Splanchnic Nerve Block for Therapy of Chronic Heart Failure (Splanchnic III)

Clinicaltrials.gov number: NCT04575428
Duke IRB number: Pro00103788

Date: May 1th 2023

Research Abstract

Please type your Research Abstract here:

The Research Abstract should summarize the main points of your study in one paragraph. The following guidelines may help you:

1. Purpose and objective (1-2 sentences)
2. Study activities and population group (2-4 sentences)
3. Data analysis and risk/safety issues (1-2 sentences)

Splanchnic vasoconstriction may contribute to decompensation of chronic heart failure (HF) 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 (SNB). 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 HF.
We have already obtained preliminary safety and efficacy data in acute and chronic heart failure patients with temporary (<24 h) SNB. Now we would like to apply a prolonged SNB in chronic heart failure patients using a long acting agent.

Research Summary

State your primary study 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.

State your secondary study objectives

N/A

Please select your research summary form:

Standard Research Summary Template

This is the regular (generic) research summary template which is required for all regular applications (unless your protocol fits under the other research summary templates in this category). Use of these instructions is helpful for ensuring that the research summary contains all necessary elements.

Standard Research Summary

Purpose of the Study

- Objectives & hypotheses to be tested

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.

Background & Significance

- Should support the scientific aims of the research

Heart failure (HF) is a leading cause of morbidity and mortality, affecting more than 6 million adults in the US alone.[1] Cardiovascular congestion with resultant limitation in physical activity is the hallmark of chronic and decompensated HF. While it is well-accepted that the extent of fluid volume congestion is closely associated with clinical outcomes [2-4], the concept of fluid and salt overload as the primary drivers of symptomatic decompensation (with resting or exercise-induced dyspnea) has been challenged.[5,6] Notably, about 50% of patients gain only minor weight (<2pounds or <2kg based on the study) in the days prior to a hospitalization.[7,8] Additionally, intracardiac filling pressures in patients with HF commonly start to increase before any significant weight changes occur preceding an admission for clinical decompensation.[9,10] In our own analysis of the ASCEND-HF trial, 26% of patients had no weight loss (+/-1kg change) and 8% actually experienced weight gain (³1kg) during a HF hospitalization, suggesting that net volume loss is not necessary for symptomatic relief.[11] **Taken together, an increase in central filling pressures occurs in many cases in the absence of weight gain or total body volume increase [4,12], which lead us and others to suggest a contribution of volume redistribution to the mechanism of cardiac decompensation**

In chronic HF, cardiopulmonary congestion is the main determinant of exercise intolerance, which manifests itself as exertional dyspnea and/or fatigue.[13,14] Many HF patients have normal hemodynamics at rest [15], but there is growing evidence of profoundly abnormal hemodynamic response to exercise characterized by rapid and marked elevation in filling pressures.[13,16] Exercise-induced intra-cardiac decompensation, whether driven by fluid overload or volume redistribution, in most cases is only an intermittent phenomenon as pressures return to baseline values during recovery.

The abdominal compartment has been implicated as a key contributor to the complex pathophysiology of HF given that it is the main storage compartment of intravascular blood volume. The highly vascular organs such as the liver, spleen and bowel are able to "store" or "recruit" large blood volumes within minutes in and out of the splanchnic vascular compartment.[17-20] Animal and human data indicates that these blood shifts can significantly alter cardiac and central vascular hemodynamics.[17-19] **The main regulatory system for the splanchnic vascular capacitance ("storage-space") are post-ganglionic sympathetic fibers originating from the celiac plexus which control arterial and venous vascular tone.** These post-ganglionic sympathetic fibers in the celiac plexus receive input from pre-ganglionic sympathetic fibers travelling via splanchnic nerves.[21,22] **Activation of splanchnic nerves results in vasoconstriction and reduces splanchnic capacitance, therefore recruiting blood volume into the central circulation.[19,21] In HF, a reduced splanchnic vascular capacitance[23,24] could be the mechanism underlying symptoms of exercise intolerance and could predispose to rapid decompensation with external fluid intake or retention (Figure 1).**[5,16,25] A compromised vascular reservoir is likely unable to buffer shifts of fluid and actively contributes to the acute or chronic expulsion of fluid from the splanchnic vascular compartment to the central thoracic compartment. The redistribution of blood volume into the central circulation may lead to a sudden rise in pulmonary and left-sided cardiac pressures in HF.[5,6,26] This makes the splanchnic vascular compartment an attractive target in HF.

