monitoring of central hemodynamics for the next 24h (q4h) (SOC).





Follow up procedures:

Following right heart catheterization and lidocaine splanchnic nerve block the patient will be monitored on the floor/CCU for at least 48 hours following nerve block (SOC).

- Continuous recording of urine output for 24 hours (SOC). They will then be asked to void again 3 and 8 hours after the placement of the nerve block and 24 hours after nerve block (CS).
- Basic vitals (SOC) and orthostatic vitals (CS) within 24 hours after nerve block, and record heart rate variability using a non-invasive wrist monitor (CS).

- Repeat labs 12-24 hours after nerve block (next morning) [BUN (SOC), BMP (SOC) and pro-BNP (CS)
- Labs: Angiotensin 2, plasma metanephrines (if on inotropes), plasma catecholamines, vasopressin and urine sodium will be collected immediately before and after the procedure
- Dyspnea questionnaire at 12-24 hours after nerve block (CS) and again at 48 hours
- Six minute walk test (CS) within 24 hours after block and again at 48 hours
- Weight the next morning after nerve block (SOC) and at 48 hours.
- Echocardiogram within 1-2 hours after nerve block (CS)
- Positional change of bending over to evaluate 'bendopnea' (shortness of breath symptoms with bending over).

Phone Call

Subjects will be contacted by study team six months (± 14 days) following their nerve block procedure. The purpose of this call will be to obtain 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) 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.

Safety endpoints:

- The duration of the anesthetic block is estimated for 1.5 hours. The subject will be monitored for up to 1.5 hours in the catheterization laboratory (acute safety). Chronic safety up to 48 hours post procedure. Hereby the patient will be observed clinically on the floor or CCU per standard clinical care routine. Further the subject's medical chart will be observed for 6 months following study enrollment to evaluate for recurrent admissions for heart failure.

  Incidence of major side effects like:
  - 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:
- Reduction in central venous pressure and/or pulmonary artery pressure (diastolic) and/or pulmonary capillary wedge pressure at 30-60 minutes after nerve block

Secondary:
- Increase in cardiac output, 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. Follow up for 48hours
- Symptomatic improvement like a decrease in dyspnea (dyspnea questionnaire) and 6-minute walk test

5. Selection of Subjects:

Subjects will be recruited from Duke University Medical Center. All potential study subjects are admitted for ADHF and are treated as inpatient on the regular floor or in the intensive care unit.

The study will enroll subjects who meet the criteria as detailed below. Potentially eligible patients will be consented and entered into a screening process, which will include a chart review and physical examination. The primary enrollment target is up to 20 subjects (10 HF with preserved ejection fraction and 10 HF with reduced ejection fraction).

Inclusion criteria:
- Age 18-90
- Established diagnosis of HFpEF or HFrEF
- Admitted to DUMC for decompensated HF (NYHA stage 3-4, Class C-D), including patients on inotropic medication
- Symptomatic with dyspnea with clinical, radiographic or echocardiographic signs of fluid overload
- Planned for elective diagnostic right (+/- left) heart catheterization
- On a stable HF drug regimen prior to admission
- Anticipated hospital stay of at least 2 nights following catheterization procedure

- Preferably “diuretic resistant”. Urine output <50ml/hour in the 24 hours preceding enrollment into the study.

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:

- 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
- 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 abdominal organ transplant (liver, pancreases, small bowel, kidney) or splenectomy

Pregnancy

Procedure

- Unable to tolerate procedure as determined by patient or investigator

- Patient will be excluded if invasive hemodynamics on study date determine that the patient does not have elevated filling pressures. Following pressures/situations will exclude the patient: wedge pressure <15mmHg (<12mmHg on inotrope) and greater than the central venous pressure or patient determined by study personnel to be at risk for nerve block related complications.

6. Subject Recruitment & Compensation:

Potential subjects will be identified via two potential pathways. Cardiology inpatient teams will be informed about the study and will be encouraged to notify the study team if a patient is planned for an elective right (+/-) left heart catheterization in the upcoming days. Subjects will also be identified by a daily review of the catheterization scheduling board, which identifies scheduled procedures for the given week. This way the study team would be able to identify subjects about whom they were not informed by the primary care taking team.

Patients that were identified to be potential candidates for this study will be screened to evaluate for inclusion/exclusion criteria before approaching the patient for study consent.

Subjects will be informed that their participation is strictly voluntary. They will be assured that the decision to decline participation will have no impact on their care or the perceptions of their providers.

There will be no compensation for participation in this clinical study.

7. Consent Process

Candidate subjects will be informed of the risks and benefits of participation of 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. If the elective catheterization procedure (SOC) is scheduled for the upcoming day than the consent will need to be signed before midnight to allow enough time to obtain pre-procedural test as outlined above.

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 patient's room or the catheterization laboratory holding area. Only after a member of the patients medical care team who is known to the patient approaches them about the study will the study team talk with the patient about this study. 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.

8. 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 patient. Any subject where the study personnel or treatment team has cause for concern regarding the patient's ability to understand the study process or follow the consent process capacity, will be excluded from the study.

9. Study Interventions:

- Regional nerve block under fluoroscopic guidance
- Lab draws
- Vital signs
- Orthostatic vital signs
- 6-minute walk test
- Non-invasive imaging with ultrasound
- Optional: Foley placement

10. Risk/Benefit Assessment:

Procedural risks of splanchnic nerve blocks have been extensively studied. Risks associated with this anesthetic nerve block are uncommon. 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 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 heart failure, which is a new indication. The splanchnic nerve block has not been studied in the setting of this disease. While we don't expect unexpected side effects other than stated above, unexpected side effects cannot be excluded. For safety purposes patients enrolled in this study will remain hospitalized for at least 48 hours (part of enrollment criteria). This way they will be closely monitored while admitted on a cardiology floor/unit.

Anticipated benefits to the patient 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, 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.

11. Costs to the Subject:

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

12. 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. Patient 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 patients with intractable cancer.

13. 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, patient's electronic medical data will be clinically screened for any traumatic complications from the nerve block for the first 24 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 requirements. 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.

The study related results will be reported to the Duke Translational Research Institute. These would include laboratory tests, imaging studies and clinical tests like 6 minute walk test and dyspnea questionnaire.

14. 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 patient enrollment and collection of data. Only de-identified data will be available for statistical analysis. All patient 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 patients 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.