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EDITORIAL COMMENT

Blood Volume Redistribution in Chronic Heart Failure With Splanchnic Nerve Blockade*

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Imagine a limp, completely unfilled balloon. As you start inflating, the first aliquots of air expand the balloon, but there is a minimal increase of wall stress and essentially no increase of pressure within the balloon. However, once the volume reaches a certain critical point, wall stress and pressure start increasing steadily with each increment of volume. The balloon's volume up to the point at which pressure starts to increase is called the unstressed volume; additional volume added to the balloon is called the stressed volume. This example provides an analogy for the relationship between blood volume and pressure in the vascular system and helps explain the concepts of stressed and unstressed blood volumes and their relationship to mean circulatory filling pressure introduced by Arthur Guyton in the 1950s (1). The unstressed blood volume is the amount of blood required to fill the vascular system before venous pressure increases above ambient pressure; stressed blood volume is the volume beyond that. It is the stressed blood volume that determines venous pressure and provides preload to the heart, regulating its generation of cardiac output via the Frank-Starling mechanism.

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The sum of stressed and unstressed blood volume is the total blood volume. The distribution between the stressed and unstressed blood volume components is a functional compartmentalization and is not anatomic in nature. Functional redistribution of blood from unstressed to stressed compartments plays a critical role in regulating systemic and pulmonary venous pressures and is believed to contribute importantly to their rapid changes seen during exercise or acute heart failure, which occur despite constant total blood volume (2).

The splanchnic circulation constitutes the body's largest reservoir for unstressed blood volume and is very responsive to sympathetic tone, because of a large concentration of adrenergic receptors in the vessel walls that regulate their resistance and capacity. Attempts to exploit this biology therapeutically in volume overload states such as heart failure are, therefore, inherently attractive. Pharmacologically, direct vasodilators such as nitrates, angiotensin-converting enzyme inhibitors, and sympathetic nervous system inhibitors (e.g., trimethaphan) have shown some promising results in improving hemodynamics (3) but have significant systemic effects. Fudim et al. (4) introduced another strategy for modulating the splanchnic bed via percutaneous splanchnic nerve block (SNB), which they previously studied in a proof-of-concept study in 11 individuals with acute heart failure in the Splanchnic-HF 1 study.

Fudim et al. (4) now expand on their original study in this issue of *JACC: Heart Failure* and provide an intriguing addition to prior published data with their report of 15 patients with chronic heart failure who

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Heart Failure* author instructions page.

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underwent SNB (5). The investigators targeted patients with New York Heart Association functional class II to III symptoms and elevated filling pressures (pulmonary capillary wedge pressure of ≥15 mm Hg at rest and/or ≥25 mm Hg at peak exercise) despite guideline-directed medical therapy. Patients underwent a battery of noninvasive tests, including a 6-min walk test, echocardiography, sonographic evaluation of the hepatic and portal veins, and thoracic fluid content estimation. Invasive testing included exercise hemodynamic testing at rest, at a workload of 20 W, at peak exercise, and during recovery from supine cycle ergometry. After baseline measurements, patients underwent fluoroscopic-guided SNB by administration of ropivacaine at the anterolateral edge of the spine at the T12/L1 level. The first 5 patients received bilateral SNB and experienced symptom-limiting orthostatic hypotension; the remaining 10 participants received unilateral nerve blocks. Test were repeated approximately 1 h later.

The study cohort was characterized by a mean age of 58 years; 47% of patients were female, 40% were African American, 60% had ischemic cardiomyopathy, and 93% had a left ventricular ejection fraction of ≤35%. SNB resulted in a reduction in all invasively recorded pressures at rest, throughout every stage of exercise, and during recovery from exercise. These findings were supported by the results of the noninvasive tests, which showed reduced abdominal venous flow and decreased thoracic fluid content. By the same token, arterial blood pressure and systemic vascular resistance decreased at rest with nonstatistically significant increases in cardiac index. Notably, exercise testing showed increased 6-min walk distance, peak workload performed, and peak VO_2 after SNB.

Bilateral nerve block produced a greater reduction in wedge pressure than unilateral block, but otherwise, there were no apparent differences with respect to other outcomes, including pulmonary pressures or exercise capacity. Despite orthostatic hypotension observed in 4 of the 5 participants with bilateral blocks, which was transient and resolved with hydration, the safety profile for nerve block was favorable, and no major adverse events were reported. Fudim et al. (4) are to be congratulated for performing a study of such a novel therapeutic approach and using a thoughtful study design that evaluated treatment efficacy with a comprehensive, multimodality hemodynamic assessment at rest and exercise.

Although not directly measured, Fudim et al. (4) suggested that the mechanism of hemodynamic benefit was that SNB harnessed the splanchnic vascular reservoir, coaxing it into storing more blood and reducing shifts of blood from the splanchnic to pulmonary vasculature beds while also causing arterial vasodilation to reduce systemic arterial resistance, thus maintaining cardiac output despite lower filling pressures. We further suggest that the effect of SNB was not only to reduce blood shifts from the splanchnic to pulmonary vasculature but that this was more generally the result of SNB-induced reductions of splanchnic stressed blood volume with a symmetrical increase of unstressed blood volume. The rationale for this conclusion is that SNB reduced both pulmonary capillary wedge pressure and central venous pressure (CVP) by very similar amounts at rest, during all stages of exercise, and during recovery. If SNB simply prevented shifting of blood, CVP and pulmonary capillary wedge pressure at rest as well as CVP during exercise might not have been expected to also decrease.

Fudim et al. (4) provided an appropriate discussion of study limitations, including the unblinded nature of the study, which was partially overcome through the use of blinded evaluations of hemodynamic parameters. One noted limitation deserving further consideration is that the repeat hemodynamic exercise tests were performed within hours of the first pre-SNB test. Exercise results in vasodilation, even in patients with heart failure; the period of time required to return to the baseline state is not established. Thus, it is possible that the current experiments could have overestimated the hemodynamic effects of SNB. Similar concerns could be raised regarding the repeated 6-min walk and metabolic exercise testing on the same day. Another potential limitation is that the studies were performed while withholding heart failure medical therapies the day of study. Although complete washout of drug effects is unlikely to occur following withholding 1 dose, this may have also affected the effects of SNB, and it remains to be studied whether similar clinically significant responses would be observed when added to full neurohormonal blocking heart failure therapies.