Prior Evidence: Mounting evidence questions the notion that congestion is merely the result of external volume overload or volume retention. Supportive evidence is provided by blood volume analysis using the I^{131}-labeled human serum albumin indicator-dilution technique. Using this technology, studies found that chronic HF patients with persistent symptoms are in 35% of cases hypovolemic or euvolemic[4] and the same was even true for patients admitted for decompensated HF (34%).[27,28] The heterogeneity of clinical presentation suggests the presence of an alternate mechanism to explain increased filling pressures at rest or with exercise despite a lack of fluid retention.

Effective measures to decrease vascular congestion acutely or chronically remain an unmet clinical need. We recently identified the splanchnic nerves as potential contributors to the pathophysiology of HF and we proposed that a heightened splanchnic sympathetic tone contributes to cardiac decompensation and a short-term interruption of the splanchnic nerve signaling would reverse the process and thus alleviate HF sign and symptoms in select patients with acute and chronic HF.[5,6,24] We first showed that splanchnic nerve stimulation results in acute hemodynamic changes, with a decrease in splanchnic vascular compliance and increase in cardiac preload.[1,7,19] HF is characterized by a heightened global sympathetic tone, yet untargeted pharmacological reduction in sympathetic tone can be insufficient to result in effective splanchnic vasodilation and be detrimental due to unintended cardiovascular effects.[29] Consequently, a targeted reduction of the splanchnic sympathetic tone in chronic HF could provide a therapy for patients with cardiopulmonary congestion at a resting state or state of activity.

Our preliminary proof-of-concept work in patients with acute decompensated and chronic HF showed promise for the concept of splanchnic nerve modulation in HF (**Figure 2**).[38] In a series of two small first-in-human studies for acute decompensated HF (N=13)[25,38] (Late-Breaker at ESC-HF 2018, Vienna, Austria, NCT02669407) and chronic HF (N=17) (Young Investigator Competition, ESC-HF 2019, Athens, Greece, NCT03453151), we found that a splanchnic nerve block (SNB) with lidocaine (90 min duration of action) and ropivacaine (24 hours duration of action) acutely **reduced resting and exercise-induced** intra-cardiac filling pressures, associated with improved patient symptoms and functional capacity.

Our two proof-of-concept studies and the well-established safety profile of permanent splanchnic nerve blockade in patients with intractable abdominal pain (e.g., due to pancreatitis or cancer) provide the foundation for our study.[30-33] A body of literature (>3,000 published cases) on non-HF patients suggests that the side effects of permanent splanchnic nerve blockade (surgical or interventional via alcohol injection) are restricted to 48-h post procedure. Most common side effects include orthostatic hypotension (80%) followed by gastrointestinal symptoms (60%). Interestingly, transient orthostatic hypotension due an increase in splanchnic vascular storage capacity, is clinically prevented by aggressive pre-procedural hydration.[33] Historically (1930-1950's) surgical denervation of splanchnic nerves has also been applied in form of the so-called splanchnicectomy for treatment of uncontrolled hypertension. While it was shown to be effective to reduce sympathetic tone and reduce blood pressure, the discovery of antihypertensive medications made this surgical procedure obsolete.[34] Long-term pharmacological blockade of the celiac plexus/splanchnic nerves with Botulinum toxin (BTX) has been previously reported to be safe and effective in a case of refractory hypertension.[35] Finally, our group has extensive experience with neuromodulation which includes the application of BTX to epicardial fat pads for prevention of post-operative atrial fibrillation [36] and stellate ganglion blockade for ventricular arrhythmias.[37,38] **Together, published evidence and our data indicates the potential importance of splanchnic nerve modulation as a treatment for HF, providing a strong scientific premise for further investigation in this field.**

Design & Procedures

- Describe the study, providing detail regarding the study intervention (drug, device, physical procedures, manipulation of the subject or the subject's environment, etc.). Discuss justifications for placebo control, discontinuation or delay of standard therapies, and washout periods if applicable. Identify procedures, tests and interventions performed exclusively for research purposes or more frequently than standard of care. Include alternative therapies, concurrent therapies discontinued per protocol, risk benefit ratio, and use of tissue/specimens. Discuss monitoring during washout periods if applicable. Include brief description of follow-up, if any.

