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RESEARCH ARTICLE

Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: first-in-human clinical trial

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Aims Inappropriate control of blood volume redistribution may be a mechanism responsible for exercise intolerance in heart failure with preserved ejection fraction (HFpEF). We propose to address this underlying pathophysiology with selective blockade of sympathetic signalling to the splanchnic circulation by surgical ablation of the right greater splanchnic nerve (GSN).

Methods and results In a single-arm, prospective, two-centre trial, 10 patients with HFpEF (50% male, mean age 70 ± 3 years) all with New York Heart Association (NYHA) class III, left ventricular ejection fraction >40%, pulmonary capillary wedge pressure (PCWP) ≥15 mmHg at rest or ≥25 mmHg with supine cycle ergometry, underwent ablation of the right GSN via thoracoscopic surgery. Patients were evaluated at baseline, 1, 3, 6 and 12 months after the procedure. The primary endpoint was a reduction in exercise PCWP at 3 months. There were no adverse events related to the blockade of the nerve during 12-month follow-up but three patients had significant peri-procedural adverse events related to the surgical procedure itself. At 3 months post-GSN ablation, patients demonstrated a reduction in 20 W exercise PCWP when compared to baseline [−4.5 mmHg (95% confidence interval, CI −14 to −2); $P = 0.0059$], which carried over to peak exercise [−5 mmHg (95% CI −11 to 0; $P = 0.016$). At 12 months, improvements were seen in NYHA class [3 (3) vs. 2 (1, 2); $P = 0.0039$] and quality of life assessed with the Minnesota Living with Heart Failure Questionnaire [60 (51, 71) vs. 22 (16, 27); $P = 0.0039$].

Conclusion In this first-in-human study, GSN ablation in HFpEF proved to be feasible, with a suggestion of reduced cardiac filling pressure during exercise, improved quality of life and exercise capacity.

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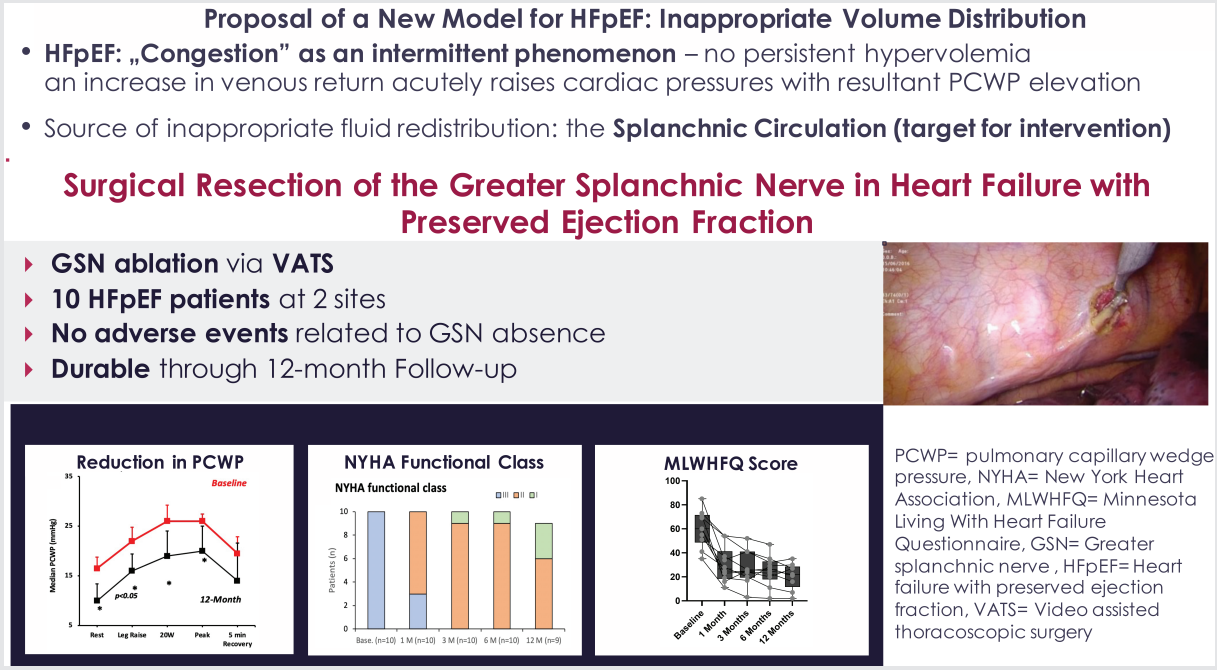
Graphical Abstract