Moving forward, the question at hand is whether the transient effects of ropivacaine-induced acute SNB can be achieved by safe and well-tolerated means with durable effects. Ganglia innervating the abdominal viscera are routinely targeted to produce months-long relief for abdominal pain in chronic pain syndromes and malignancy-associated pain with long-acting anesthetics or neurolysis. Can this be replicated for patients with heart failure using longer-lasting drugs or other means, such as surgical disruption of the ganglion, electrical

neurostimulation approaches, or ablation techniques? In addition, can the findings of the present study be extended further: in the same way that Fudim et al. (4) extended their initial findings in patients with acutely decompensated heart failure to patients with chronic heart failure, is SNB applicable in other pressure and volume overload conditions, such as heart failure with preserved ejection fraction?

For now, Fudim et al. (4) have provided evidence suggesting that the splanchnic reservoir can be manipulated to favorably affect filling pressures and systemic vascular resistance to improve resting and exercise hemodynamics. Long-term safety for whatever approach may evolve will be of paramount importance. Nevertheless, as a consequence of this study, the armamentarium for nonpharmacologic strategies to treat advanced heart failure may grow, as will our understanding of the important contributions of volume distribution to the pathophysiology of heart failure.

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KEY WORDS congestion, heart failure, splanchnic nerve block, sympathetic nervous system

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Splanchnic Nerve Block for Chronic Heart Failure

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ABSTRACT

OBJECTIVES We hypothesized that splanchnic nerve blockade (SNB) would attenuate increased exercise-induced cardiac filling pressures in patients with chronic HF.

BACKGROUND Chronic heart failure (HF) is characterized by limited exercise capacity driven in part by an excessive elevation of cardiac filling pressures.

METHODS This is a prospective, open-label, single-arm interventional study in chronic HF patients. Eligible patients had a wedge pressure ≥15 mm Hg at rest or ≥25 mm Hg with exercise on baseline right heart catheterization. Patients underwent cardiopulmonary exercise testing with invasive hemodynamic assessment, followed by percutaneous SNB with ropivacaine.

RESULTS Nineteen patients were enrolled, 15 of whom underwent SNB. The average age was 58 ± 13 years, 7 (47%) patients were women and 6 (40%) were black. Left ventricular ejection fraction was ≤35% in 14 (93%) patients. No procedural complications were encountered. SNB reduced mean pulmonary arterial pressure at peak exercise from 54.1 ± 14.4 (pre-SNB) to 45.8 ± 17.7 mm Hg ($p < 0.001$) (post-SNB). Similarly, SNB reduced exercise-induced wedge pressure from 34.8 ± 10.0 (pre-SNB) to 25.1 ± 10.7 mm Hg ($p < 0.001$) (post-SNB). The cardiac index changed with peak exercise from 3.4 ± 1.2 (pre-SNB) to 3.8 ± 1.1 l/min/m^2 ($p = 0.011$) (post-SNB). After SNB, patients exercised for approximately the same duration at a greater workload (33 ± 24 W vs. 50 ± 30 W; $p = 0.019$) and peak oxygen consumption VO_2 (9.1 ± 2.5 vs. 9.8 ± 2.7 ml/kg/min; $p = 0.053$).

CONCLUSIONS SNB reduced resting and exercise-induced pulmonary arterial and wedge pressure with favorable effects on cardiac output and exercise capacity. Continued efforts to investigate short- and long-term effects of SNB in chronic HF are warranted. Clinical Trials Registration (Abdominal Nerve Blockade in Chronic Heart Failure; NCT03453151) (J Am Coll Cardiol HF 2020;8:742–52) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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In heart failure (HF), the concept of volume retention as the primary cause of acute or chronic cardiac decompensation has been challenged. An alternative hypothesis suggests volume redistribution as an important contributor to cardiopulmonary congestion (1–5). In chronic HF, cardiopulmonary congestion, whether driven by volume retention or volume redistribution, is an important determinant of exercise intolerance, manifested either as exertional dyspnea and/or fatigue (1,5–8). A key mechanism limiting activity is an abnormal hemodynamic response, evidenced by a temporary and severe elevation in cardiopulmonary filling pressures that are not seen in healthy adults (6,7,9).

The abdominal compartment, which contains highly vascular organs such as the liver, spleen, and bowel, is the main storage compartment of intravascular blood volume (10) and has been implicated as a major contributor to volume redistribution in HF (1,3–5). Blood volume can be recruited in and out of the splanchnic vascular compartment, which in healthy adults is a compensatory mechanism to increase the central blood volume and cardiac output in the setting of exercise or acute blood loss (11). In HF, the ability of the splanchnic vascular compartment to store or buffer blood volume (capacitance) is impaired (3,4). The main regulatory system for the splanchnic vascular capacitance includes sympathetic fibers in the splanchnic nerves that control arterial and venous vascular tone (12). This makes the splanchnic vascular compartment and greater splanchnic nerves potential therapeutic targets in HF.

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A prior study in 11 patients hospitalized for acute HF has shown that bilateral temporary splanchnic nerve block (SNB) with lidocaine can reduce resting cardiopulmonary filling pressures and improve the cardiac output without complications (Splanchnic Nerve Anesthesia in Heart Failure [Splanchnic HF-1]; NCT02669407) (13,14). Following the initial experience with SNB, the present study (Splanchnic HF-2) investigated the safety and efficacy of a prolonged SNB on exercise hemodynamics and function in ambulatory patients with HF.

METHODS

STUDY DESIGN AND POPULATION. This was a single-arm, open-label pilot study. Patients were enrolled between May 2018 and June 2019 at Duke University Medical Center (Durham, North Carolina). The protocol was approved by the local Institutional Review Board, and all patients provided written informed consent (Abdominal Nerve Blockade in Chronic Heart Failure; NCT03453151). To qualify for enrollment, patients had to be ambulatory, have an established history of HF, be on guideline-directed medical therapy, and have New York Heart Association functional class II–III symptoms. The final qualifying criterion was a resting mean pulmonary capillary wedge pressure (mPCWP) ≥15 mm Hg and/or ≥25 mm Hg at peak exercise during the initial (pre-SNB) invasive cardiopulmonary exercise test (iCPET). Patients with chronic kidney disease stage V, known coagulopathies, and those on oral anticoagulants or oral antiplatelet agents other than aspirin were excluded. A full list of study inclusion and exclusion criteria is available (Supplemental Table 1). Patients were not allowed to eat or drink 8 h before the procedure and were allowed to resume oral intake after completion of second exercise study.