Study design. The present study will be a prospective open-label pilot study to help establish feasibility, safety and enable dose finding for BTX. The schedule of events is presented in **Figure 3**. Following a baseline invasive (right heart catheterization) cardiopulmonary exercise testing (CPX) patients will undergo unilateral celiac plexus block (**Figures 2 and 4**), followed by repeat hemodynamic testing in the following 90 minutes. Repeat CPX (with and without hemodynamic testing) will occur at 2, 4, 8 weeks. A 12 month phone call to investigate vital status, HF hospitalizations will conclude the study. Functional testing at baseline and follow up will be supplemented by a series of minimally invasive and non-invasive measures of static and dynamic blood volume distribution (radionuclear plethysmography, bioelectrance, hepatic vein ultrasound), congestion parameters (biomarkers, BVA), autonomic nervous tone (catecholamines,

baroreflex, and heart rate variability) and symptom questionnaires (Likert and Visual Analog scale). Given high volume of patients and right heart catheterizations (>1,000 per year) and our experience with enrolling patients in the preliminary studies, we anticipate to complete recruitment within 2 years.

Figure 2. Splanchnic Nerve Block Procedure (A) and Prior Data of Nerve Blockade in Acute (B) and Chronic Heart Failure (C). * indicates p<0.05

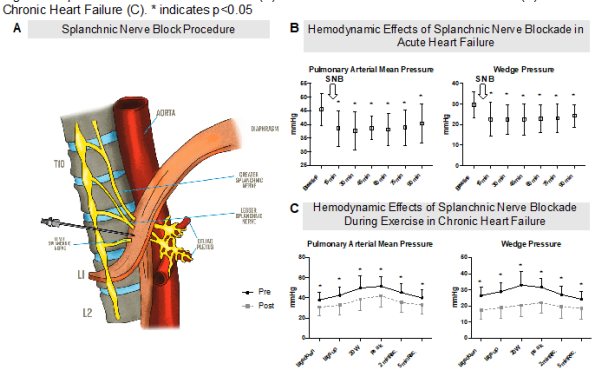

Figure 3. Study Flow

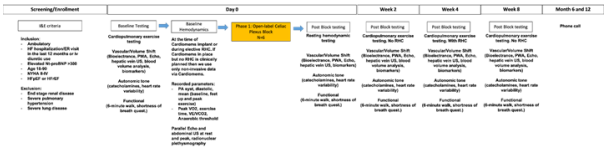

Figure 4. Study set-up: Invasive hemodynamic testing

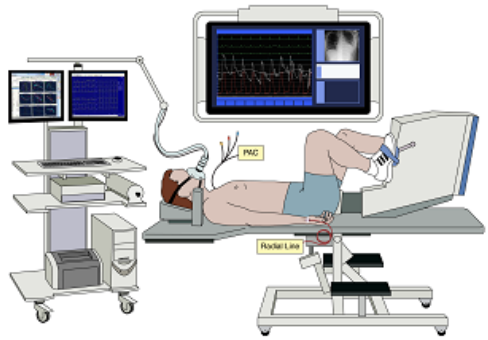

Table 1: Schedule of events (CS, clinical study; SOC, standard of care/clinical)

Required Assessment	Pre-Procedure (Day 1)	Baseline (Intra-Procedure)	Block	Post-Block Procedure	48 Hours	Week 1	Week 2	Week 4	Week 8	Month 6	Month 12
Vitals (BP, HR, RR, SpO2, weight)	X (CS)			X(CS)			X(CS)	X(CS)	X(CS)		
Orthostatic vitals	X(CS)			X(CS)			X(CS)	X (CS)	X (CS)		
Non-Invasive Testing*	X(CS)			X(CS)			X(CS)	X (CS)	X (CS)		
Pregnancy test	X (SOC)										
Labs: BMP (SOC), pro-BNP (CS), CA-125 (CS), urine sodium (CS),	X (CS /SOC)			X (CS /SOC)			X (CS /SOC)	X (CS /SOC)	X (CS /SOC)		
Labs Renin, Angiotensin II, Vasopressin, Plasma Catecholamines	X (CS)			X (CS)			X (CS)	X (CS)	X (CS)		
					X(CS)	X(CS)				X(CS)	X(CS)

