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Splanchnic Nerve Block for Acute Heart Failure

Fudim et al: Splanchnic Nerve Block for Heart Failure

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The abdominal vascular compartment is the main storage of intravascular blood volume, and decreased abdominal vascular capacitance has been proposed as a major contributor to the complex pathophysiology of heart failure (HF) in animals and humans.[1, 2] In HF, as a result of neurohormonal imbalance, the vascular capacitance ("storage-space") is decreased and acute sympathetic nerve activation can result in acute volume redistribution[3] from the abdominal compartment to the thoracic compartment (heart and lungs), which increases intra-cardiac pressures and precipitates HF symptoms (**Figure 1A**). The sympathetic nervous system controls the splanchnic compartment via branches from the sympathetic thoracic ganglia (T6 through T11).[4] We have identified the splanchnic nerves as a potential target for treating HF.

Patients were enrolled in an approved protocol (URL: https://www.clinicaltrials.gov. Unique identifier: NCT02669407) from April 2017 to November 2017 at Duke University Medical Center. The protocol was approved by the Institutional Review Board, and all patients provided written informed consent. To qualify for enrollment, patients had to be admitted for acute HF with New York Heart Association class III/IV symptoms. Patients were required to have a pulmonary capillary wedge pressure (PCWP) >15 mmHg (>12 mmHg if on inotropes).

Before, and immediately after the splanchnic nerve block (SNB) all patients were tested for catecholamine levels and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, transthoracic echocardiogram, aortic pulse wave velocity (SphygmoCor, AtCor Medical, Itasca, IL), 6-minute walk test, and Likert shortness of breath questionnaires. Following baseline evaluation, all patients underwent a right heart catheterization (via internal jugular vein) in the supine position, followed by bilateral SNB (15 mL of 1% lidocaine on each side), at the level of T11–T12, in the prone position using fluoroscopic guidance (**Figure 1B**). Expected duration of sympatholytic effects were up to 90 minutes. All pressures were recorded in the supine position.

Statistical methods included paired t-tests or Wilcoxon rank sum tests. Repeated measures analyses (0, 15, 30, 45, 60, 75, and 90 minutes) with a mixed-effects model were used to compare pulmonary arterial mean, PCWP, cardiac index and systemic vascular resistance (SVR). Tukey's method was used to adjust for multiple pairwise comparisons of each post-procedure time point to baseline.

Five patients underwent the SNB. The average age was 56 years, 4/5 patients were male, and ischemic cardiomyopathy was observed in 2 cases. All patients had acute advanced systolic HF with a left ventricular ejection fraction of ≤20% as assessed by transthoracic echocardiogram.

No procedural or hemodynamic complications were observed for 48 hours. Bilateral SNB resulted in a temporary reduction of intra-cardiac pressures such as mean pulmonary arterial pressures and PCWP (**Figure 1C**). Cardiac index increased from 1.92 L/min/m^2 (95% confidence interval [CI] 1.55–2.29) at baseline to 2.54 L/min/m^2 (95%CI 2.17–2.91) ($p<0.008$) at 30 minutes, before starting to return to baseline values at 90 minutes. Furthermore, SNB resulted in a decrease in mean right atrial pressure from 21 mmHg (95%CI 13-28) at baseline to 16 mmHg at 90 minutes (95%CI 8-23) (p=0.034). Mean arterial pressure decreased from 89 mmHg (95%CI 77-102) at baseline to 72 mmHg (95%CI 59-84) ($p<0.001$) at 30 minutes after SNB and SVR decreased from 1407 dynes·sec·cm^{-5} (95%CI 1041–1772) at baseline to 808 dynes·sec·cm^{-5} (95%CI 442–1173) ($p<0.001$) at 30 minutes. Acute hemodynamic effects peaked at 30 minutes after SNB and mostly recovered towards the end of the acute monitoring phase (90 minutes).

We assessed changes in biomarkers and symptoms following SNB. Levels of serum norepinephrine were baseline [median, interquartile range (IQR)]: 1202 pg/dL, 892–3045, vs. post-procedure: (minute 90) 936 pg/dL, 462–2095 (p=0.125); serum epinephrine levels were baseline: 250 pg/dL, <25–616 vs. post-procedure 56.5, 27.5–73 (p=0.5). Similarly, we observed

a nonsignificant decrease in median NT-proBNP levels of 362 pg/dL within 6 hours after the procedure (p=0.19) (**Figure 1D**) as well as a nonsignificant change in central vascular pulse wave velocity, an index of vascular stiffness, from 7.8±2.4 meters to 6.8±1.5 meters (p=0.153). Finally, patients reported an acute improvement in symptoms during the procedure (**Figure 1D**). The average 6-minute walk distance was +31.2 ± 34.5 meters from immediately before to after the procedure (p=0.11).