Concept and results for the study of splanchnic nerve modulation in heart failure with preserved ejection fraction.

Keywords Heart failure • Heart failure with preserved ejection fraction • Greater splanchnic nerve ablation

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) makes up about 50% of today's heart failure population with rising prevalence worldwide.[1–4] Unlike in HF with reduced ejection fraction (HFrEF), to date there have been a paucity of medical or device therapies proven to modify disease progression and improve outcomes in patients with HFpEF.[5,6]

Exercise intolerance manifested either as exertional dyspnoea and/or fatigue is a hallmark of HFpEF.[5,6] While many mechanisms likely contribute to the limitations in exercise and the ability to perform activities of daily living in HFpEF, there is growing evidence of profoundly abnormal haemodynamic response to exercise characterized by rapid and marked elevation in filling pressures, which typically promptly return to baseline values during recovery.[7,8] Additionally, as many of them have normal haemodynamics at rest, congestion (with resultant symptoms) seems to be only an intermittent phenomenon in these cases.[9] Therefore, recently, an inappropriate control of blood volume distribution in the body has been proposed as a mechanism underlying exercise intolerance in HFpEF.[10,11]

Animal and human data indicate that blood shifts in and out of the splanchnic vascular compartment can significantly alter cardiac and central vascular haemodynamics, given the ability to 'store' or 'recruit' large blood volumes within minutes.[12–14] The main regulatory system for the splanchnic vascular capacitance ('storage space') are sympathetic fibres originating from the splanchnic nerves which control arterial and venous vascular tone. Activation of splanchnic nerves results in vasoconstriction, reduces splanchnic capacitance, therefore recruiting blood volume into the central circulation.[14,15] It is thought that this redistribution of blood volume (caused by sympathetic activation), even if by a relatively small amount,[16] may lead to a sudden rise in pulmonary and left-sided cardiac pressures in HF, which may either be a mechanism underlying symptoms of exercise intolerance but also may lead to rapid development of decompensation.[7,11] The source of the increased pressure appears to be a compromised vascular reservoir with the inability to buffer shifts in fluid and actively contributing to the acute or chronic expulsion of fluid from the splanchnic vascular compartment to the central thoracic compartment, resulting in increased volume in the central circulation and high cardiac filling

pressures.[10,17] There is evidence of impaired splanchnic capacitance in HF.[18–20]

We developed a novel approach to restore the normal function of the splanchnic vascular reserve in order to relieve resting and exercise induced intra-cardiac pressure elevations that occur in HFpEF.[14,21] Recent proof-of-concept work in patients with acute decompensated HF showed promise for the concept of splanchnic nerve modulation in HF.[22] We believe that selective ablation of the right greater splanchnic nerve (GSN) in patients with HFpEF, with resultant reduction in the sympathetic nerve traffic to the splanchnic bed, will lead to greater vascular compliance during exercise, lower pulmonary and cardiac filling pressures, and improved exercise tolerance, ultimately leading to improvements in quality of life. The purpose of the present study was to show proof-of-concept with surgical GSN ablation prior to the development of percutaneous/endovascular splanchnic nerve ablation.

Methods

Study design and participants

This is a single-arm, open-label, prospective investigation of right-sided GSN ablation in patients diagnosed with HFpEF. There were two participating centres, one in Wroclaw, Poland, and one in Prague, Czech Republic. The study was approved by the local ethics committees and was conducted in accordance with the Declaration of Helsinki. All patients provided informed consent prior to enrolment.