Dyspnea and EQ-5D-3L Questionnaires	X (CS)			X(CS)			X(CS)	X (CS)	X(CS)		
Six minute walk test	X (CS)			X(CS)			X(CS)	X (CS)	X(CS)		
Blood volume - Daxor	X (CS)							X (CS)			
Heart rate variability	X (CS)	X (CS)		X (CS)			X (CS)	X (CS)	X (CS)		
Right Heart Cath (RHC)		X (CS, SOC)						X (CS)			
Scintigraphy	X (CS)							X (CS)			
Invasive CPX (peak VO2)		X (CS)						X (CS)			
CPX (peak VO2)							X (CS)		X (CS)		
Echocardiogram		X (CS)		X (CS)			X (CS)	X (CS)	X (CS)		
Renal ultrasound (to be done by Marat)	X (CS)			X (CS)			X (CS)	X(CS)	X (CS)		
Splanchnic nerve block			X (CS)								
Phone Call					X (CS)	X (CS)				X (CS)	X (CS)

***Non-Invasive Testing**

Device Name	**Approval**	**Indication**
CardioSet	Investigational	measures lung volume using impedance technology
ReDS unit	FDA	measures lung fluid content using radiofrequency waves
Sphygmocor	FDA	measures arterial stiffness through a brachial cuff
Bedside Ultrasound	FDA	performed of the heart, abdomen, kidney and diaphragm to assess left ventricular function, inferior vena cava dimensions and collapsibility, hepatic vein blood flow and portal vein flow and peripheral renal flow of the kidney
Musculoskeletal Ultrasound	FDA	Utilizes muscle metabolic imaging derived from point of care musculoskeletal ultrasound for muscle mass, intramuscular glycogen content and intramuscular adipose tissue content
InBody	FDA	Bioelectrical Impedance Spectroscopy: Segmental bioelectrical impedance spectroscopy (BIS) is another non-invasive way of assessing muscle quality assessment.
VO2Master Pro	FDA	compact, mobile and wireless (bluetooth) breath-by-breath metabolic cart to assess the cardio-metabolic and cardio-respiratory capacity /effort during training (Rehab)
PhysioFlow Hemodynamics	FDA	non-invasive hemodynamic monitor. It provides continuous, accurate, reproducible and sensitive measurements of cardiac output, stroke volume, systemic vascular resistance and left cardiac work index.
Portalite and Moxy	Investigational	assessment of muscle- and brain mitochondrial function during cardiopulomonary exercise testing. The device is developed to measure concentration changes of oxyhemoglobin and deoxyhemoglobin with near infrared light.
WHOOP strap 3.0	Investigational	measures heart rate variability and heart rate
Questionnaire		
Dyspnea		7-point Likert scale and Visual Analog Scale
EQ-5D-3L		Quality of Life

Device Name	FDA Approval (Yes/No)	Indication
CardioSet	No	measures lung volume using impedance technology
ReDS unit	Yes	measures lung fluid content using radiofrequency waves
Sphygmocor	Yes	measures arterial stiffness through a brachial cuff
Bedside Ultrasound	**Yes**	performed of the heart, abdomen, kidney and diaphragm to assess left ventricular function, inferior vena cava dimensions and collapsibility, hepatic vein blood flow and portal vein flow and peripheral renal flow of the kidney
Musculoskeletal Ultrasound	**Yes**	Utilizes muscle metabolic imaging derived from point of care musculoskeletal ultrasound for muscle mass, intramuscular glycogen content and intramuscular adipose tissue content
InBody	**Yes**	Bioelectrical Impedance Spectroscopy: Segmental bioelectrical impedance spectroscopy (BIS) is another non-invasive way of assessing muscle quality assessment.
VO2Master Pro	**No**	compact, mobile and wireless (bluetooth) breath-by-breath metabolic cart to assess the cardio-metabolic and cardio-respiratory capacity /effort during training (Rehab)
PhysioFlow Hemodynamics	Yes	non-invasive hemodynamic monitor. It provides continuous, accurate, reproducible and sensitive measurements of cardiac output, stroke volume, systemic vascular resistance and left cardiac work index.
Portalite and Moxy	No	assessment of muscle- and brain mitochondrial function during cardiopulomonary exercise testing. The device is developed to measure concentration changes of oxyhemoglobin and deoxyhemoglobin with near infrared light.
WHOOP strap 3.0	No	measures heart rate variability and heart rate

Testing procedures

Blood volume analysis and scintigraphy: Blood volume analysis will be performed using I131-radiolabelled albumin. The injection of the drug and associated blood draws will be completed in the nuclear lab. Patients will have a baseline blood sample drawn (4ml). Then, patients will be injected the radiolabeled albumin. After 12, 16 and 20 minutes we draw additional blood samples. The blood samples will be processed at the Duke nuclear laboratory using the Daxor analyzer or sent to Daxor Inc. for processing. If sent to Daxor for processing we will only share deidentified blood samples. Samples will be labelled with case number. We will provide patients age, gender and weight, which are needed for data calculation.