INVASIVE HEMODYNAMIC TESTING. All testing was performed in 1 day (**Figure 1**) in a fasting state, with a follow-up phone call at 48 h. HF-related medications such as neurohormonal blockers and diuretic agents were held the morning of the study and resumed after completion of testing. The experimental set-up in the catheterization laboratory is presented in **Figure 2**. All invasive hemodynamic measurements were recorded in the supine position. Right heart catheterization through the internal jugular vein (8-F sheath, and 7-F pulmonary artery catheter) and a radial arterial catheterization (5-F sheath) were used to assess central hemodynamics, arterial pressures, and for blood gas analysis. Resting invasive measurements were obtained ~15 min after placement of central lines, sensors and mask fitting (30 to 45 min), once steady

ABBREVIATIONS AND ACRONYMS

AVO_2-diff = arterio-venous O_2 difference

HF = heart failure

iCPET = invasive cardiopulmonary exercise test

LVEF = left ventricular ejection fraction

mPAP = mean pulmonary arterial pressure

mPCWP = mean pulmonary capillary wedge pressure

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SNB = splanchnic nerve block

TFC = thoracic fluid content

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Heart Failure* author instructions page.

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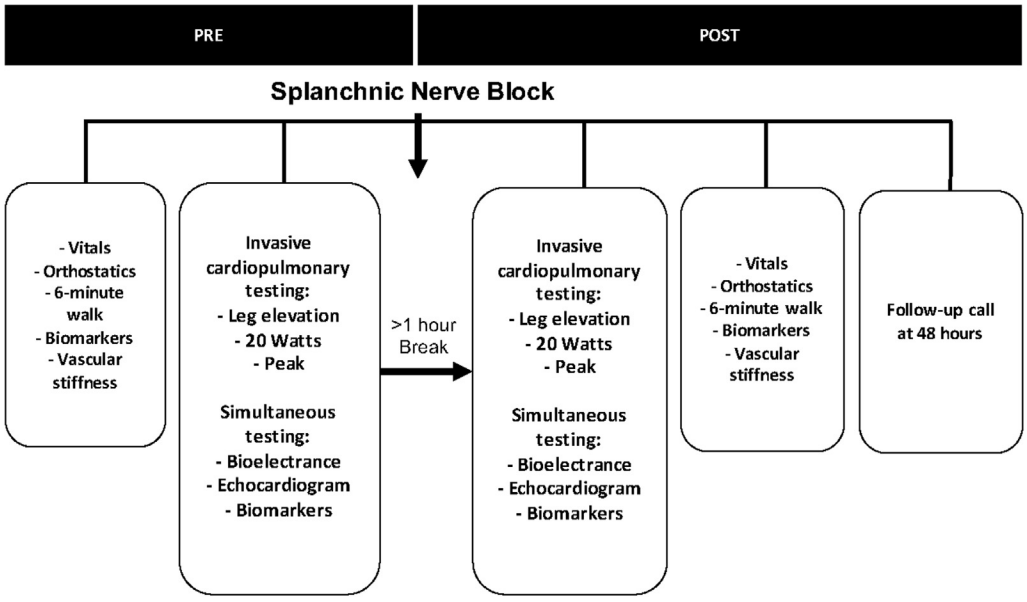
FIGURE 1 Study Flow Diagram



Study measures and procedures for Splanchnic HF-2.

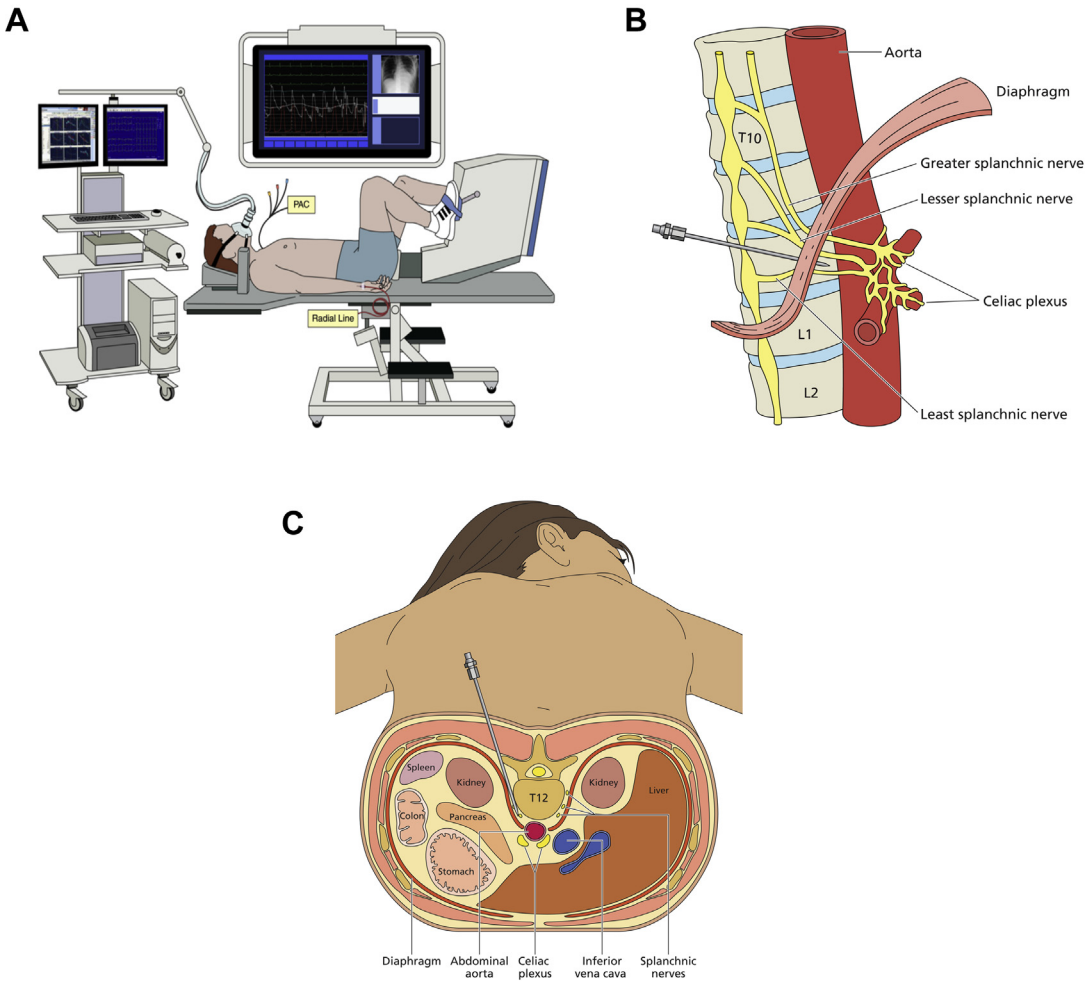
state was achieved (legs down and up on the bike pedals). At baseline, 2 pressure recordings were obtained and values were averaged across recordings. Following resting hemodynamics, patients underwent supine cycle ergometry testing with simultaneous expired gas analysis. Patients were tested at a fixed workload of 20 W until patients reached a steady state of expired VO_2 or up to 7 min. Patients were encouraged to maintain a pedaling speed of 55 to 65 revolution/min. After reaching steady state, patients were exercised to peak with a stepwise increase of 20 W every minute. Hemodynamic assessment during exercise was performed at 20 W and at peak exercise. Following exercise, recovery hemodynamics were assessed at 2 and 5 min after peak exercise. Pressure tracings were recorded and stored for off-line blinded analysis. Intracardiac pressures were obtained as the average end-expiratory values across multiple respiratory cycles over a 10-s period. Patients repeated the exercise protocol after placement of the SNB with a recovery time of 1 to 1.5 h between exercise studies.