In this first-in-man study, we tested a new therapeutic approach to the treatment of acute HF. The procedure, which aimed to modulate the splanchnic sympathetic tone through a minimally invasive regional nerve block, resulted in a marked reduction in intra-cardiac filling pressures and increase in cardiac output, primarily driven by a significant reduction in SVR and improved arterial vascular capacitance. The splanchnic vascular compartment may be a key player in the volume dysregulation in acute and chronic HF, even in the absence of increases of total body fluid volume.[1, 2]

The observed temporary hemodynamic effects are possibly the result of a reduced splanchnic autonomic and vascular tone, leading to a redistribution of blood volume from the chest to the abdomen.[5] Hemodynamic changes could also have been modulated by sympatholysis/vasodilation outside of the splanchnic vascular bed. Acute hemodynamic changes were associated with improved self-reported shortness of breath. These findings suggest that continued research into therapeutic use of SNB for the treatment of acute and potentially also chronic HF is of interest. Lack of a control group is a major limitation of this study. Further testing for safety and efficacy is needed before potential clinical application.

Data Sharing

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure via email contact with the corresponding author.

Sources of Funding

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Disclosures

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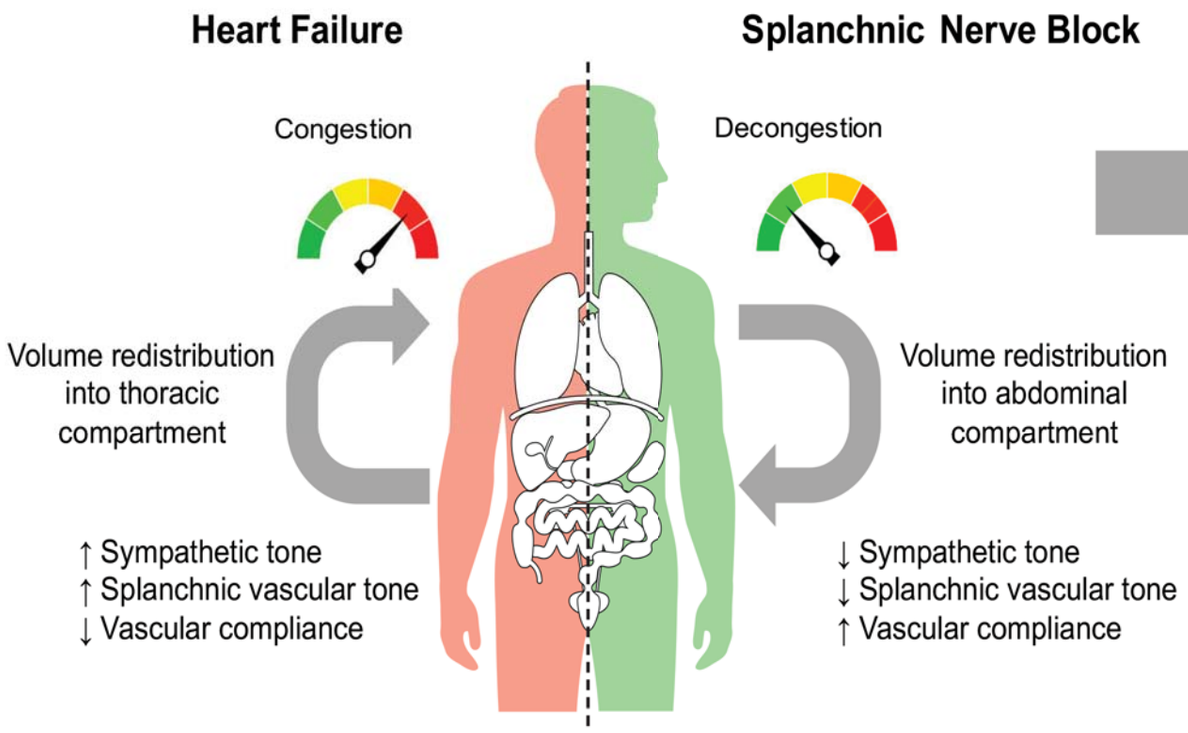
Figure Legend