Patients included in this study had to meet the following inclusion criteria: ≥18 years of age with guideline-defined HFpEF,[6] a left ventricular ejection fraction >40%, HF symptoms in New York Heart Association (NYHA) class III/IV, history of exertion-related dyspnoea in the last 3 months, with no evidence of clinically significant peripheral oedema/fluid overload, pulmonary capillary wedge pressure (PCWP) ≥15 mmHg at rest or ≥25 mmHg during exercise (see below for details of exercise testing protocol).

Key exclusion criteria comprised: myocardial infarction, percutaneous cardiac intervention or coronary artery bypass graft in the past 3 months, admission for HF within the past month, systolic blood pressure <120 mmHg or >170 mmHg despite appropriate medical management, presence of severe regurgitant or stenotic valve disease, atrial fibrillation with resting heart rate >100 bpm. Complete eligibility criteria for both studies are listed in the online supplementary *Table S1*.

Procedures

Patients underwent assessment at baseline as well as 1, 3, 6 and 12 months after surgery (*Figure 1*). At all time-points the tests included: physical examination, quality of life assessment with the Minnesota Living With Heart Failure Questionnaire (MLWHFQ) and New York Heart Association (NYHA), blood work, echocardiography and cardiopulmonary exercise testing (CPET). Participants recruited in Prague, Czech Republic, conducted CPET using a treadmill spiroergometry and those recruited in Wroclaw, Poland, conducted the test with upright cycle ergometry.

At baseline, 1, 3 and 12 months, all enrolled patients underwent right heart catheterization with assessment of central haemodynamics (right atrial pressure, pulmonary artery pressure, and PCWP) at rest, during leg-up manoeuvre and during supine bicycle exercise. Following baseline haemodynamic measurements, symptom-limited supine bicycle exercise commenced at 20 W with 10 W increments every 90 s until the patient achieved maximum effort (as defined by symptom limiting dyspnoea or fatigue).

Splanchnicectomy

Splanchnicectomy (ablation of the GSN) was performed by thoracic surgeons (Dariusz Janczak, MD and Mariusz Chabowski, MD in Poland, and Tomas Martinca, MD in Czech Republic) using previously described