Breath-by-breath oxygen consumption was measured continuously throughout the study (Vmax e29, Vyaire Medical, Loma Linda, California). Simultaneous pulmonary arterial and systemic arterial blood samples were collected to determine the arterio-venous O_2 difference (AVO_2-diff). Cardiac output was calculated via direct Fick method ($VO_2 \div AVO_2$-diff). Peak VO_2 values were determined by 2 readers independently (A.C., A.P.). The Borg scale of perceived exertion (6–19) and assessments of leg fatigue (scale: 0 to 10) and shortness of breath (scale: 0 to 10) were obtained throughout the exercise phases at the same intervals as the cardiac hemodynamic measurements. No general anesthetic agents were used during the study. If pain medications were required, short-acting fentanyl was used in low doses before initiation of the first exercise study.

NONINVASIVE TESTING. Noninvasive testing was performed before and after the SNB. All patients underwent simultaneous sonographic recording of the heart, hepatic, and portal veins at rest, 20 W, and peak exercise. All echocardiographic examinations were performed using a GE E95 echocardiography system (GE Healthcare, Chicago, Illinois) by the same team of experienced sonographers. Images were analyzed using GE PACS (GE Healthcare) by the Duke Echo Core Laboratory.

During the invasive exercise, thoracic fluid content (TFC) was continuously measured by reading the impedance to electric conductivity through the chest wall. It is calculated as the inverse of the impedance

FIGURE 2 Study Set-Up



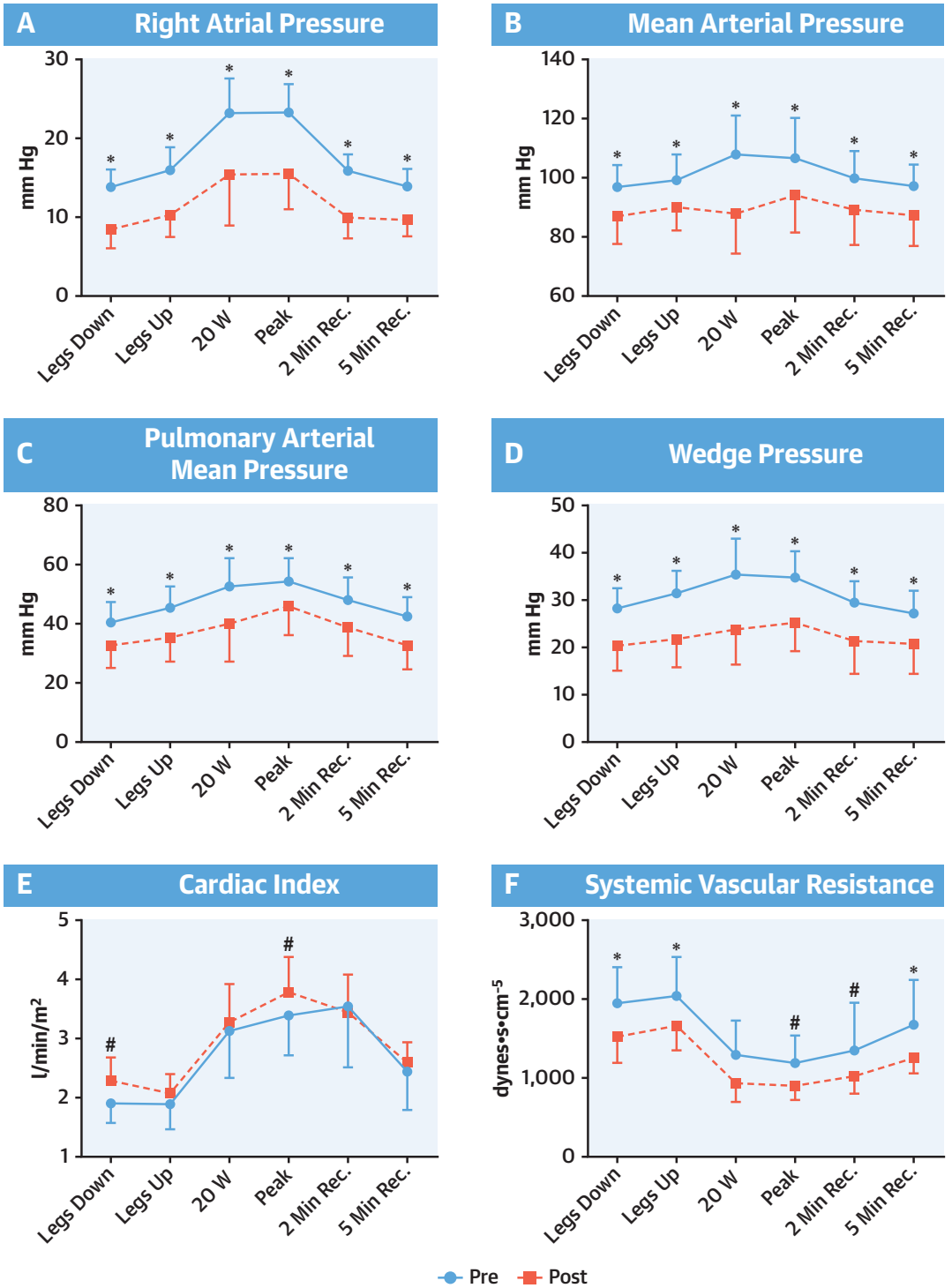
(A) In the catheterization laboratory. **(B and C)** Study intervention.