Following injection of the agent, the patient will also receive a **MUGA Scan** (Multiple Gated Acquisition **sca n**) is a noninvasive tool for assessing the function of the heart. The **MUGA scan** produces a moving image of the beating heart but also allows to image the abdomen, and from this image several important features can be determined about the health of the cardiac ventricles and blood distribution.

Following injection of the technetium99, patients will be placed under a scintigraphy camera which will pick up the counts of radiation over the chest and abdomen. We will record resting counts over both compartments (chest /abdomen). Then patient will perform up to 5 min low resistance leg exercise while supine on a stepper placed at bed end. Counts will be recorded over both compartments during exercise.

Blood draws reported above will occur during resting recording. The exercise will occur after the 20 min blood draw is complete. Total duration of the study is anticipated to be 30 min.
The I-131 (Volumex) will either be administered by the nuclear medicine technician or Marat Fudim, MD. Both have received training from the manufacturer.

Nerve Block Procedure. The unilateral, left-sided, temporal bilateral celiac plexus block will be performed by the interventional pain specialty team in the catheterization laboratory, with continuous hemodynamic monitoring similarly to our previously published experience.[24] The celiac plexus block will be performed under fluoroscopic guidance in the posterior chest wall (vertebral space L1) to guarantee maximal safety (**Figure 2**). We will use a mix of 3 ml of lidocaine 1.55 with 1:10000 epinephrine, 10 ml of 0.5% ropivacaine and up to 1.5 U/kg of BTX Type A. Lidocaine with epinephrine is used for procedural

safety to exclude intravascular injection. In the present study we will start at a lower dose of the BTX (dose finding). We will plan to increase dose or decrease per Kg unit does for Botox based on 4 week assessment.

The dosing up titration scheme (Scenario 1) is as following:

1. The 1st and 2nd subject receiving the block splanchnic procedure - 75Units of Botox, (not more than 1.5 Units/kg) follow up at 2 weeks with CPX and 4 weeks with invasive CPX and 8 weeks with CPX
2. The 3rd and 4th subject receiving the block splanchnic procedure - if prior dose tolerated, no safety issues at 4 weeks than proceed with dose increase to: 100Units of Botox, (not more than 1.5Units/kg) follow up at 2 weeks with CPX and 4 weeks with invasive CPX and 8 weeks with CPX
3.The 5th and 6th subject receiving the block splanchnic procedure - Scenario 1: if prior dose tolerated, no safety issue and satisfactory efficacy at 4 weeks than patient 5/6 will get injection of 100Units of Botox again (not more than 1.5Units/kg) with follow up at 2 weeks with CPX and 4 weeks with invasive CPX and 8 weeks with CPX Satisfactory efficacy is defined as >25% reduction with exercise wedge pressure
Scenario 2: if prior dose tolerated, no safety issue and efficacy not satisfactory at 4 weeks than patient 5 /6 will get injection of 125Units of Botox (not more than 1.5Units/kg) with follow up at 2 weeks with CPX and 4 weeks with invasive CPX and 8 weeks with CPX.

Dose down titration scheme is as following: If BP is too low (newly <90mmHg, independent of heart failure medication changes done clinically) or patient report orthostatic symptoms we will return for the next patient to the preceeding lower Botox dose. If symptoms of orthostasis of hypotension are experienced already at the lowest dose we will drop the injection dose to 50 Units (not more than 1.5U/kg) . The effects of ropivacaine are expected to occur as early as 15 minutes and last for 24h. The acute effects will serve as confirmation of procedural success and provide reassurance that BTX was injected in the right location. BTX is a neurotoxin that blocks cholinergic neurotransmission and offers temporary autonomic modulation via ganglionic block. The peak pharmacological properties of BTX are expected at 2 weeks post injection. The estimated duration of BTX effect is up to 4-6 months.[39,40]

Selection of Subjects

- List inclusion/exclusion criteria and how subjects will be identified.