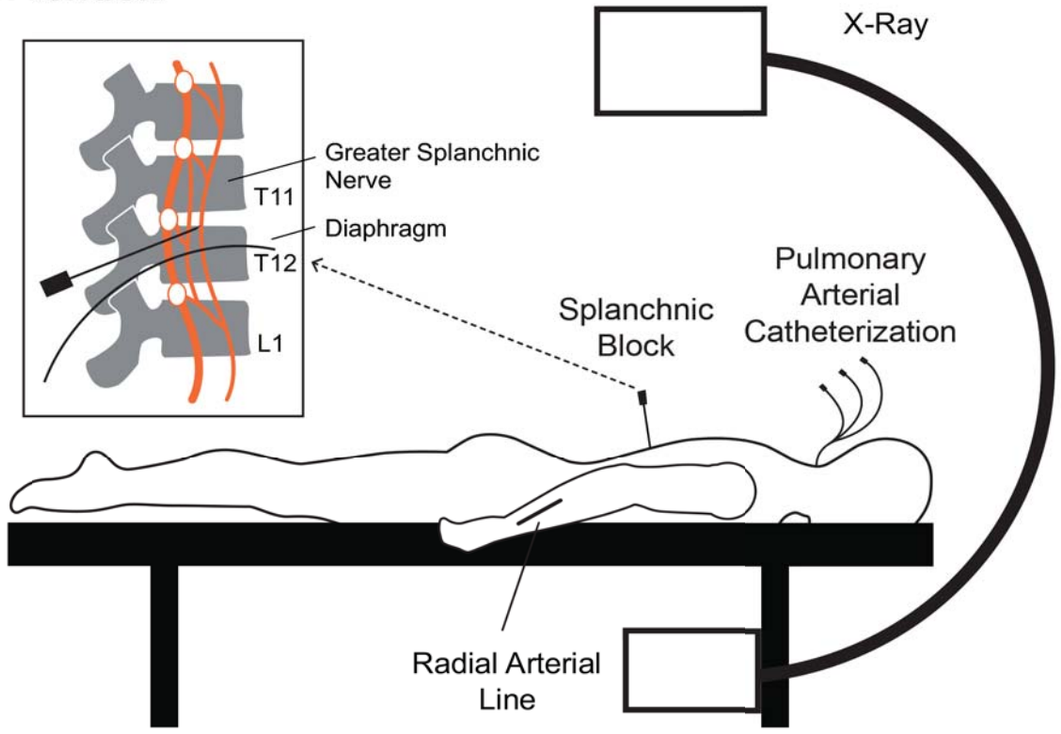
Figure. Splanchnic nerve block in heart failure: A. Concept for fluid redistribution in heart failure; B. Splanchnic nerve block procedure; C. Effects of the splanchnic nerve block on hemodynamics. * indicates a P<0.05 for a pairwise comparison with the baseline value; D. Effect of the splanchnic nerve block on laboratory and functional outcomes. For Likert Scale, p<0.05 for Minute 90 and 24 hours.