(1/Zo) across the thorax (NICOM, Cheetah Medical, Tel Aviv, Israel). TFC changes reflect directional changes in thoracic fluids, whether increasing or decreasing. We compared the change in TFC during exercise before and after SNB. Central vascular stiffness was evaluated via automated aortic pulse wave analysis and velocity (SphygmoCor, AtCor Medical, Itasca, Illinois). These parameters were measured 60 min before and 90 min after SNB. Finally, a 6-min walk test was performed before and within 3 h after the SNB.

Biomarker testing included a basic metabolic panel, urine sodium, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (Duke University Clinical Laboratories, Durham, North Carolina). Additionally, serum catecholamine, vasopressin levels (Mayo Medical Laboratories, Rochester, Minnesota), and serum angiotensin levels (Inter Science Institute, Inglewood, California) were measured.

STUDY INTERVENTION. In the present study, SNB was performed following baseline functional and hemodynamic testing. All patients underwent a fluoroscopic-guided SNB by 2 anesthesiologists with subspecialty training in interventional pain medicine (R.B.M., A.G.). A 22-g spinal needle was guided to the anterolateral edge of the thoracolumbar spine at the T12/L1 level (Figure 1). Once the needle was in final position, iodinated contrast followed by a "test" dose of 3 ml of 1.5% lidocaine with 1:200,000 epinephrine were injected to confirm extravascular location of the needle. This was followed by injection of 12 ml of 0.5% ropivacaine. The patient remained in a supine

CENTRAL ILLUSTRATION Hemodynamic Results



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Resting and exercise hemodynamic profile before and after SNB are shown. **(A)** Right atrial pressure. **(B)** Mean arterial pressure. **(C)** Pulmonary arterial mean pressure. **(D)** Wedge pressure. **(E)** Cardiac index. **(F)** Systemic vascular resistance. *Adjusted $p < 0.01$ for a pairwise comparison with the pre-SNB value. #Unadjusted $p < 0.05$, adjusted >0.05.

position throughout the study, except during the SNB when the patient was prone on his/her abdomen. The procedure was performed bilaterally in the first 5 cases and unilaterally in the subsequent 10 cases. The expected duration of sympatholytic effects was up to 24 h. After SNB, the first measurements were obtained after a 30-min wait period.

ENDPOINTS. Primary outcomes were the cardiopulmonary filling pressures (mean pulmonary arterial pressure [mPAP] and mPCWP) and exercise capacity as measured by peak VO_2. Secondary outcomes were changes in cardiac output, 6-min walk distance, biomarkers, and sonographic parameters.

STATISTICS. Continuous variables are presented using the mean ± SD, median (25th and 75th percentile), and the minimum and maximum, as appropriate, based on the underlying distribution. Statistical comparisons between variables assessed only once post-SNB used the paired Student's *t*-test or Wilcoxon rank-sum test (change from baseline in echocardiographic function, as well as 6-min walk test, and biomarker profile variables). A value of zero was imputed for norepinephrine and epinephrine levels if the value was below the level of quantitation. Repeated measures models with compound symmetry variance structure were used to evaluate the change of hemodynamic parameters from pre-SNB tests (legs down, legs elevated, 20 W, peak, 2-min, and 5-min recovery) using a simulation method to adjust for multiple pairwise comparisons of each post-procedure time to pre-SNB values (**Central Illustration**, Supplemental Figure 1). Each model included the test, pre-SNB test value, time (pre- or post-SNB), and test-by-time interaction. An interaction term for SNB method (bilateral or unilateral) was also evaluated for the primary hemodynamic endpoints (mPAP and mPCWP) at peak assessment time, as well as for peak VO_2. Statistical analyses were completed by the Duke Department of Biostatistics (Durham, North Carolina) using SAS version 9.4 (SAS, Institute, Inc., Cary, North Carolina). A p value <0.05 was considered statistically significant.

RESULTS

Nineteen patients were enrolled in the study. Of these, 3 patients did not undergo SNB due to a low pulmonary capillary wedge pressure (PCWP) at rest or during peak exercise during the baseline assessment and 1 patient withdrew consent before undergoing SNB. The remaining 15 patients underwent SNB. Baseline characteristics are displayed in **Table 1**. The average age was 58 ± 13 years, 7 (47%) patients were women, and 6 (40%) were black. The majority of patients had ischemic (n = 9 [60%]) cardiomyopathy. All patients had established HF; 14 (93%) patients had a left ventricular ejection fraction (LVEF) of ≤35% and 1 patient had a recovered LVEF of 55%. Mean NT-proBNP was 2,172 pmol/l (range 112 to 9,319 pmol/l). All patients had an implantable cardioverter-defibrillator in place.

TABLE 1 Baseline Characteristics

Men	8 (53)
Age, mean (range), yrs	58 (33-73)
Ischemic cardiomyopathy	9 (60)
History of hypertension	5 (33)
History of diabetes	4 (27)
History of atrial fibrillation	8 (53)
LVEF	
≤35%	14 (93)
>35%	1 (8)
BMI, mean (min-max), kg/m^2	32 (22-56)
Implantable cardioverter-defibrillator	15 (100)
Creatinine, mean (min-max), mg/dl	1.2 (0.7-1.9)
BUN, mean (min-max), mg/dl	19 (7-38)
NT-proBNP, mean (min-max), pmol/l	2,172 (112-9,319)
Inotrope	0 (0)
Beta-blockers	15 (100)
ACE-I/ARB	11 (73)
Mineralocorticoid receptor antagonists	10 (67)

Values are n (%), unless otherwise indicated.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; max = maximum; min = minimum; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Table 3.

SAFETY. Known side effects of the SNB such as orthostatic hypotension (preload and afterload reduction) and gastrointestinal upset were observed. The first 5 patients had bilateral SNB and 4 of them developed symptomatic orthostatic hypotension (systolic blood pressure decrease >20 mm Hg with 5-min standing) after acute hemodynamic testing when first given the chance to ambulate (Supplemental Table 2). In all cases the orthostatic hypotension resolved with oral or intravenous hydration and patients were discharged home the same day without recurrence of symptoms. Subsequently, the SNB was performed only unilaterally and no further cases of symptomatic orthostatic hypotension were observed. Loose stools were only observed in 1 patient for the first 24 h after bilateral SNB.