Subjects will be identified by screening the Duke University Medical Center or Duke Raleigh outpatient heart failure and catheterization clinic environments. All study subjects will have an electively scheduled right heart cathetherization, by the cardiologist, with or without an invasive cardiopulmonary exercise. Subjects with Cardiomems device will already have the device in place prior to the electively scheduled right heart catheterization.

Inclusion Criteria:

1. Age 18-90
2. Patients with or without Cardiomems device implanted
3. Followed at DUMC for known or suspected diagnosis of HF (NYHA stage 2-3, Class C-D), including patients on inotropic medication
4. Systolic blood pressure (SBP) > 100mmHg
5. History of HF hospitalization or ER visit or IV diuretic use in the last 12 months.
6. Patients will be included regardless of left ventricular ejection fraction.

Exclusion Criteria:

1. 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

2. 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,

3. Recent acute MI or hemodynamic instability:

- · Acute MI (STEMI or Type I NSTEMI) within 7 days.
- · Evidence of progressive cardiogenic shock within 48 hours

4. Certain forms of HF:

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

5. Severe bleeding risk:

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

6. Significant comorbidities:

- · End-stage renal disease CKD stage 5 due to primary renal pathology
- · Severe scoliosis of the thoracic spine
- · 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 fixed pulmonary hypertension

- · History of organ transplant (heart , lung, liver, pancreases, small bowel).

7. Pregnancy: patients of childbearing age will be tested with pregnancy tests, unless they had a hysterectomy or removal of their ovaries.

8. Procedure
Unable to tolerate procedure as determined by or investigator
Will be excluded if invasive hemodynamics on study date determine that the does not have elevated filling pressures at rest or stress. Following pressures/situations will exclude the : 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 block related complications.

Subject Recruitment and Compensation

- Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

  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 agred to the study. 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 case. In both cases the subject will be notified about being approached on the day of the study about a second approach in person by a heal care provider known to the patien for potential 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.

  The subject will be compensated for a total of $300 for their participation in this clinical study. The subjects will receive $100 at the following visits: Procedure visit, 2 week follow-up, and 2 month visit.

Consent Process

- Complete the consent section in the iRIS Submission Form.

Subject's Capacity to Give Legally Effective Consent

- If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

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.

This is a FDA regulated study, therefore, this eConsent platform will comply with 21 CFR Part 11 requirements, which include regulations on electronic records and electronic signatures.

Study Interventions

- If not already presented in #4 above, describe study-related treatment or use of an investigational drug or biologic (with dosages), or device, or use of another form of intervention (i.e., either physical procedures or manipulation of the subject or the subject's environment) for research purposes.

The study subjects will participant in the following study tests and procedures:

Invasive Test:

1. Regional nerve block under fluoroscopic guidance: A solution of ropivacaine 12 cc (approximately 2.5 teaspoons) and Botox 75-125 units (approximately 0.25 teaspoons), into the space around a nerve, called the splanchnic nerve, which controls the blood vessels in your intestines. These drugs will be delivered using a long needle placed between the patient's ribs in the mid-region of the back. The placement of the needle will be performed by an anesthesiologist experienced with the needle placement, with the assistance of x-ray guidance. The subject's measurement will be monitored for 60 minutes post-block.
2. Cardiopulmonary exercise: The subject will exercise by pedaling on a bike in a supine position for about 2-5 minutes, before stopping to rest. The catheter will remain in the subject's heart to measure pressures while exercising to provide information about the subject's exercise ability.