Abbreviations: CI=confidence interval, PRO BNP=NT-pro brain natriuretic peptide

A: Concept

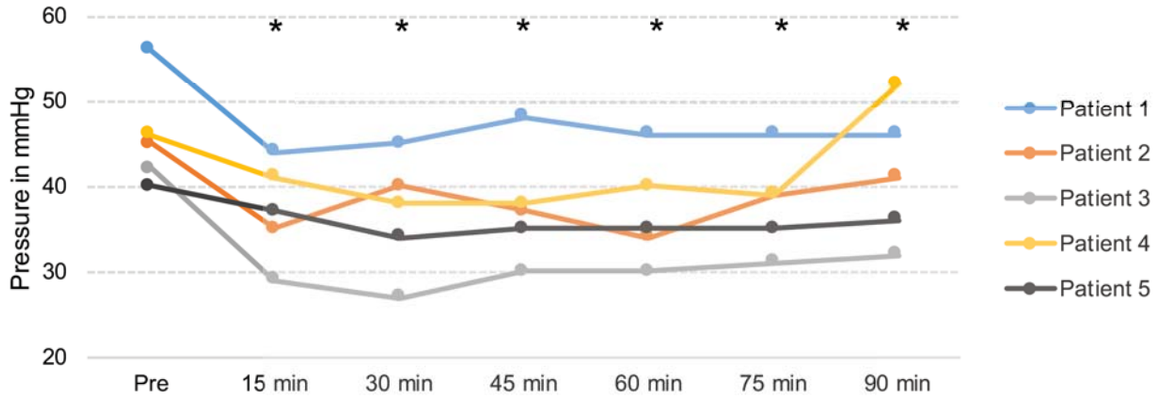


B: Intervention



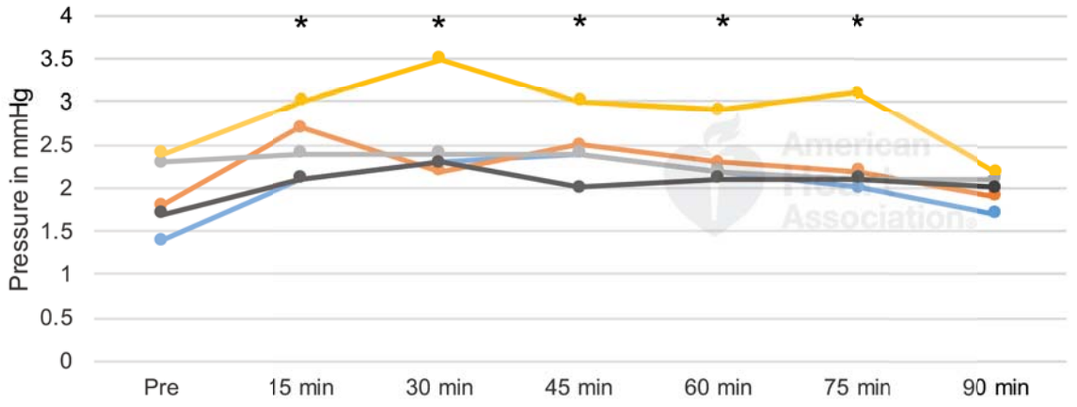
C: Hemodynamics

PULMONARY ARTERIAL MEAN PRESSURE



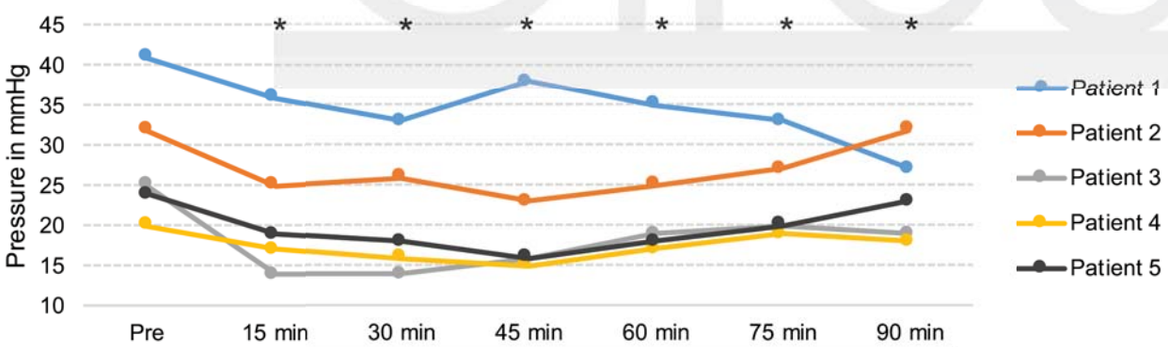
	Pre	15 min	30 min	45 min	60 min	75 min	90 min
Mean in mmHg	46	37	37	38	37	38	41
95% CI	40-52	31-43	31-43	32-44	31-43	32-44	35-47

CARDIAC INDEX



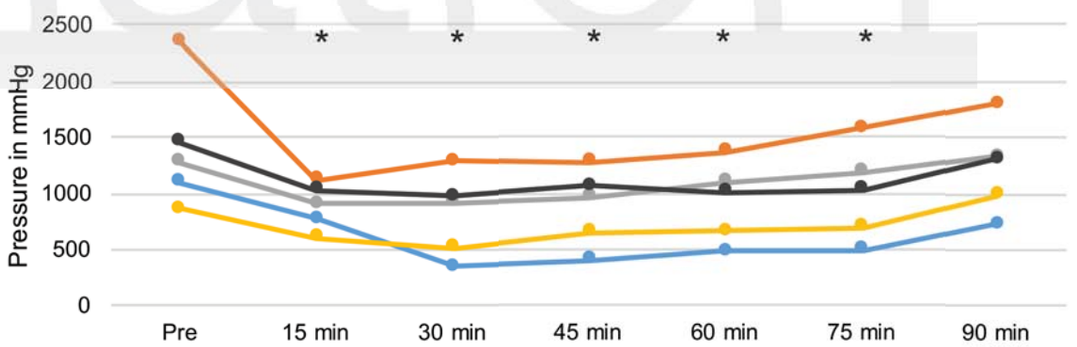
	Pre	15 min	30 min	45 min	60 min	75 min	90 min
Mean in l/min/m^2	1.9	2.5	2.5	2.5	2.3	2.3	2
95% CI	1.6-2.3	2.1-2.8	2.2-2.9	2.1-2.8	2-2.7	1.9-2.7	1.6-2.3