INVASIVE HEMODYNAMICS. SNB resulted in a reduction of right atrial pressure at rest from 13.8 ± 4.0 to 8.4 ± 4.1 mm Hg ($p < 0.001$) and with peak exercise from 23.2 ± 6.2 to 15.4 ± 7.8 mm Hg ($p < 0.001$) (**Central Illustration**). mPAP decreased at rest from 40.5 ± 12.3 to 32.7 ± 13.8 mm Hg ($p < 0.001$)

TABLE 2 Change in Cardiopulmonary Exercise Functional Parameters After Splanchnic Nerve Blockade

	Pre-SNB	Post-SNB	p Value
Workload, W	33 ± 24	50 ± 30	0.019
Exercise time, min (s)	4:48 ± 96	5:03 ± 91	0.181
Peak VO_2, ml/kg/min	9.1 ± 2.5	9.8 ± 2.7	0.053
VE/VCO_2 slope, %	37.1 ± 7.6	35.1 ± 6.0	0.067
RER	1.14 ± 0.13	1.08 ± 0.11	0.081
Lactate mg/dl	4.5 ± 1.8	4.9 ± 1.7	0.786
Borg perceived exertion*	17.5 ± 1.5	17.9 ± 1.5	0.189
Shortness of breath†	8.6 ± 1.6	6.7 ± 3.3	0.032
Leg fatigue‡	6.1 ± 4.7	7.8 ± 3.4	0.057
6-min walk distance, m	311 ± 68	330 ± 73	0.033
Oscillatory breathing during exercise	6/15	3/15	0.082

Values are mean ± SD, unless otherwise indicated. *Borg Scale of Perceived Exertion: scale ranges from 6 to 20, with 20 as the worst. †Visual Analog Scale: scale ranges from 0 to 10, with 10 as the worst. ‡Scale ranges from 0 to 10, with 10 as the worst.

RER = respiratory exchange rate; SNB = splanchnic nerve block; VE/VCO_2 = minute ventilation carbon dioxide production relationship; VO_2 = maximal oxygen uptake.

after SNB. mPAP was also lower with peak exercise (pre-SNB 54.1 ± 14.4 mm Hg vs. post-SNB 45.8 ± 17.7 mm Hg; $p < 0.001$). Similarly, there was a reduction in resting and exercise-induced PCWP. At rest, PCWP decreased from 28.3 ± 7.6 to 20.3 ± 9.5 mm Hg ($p < 0.001$). After the SNB, exercise-induced PCWP at peak stress decreased from 34.8 ± 10.0 to 25.1 ± 10.7 mm Hg ($p < 0.001$).

An interaction analysis showed that bilateral SNB resulted in a greater reduction in wedge pressure when compared with unilateral SNB (bilateral: 12.8 mm Hg vs. unilateral: 8.1 mm Hg; $p = 0.032$) (Supplemental Figure 1). There was no interaction for mPAP (bilateral: 13.8 mm Hg vs. unilateral: 5.6 mm Hg; $p = 0.084$).

Changes in arterial pressure were paralleled by a reduction in systemic vascular resistance, as evidenced by a decrease at baseline from 1,947 ± 825 to 1,523 ± 602 dynes·s·cm^{-5} ($p < 0.001$) after SBN. Systemic vascular resistance decreased at peak exercise from 1,189 ± 631 to 895 ± 312 dynes·s·cm^{-5} ($p = 0.108$) after SNB. The resting cardiac index changed from 1.9 ± 0.6 to 2.3 ± 0.7 l/min/m^2 at rest ($p = 0.077$) after SNB, and the cardiac index at peak exercise changed from 3.4 ± 1.2 to 3.8 ± 1.1 l/min/m^2 ($p = 0.069$) after SNB (for a break-down of measured Fick components, see Supplemental Table 3). Although only trending after multiple comparison adjustment, cardiac index change was significant before alpha adjustment at both rest ($p = 0.013$) and peak ($p = 0.011$).

EXERCISE CAPACITY AND SYMPTOMS. The change in cardiopulmonary exercise function parameters from pre- and post-SNB are presented in Table 2. Exercise duration was similar pre- and post-SNB (4:48 min [96 s] vs. 5:03 min [91 s]; $p = 0.181$), but patients had a greater workload (33 ± 24 W vs. 50 ± 30 W; $p = 0.019$) and peak VO_2 (9.1 ± 2.5 ml/kg/min vs. 9.8 ± 2.7 ml/kg/min; $p = 0.053$). Despite similar perceived exertion (Borg scale) before and after the SNB, patients reported less dyspnea ($p = 0.032$) and more leg fatigue ($p = 0.057$) at peak exercise after SNB. The 6-min walk distance increased after the SNB (311 ± 68 m vs. 330 ± 73 m; $p = 0.033$).

No difference in the change in peak VO_2 between unilateral and bilateral SNB was determined using an interaction test ($p = 0.444$).

NONINVASIVE HEMODYNAMICS AND BIOMARKERS. Two indices of vascular stiffness were evaluated. After SNB there was a decrease in central vascular pulse wave velocity from 6.9 ± 0.7 m/s to 6.5 ± 0.4 m/s ($p = 0.037$) and a decrease in aortic augmentation index from 129 ± 20% to 120 ± 12% ($p = 0.047$).