Non-Invasive Tests:

1. Vital Signs (Orthostatic vital signs)
2. Imaging with ultrasound, impedance, radiofrequency
    1. Fluid content in the body and lungs: The subject will wear a vest that emits radiofrequency waves to measure fluid content (ReDs Vest). The InBody uses Bioelectrical Impedance Spectroscopy to determine fluid content in the subject's body.
    2. Lung impedance: electrodes will be attached to the subject's upper back and chest to determine the intra-thoracic blood volume (CardioSet)
    3. Arterial stiffness using a brachial cuff. A cuff will be applied to your arm, similar to a blood pressure cuff, and a hand held probe will be placed on your groin and arm. The cuff will inflate and will measure pulse wave changes in your blood vessels (Sphygmocor)
    4. Cardiac Hemodynamics: the PhysioFlow device measures the subject's cardiac output, stroke volume, systemic vascular resistance and left cardiac work index.
    5. Oxygen Utilization: VO2 Master Pro (Oxygen consumption) will be used to measure oxygen consumption during rest and exercise. PortaLite and MOXY will measure oxygen concentration during exercise.
    6. Heart Rate Variability: The WHOOP strap 3.0 will measure heart rate and heart rate variability and will be worn for approximately one hour.
3. 6 minute walk test to measure your exercise capacity and endurance.
4. Questionnaires about the subject's feeling about their shortness of breath and breathing at rest
5. Cardiopulmonary (CPX) Testing: Exercise testing with the subject using an upright bike. The subject will exercise at their maximum effort. The subject will be monitored for exercise intolerance, shortness of breath, or pain in the chest. The subject will wear a face mask to measure oxygen intake and carbon dioxide output.
6. MUGA Scan: non-invasive imaging method to evaluate the function of your heart. This scan will help determine more information about the health of the subject's cardiac ventricles and blood distribution.

Laboratory Tests:

1. Blood Volume Analysis: Administration of a small amount of plasma protein, albumin, containing a small amount of radioactive iodine (injected through the PIV). The radioactive iodine labeled albumin

protein (blood volume solution) will be administered through the PIV line. Blood samples will be withdrawn before administration of the blood volume solution and 12, 16 and 20 minutes after administration. The blood samples will be processed at the Duke Nuclear Laboratory using the Daxor Analyzer for further processing

2. Biomarkers: Blood samples will be taken before the procedure and after the procedure for analysis of NT pro-BNP (indication of worsening heart failure) and CA-125 (indication of inflammation).
3. Autonomic Nervous System regulators: Blood samples will be taken in the catheterization lab before and after the splanchnic block. The samples will be processed and sent out to labs that specialize in analyzing these samples for hormones angiotensin II, vasopressin, catecholamines, and metanephrines.

Risk/Benefit Assessment

- Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant women, prisoners or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

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 28 cases in the first pilot trial using lidocaine/ropivacaine 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):

1. Pain at puncture site and intercostal neuralgia
2. Gastrointestinal dysmotility including diarrhea, constipation and abdominal cramping as well as nausea
3. 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 /chronic 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-examined at 2 weeks.

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 (up to 6 months, the benefit provided by the brief episode of decongestion can provide lasting symptomatic improvement.

Given prior pilot studies and theoretical framework we expect a symptomatic improvement of patients during the nerve block. Given that we have not seen any side effects in acute heart failure patients after the nerve block wore off we do not expect comparable effects in chronic heart failure patiens when their block wears off given similar pathophysiology.

Costs to the Subject

- Describe and justify any costs that the subject will incur as a result of participation; ordinarily, subjects should not be expected to pay for research without receiving direct benefit.

All testing and services performed only for the purposes of the clinical study will be provided at no cost to the research subject. However, the subject or the subject's health insurance or Medicare is responsible for all costs that are part of usual medical care that would have happened if the subject were not in the clinical study. If the subjects health insurance or Medicare requires any co-payment, co-insurance, or deductible, the subject will be responsible for making that payment. Anything not paid by either the study sponsor or the subject's health insurance company will be billed directly to the subject for payment.

Data Analysis & Statistical Considerations

- Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

Cynthia Green in the Duke Heart Center will be preforming the statistics for the Splanchnic III study. We will perform descriptive statistics. Statistical comparisons will be made using t-tests for continuous outcomes and chi square or fisher's exact test. Unless otherwise specified, a two-sided 0.05 level of significance will be used to declare change in pre-and post-procedure variables different.

There is no direct measure of technical success following attempted block of the splanchnic nerves. 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.

Data & Safety Monitoring

- Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

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 2 weeks, and 6 months post-procedure.

Unanticipated severe adverse events will be reported to the IRB per IRB policy.

In accordance with federal regulations the PI will monitor for review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head, all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in research study, in accordance with (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)), all AE reports will be reported per the DUHS IRB policies.

Privacy, Data Storage & Confidentiality

- Complete the Privacy and Confidentiality section of the iRIS submission form.

Describe Role of External Personnel:

N/A