PULMONARY CAPILLARY WEDGE PRESSURE



	Pre	15 min	30 min	45 min	60 min	75 min	90 min
Mean in mmHg	28	22	21	22	23	24	24
95% CI	22-36	15-29	14-29	14-29	16-30	17-31	17-31

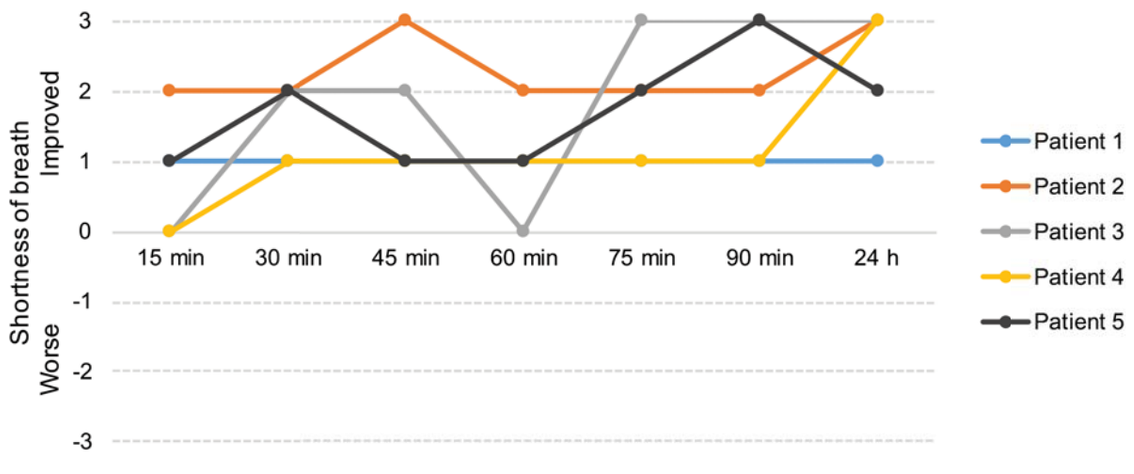
SYSTEMIC VASCULAR RESISTANCE



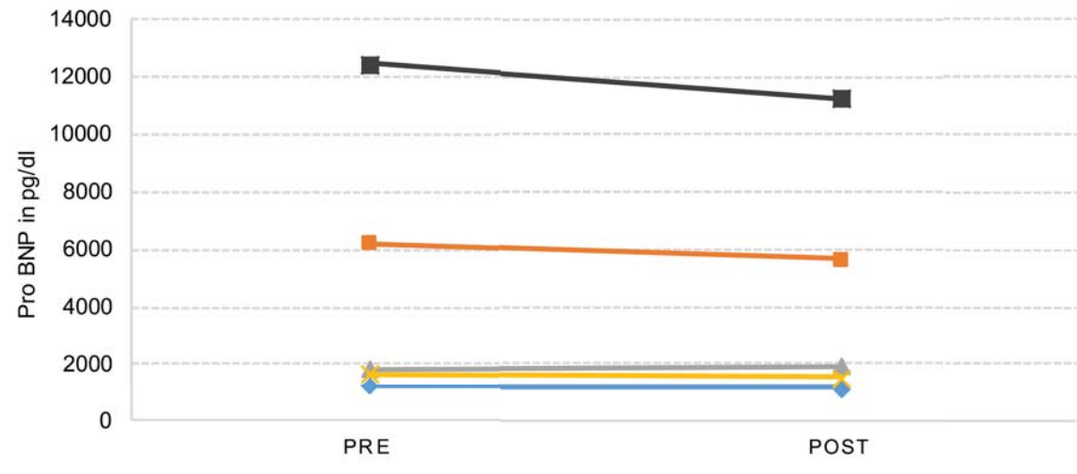
	Pre	15 min	30 min	45 min	60 min	75 min	90 min
Mean in dynes·sec·cm^{-5}	1407	887	808	874	921	998	1232
95% CI	1041-1772	521-1252	442-1173	508-1239	556-1287	633-1364	867-1598

D: Symptoms/Natriuretic Peptides

SHORTNESS OF BREATH - LIKERT SCALE



PRO BNP



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