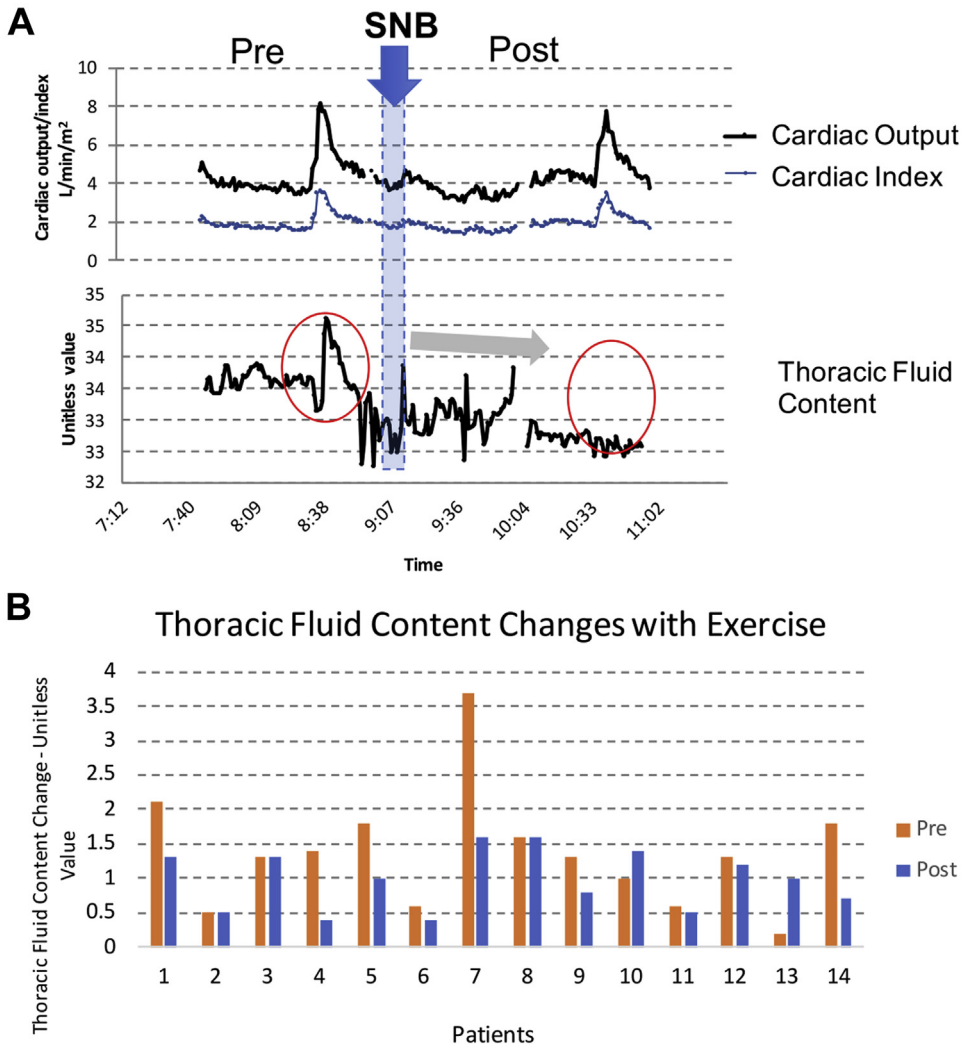
After SNB, there was an average 29% relative decrease in TFC during exercise when compared with pre-SNB TFC (9 patients had a decrease, 3 had no change, 2 had an increase, and 1 had missing data; $p = 0.064$) (Figure 3). Changes in biomarker profile from before invasive hemodynamic testing to after the SNB are presented in Table 3. SNB did not result in clinically significant changes in renal function or vasoactive hormone levels.

ECHOCARDIOGRAPHY AND ABDOMINAL SONOGRAPHY. A series of echocardiographic and abdominal vascular parameters were evaluated at rest and during exercise, before and after the SNB (Table 3). There was an improvement in diastolic function parameters (early diastolic transmitral flow/early diastolic mitral annular velocity) measured at rest without a significant change in systolic functional parameters (LVEF and global longitudinal strain). Venous flow from the abdominal cavity tended to be lower after the SNB. Hepatic venous flow decreased at peak exercise from 75 ± 23.9 to 62.5 ± 21.1 cm/s ($p = 0.093$) and resting portal vein flow decreased from 18.9 ± 3.7 to 16.8 ± 2.7 cm/s ($p = 0.049$).

DISCUSSION

In this study, we evaluated the safety and efficacy of SNB in patients with chronic HF. In a patient population that predominantly had HF with reduced ejection fraction, SNB decreased exercise-induced intracardiac pressure elevations with an improvement in cardiac output and a trend towards an improved exercise capacity. SNB effects were driven by a reduction in preload and afterload.

FIGURE 3 Bioelectrance Monitoring of Thoracic Fluid Content From Pre- to Post-SNB



Bioelectrance monitoring of thoracic fluid content from pre- to post-SNB. **(A)** Case example, in 1 patient case. **(B)** Relative change in thoracic fluid content during exercise for all patients. SNB, splanchnic nerve blockade.

The key hallmark of HF is vascular congestion with resultant limitation in physical activity. Despite its central role in the pathophysiology of HF, our understanding of congestion remains limited. The current HF pathophysiologic model suggests that congestion is the result of volume retention; therefore, therapies (such as diuretic agents and ultrafiltration) have generally been targeted at volume overload. Despite this, the therapeutic benefits of fluid removal strategies on short- and long-term outcomes have been limited. The concept of fluid gain as a cause of cardiac decompensation has some limitations (3,4). Despite evidence of elevated intracardiac pressures, as many as 50% of patients with HF do not experience fluid/weight gain before HF hospitalization (3,15). Thus, cardiovascular congestion may be the result of blood volume redistribution from the abdominal (splanchnic) compartment to the heart and lungs (1,5,16,17). This hypothesis arises from the fact that the autonomic nervous system is the main determinant of blood volume distribution in the body (1,2,5). Prior work has identified the greater splanchnic nerve as a novel target to treat HF, and the present findings confirm the results of the first-in-human pilot study (Splanchnic HF-1, N = 11) (13,14). This study tested the effects of a short-term SNB in patients who were

TABLE 3 Biomarker Profile Before and After SNB

	Pre-SNB	Post-SNB	p Value
Laboratory tests			
Creatinine, mg/dl*	1.2 ± 0.4	1.2 ± 0.4	0.250
BUN, mg/dl*	19 ± 10	18 ± 10	0.014
Urine spot sodium, mEq/l*	69 ± 48	86 ± 66	0.136
Serum norepinephrine, pg/ml†	866 ± 793	675 ± 520	0.084
Serum epinephrine, pg/ml†	89 ± 57	155 ± 144	0.096
Serum vasopressin, pg/ml†	2.7 ± 2.5	8.6 ± 9.5	0.127
Serum angiotensin, pg/ml†	55.1 ± 24.9	46.2 ± 20.7	0.187
Echocardiogram/abdominal ultrasound			
LVEF, %	25 ± 11	27 ± 15	0.548
LV end diastolic volume, cm^3	227 ± 122	225 ± 119	0.779
E/e', cm	20 ± 10	16.7 ± 6.3	0.049
Left atrial 4-chamber area, cm^2	94 ± 35	87 ± 37	0.021
Left atrial volume, ml^3	98 ± 32	92 ± 36	0.042
GLS average	-6.2 ± 3.3	-6.7 ± 4.3	0.621
Resting hepatic vein flow, cm/s	47.2 ± 12.9	42.8 ± 9.7	0.316
Peak hepatic vein flow, cm/s	75 ± 23.9	62.5 ± 21.1	0.093
Resting portal vein flow, cm/s	18.9 ± 3.7	16.8 ± 2.7	0.049

Values are mean ± SD, unless otherwise indicated. *Pre-SNB samples were collected before first invasive cardiopulmonary exercise test and post-SNB samples were collected 1 h after completion of second exercise ± ~2 h after SNB). †Pre-SNB samples were collected before first invasive cardiopulmonary exercise test and post-SNB samples were collected at rest before start of second exercise.

BUN = blood urea nitrogen; GLS = global longitudinal strain; E/e' = early diastolic transmittal flow velocity/early diastolic mitral annular velocity; LV = left ventricular; LVEF = left ventricular ejection fraction; SNB = splanchnic nerve block.

hospitalized for HF. SNB led to a reduction in cardiac filling pressures (PCWPs from 30 ± 7 mm Hg at baseline to 22 ± 7 mm Hg at 30 min, $p < 0.001$), and improved cardiac output (cardiac index increased from 2.17 ± 0.74 l/min/m^2 at baseline to 2.59 ± 0.65 l/min/m^2 at 30 min; $p = 0.007$). Additionally, in the unblinded and uncontrolled study, SNB improved symptoms of shortness of breath and functional capacity as measured by a 6-min walk test. Similar to the hospitalized HF population, in the present study, SNB safely reduced resting cardiac filling pressures of patients with chronic ambulatory HF. Further, the present study extends the prior work as the same treatment mechanism appears to improve exercise-induced hemodynamic derangement and functional capacity alike. Evidence of orthostatic hypotension with a bilateral block seen in the ambulatory but not the hospitalized population suggests that there are dose effects and intravascular pressure/volume-dependent effects of the SNB that must be further explored.

The human body is able to "store" or "recruit" large blood volumes within minutes in and out of the splanchnic vascular compartment (2,18,19). Activation of splanchnic nerves results in vasoconstriction and reduces splanchnic capacitance, therefore recruiting blood volume into the central circulation in animals and humans alike (2,12,20). During exercise in healthy adults, sympathetic activation recruits approximately 400 ml of splanchnic blood volume centrally (21). In patients with chronic HF, unlike in healthy adults, the redistribution of blood volume, even if a relatively small amount, is more likely to lead to a sudden increase in pulmonary and left-sided cardiac pressures (5,22). This appears to be true whether resting filling pressures are normal or elevated, suggesting that exercise-induced congestion and associated symptoms are often only of temporary nature (23). Further, in HF, reduced splanchnic vascular capacitance combined with a stiff central vasculature could be the mechanisms underlying symptoms of exercise intolerance and could predispose patients to rapid decompensation with external fluid intake or retention (1,5,9,14,24,25). The present findings indicate a decreased blood flow out of the splanchnic vascular compartment and a reduced TFC during exercise as a result of SNB. Both findings suggest increased abdominal pooling of blood volume as a result of regional SNB. Finally, a decrease in arterial tone in the large splanchnic vascular bed decreases the cardiac afterload at rest and exercise is also a likely contributor to the observed hemodynamic effects. To what degree abdominal venous pooling versus arterial vasodilation contribute to the observed hemodynamic effects remains to be determined.

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 can be detrimental due to unintended cardiac effects (26). Consequently, a targeted reduction of the splanchnic sympathetic tone in acute or chronic HF could be a potential new therapeutic option for patients with cardiopulmonary congestion. Currently, SNBs are commonly performed for the treatment of abdominal pain, as fibers of the splanchnic nerves not only carry autonomic fibers but also nociceptive visceral fibers (27). Whether this interventional approach is best suited for patients with acute or chronic congestive HF or particularly effective in patients with exercise-induced symptoms or specific HF subtype must be further explored (5). Future studies will need to investigate the comparative effect of unilateral compared with bilateral SNB, as the present data indicate an enhanced effect of bilateral compared with unilateral nerve block at the expense of potentially excessive preload reduction. Finally, and most importantly, whether favorable hemodynamic effects can be sustained and lead to

improved functional outcomes remains to be determined.

STUDY LIMITATIONS. First, the study was unblinded and had no control arm; thus, the study could be subject to unmeasured bias. However, the close temporal relationship of objective parameters such as hemodynamic, cardiopulmonary function, and sonographic changes following SNB argue for the observed changes to be the result of SNB rather than positional in nature or the result of repeat exercise or placebo (28). Further, endpoints were measured using blinded and core lab review. Second, the SNB procedure was limited by the inability for direct visualization of the target nerves. This limitation was overcome by a relatively fixed splanchnic nerve anatomy in the target region and the use of a large anesthetic volume. While direct surgical resection would improve the certainty of technical success, it must be balanced with the risk of the surgical procedure. Third, the use of repeat maximal exercise studies in patients with chronic HF in 1 day likely led to an underestimation of SNB effects and could explain the discrepant findings between exercise hemodynamics and exercise functional capacity. A training effect of same day iCPET is unlikely; however, with repeat testing on the same day, the risk of a submaximal exercise study is high (29,30). Deconditioning as a major limitation during the second iCPET is supported by lower respiratory exchange ratio (lower effort), and leg fatigue as the primary indication of exercise discontinuation when compared with the first iCPET study. Yet, exercise parameters (workload, peak VO_2, and ventilation/carbon dioxide production) showed a trend towards improvement after SNB. Delayed testing after SNB would have allowed for more recovery time and thus could have uncovered greater changes in cardiorespiratory exercise capacity. Finally, hemodynamic/exercise testing was limited to the supine position and in the absence of neurohormonal blocker therapy. Taken together, this potentially underestimated a limiting effect of exaggerated orthostatic splanchnic venous pooling.

CONCLUSIONS

SNB reduced resting and exercise-induced pulmonary arterial and wedge pressures with favorable effects on cardiac output and exercise function. SNB induced favorable changes in central and peripheral hemodynamics. Targeting the splanchnic autonomic nervous system to treat HF may present a potential therapeutic target not currently used for HF care. Continued efforts to investigate short- and long-term effects of SNB in chronic HF and upright position are warranted.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Splanchnic HF-2 tested the safety and efficacy of SNB in ambulatory patients with HF. The main findings are reduced resting and exercise-induced pulmonary arterial and wedge pressures following SNB, with favorable effects on cardiac output and exercise function.

TRANSLATIONAL OUTLOOK: The study provides novel insight into the contribution of the splanchnic vascular compartment on chronic HF physiology and supports the potential role of splanchnic nerve modulation in the treatment of HF. Targeting the splanchnic autonomic nervous system to treat HF may present a potential therapeutic target not currently used for HF care.

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KEY WORDS congestion, heart failure, splanchnic nerve block, sympathetic nervous system

APPENDIX For supplemental tables and a figure, please see the online version of this paper.

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