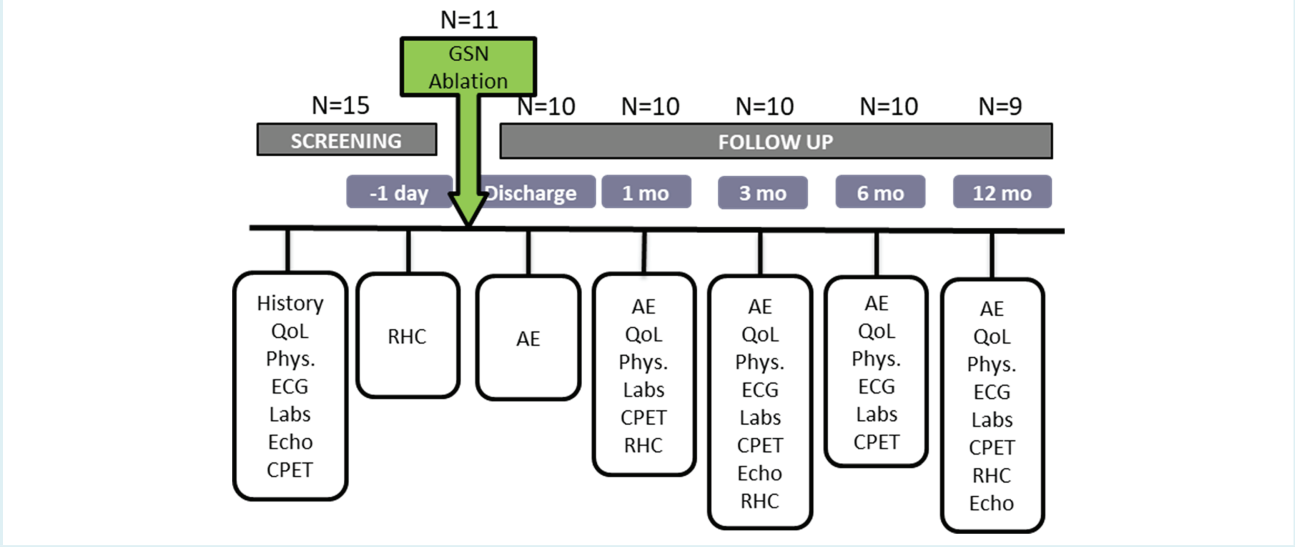


Figure 1 Study design. Study flow diagram together with the number of patients reviewed at each stage. AE, adverse event; CPET, cardiopulmonary exercise test; ECG, electrocardiogram; GSN, greater splanchnic nerve; Phys., physical; QoL, quality of life; RHC, right heart catheterization.

techniques with the patient under general anaesthesia, in the lateral decubitus position, with single-lung ventilation using multi-port video-assisted thoracoscopic surgical techniques.[23] Briefly, two or three 5 mm ports were placed in the 6th or 7th intercostal space. The camera port was placed in the midaxillary line and the working ports were placed at the anterior axillary line. The entire intrathoracic sympathetic chain was identified and the GSN was visualized through the parietal pleura from its first root to the diaphragm. The GSN was then exposed distally and excised for histopathology analysis.

Outcomes

The study aimed to assess the safety, tolerability and clinical effectiveness of GSN ablation in patients with HFpEF. The primary safety endpoint was peri-procedural and up to 3-month major adverse cardiac or gastrointestinal effects, defined as death, myocardial infarction, persistent orthostatic hypotension, or persistent gastrointestinal dysmotility. The primary efficacy endpoint was a reduction in exercise-related PCWP (at 20 W and peak exercise) from baseline to 3 months. Secondary outcomes included changes in resting PCWP [reduction in exercise-related PCWP (at 20 W and peak exercise) from baseline to 1 month], quality of life (assessed with the MLWHFQ), NYHA class, and exercise capacity. Unblinded haemodynamic data were independently reviewed by an external reader. PCWP was measured at mid a wave in end-expiration. Echocardiographic images were reviewed in a blinded fashion.

Data and statistical analysis

In this prospective, proof-of-concept first-in-human study designed to evaluate the safety and potential efficacy of GSN ablation in the treatment of HFpEF, we did not perform specific study sample size calculation. It was assumed that results from 10 enrolled subjects will provide adequate inferences on the safety and potential efficacy of unilateral GSN ablation in the treatment of HFpEF patients. Patient data before and at various time-points after GSN ablation surgery were compared using Wilcoxon signed-rank test (SAS v9.4 for Windows, SAS Institute Inc., Cary, NC, USA). Summaries within a visit are presented as mean ± standard deviation or median (Q1, Q3), unless otherwise noted, and change from baseline is presented as median [95% confidence interval (CI)]. The CI for the median was calculated using a distribution free method by Hahn and Meeker.[24] A *P*-value <0.05 was considered statistically significant.

Results

Study participants

Between June 2016 and July 2017, 15 patients were actively screened for this study across two centres, of whom 11 met the inclusion and exclusion criteria. Three patients were excluded for failure to meet the haemodynamic inclusion criteria and one patient was excluded due to severe cirrhosis discovered by ultrasound just prior to surgery. One additional patient withdrew 2 days after the surgical intervention with prolonged pleural drainage. The patient chose to withdraw due to personal preference and no follow-up testing was performed in this patient. Thus, the patient was excluded from the analysis. The demographics and clinical characteristics of the remaining 10 participants are summarized in *Table 1*. Patients ranged from 48–82 years of age (mean 70 years), 50% were men, and had high burden of comorbid disease, including a high prevalence of atrial fibrillation and arterial hypertension. At the time of screening, all patients were in NYHA class III. The mean left ventricular ejection fraction was 58 ± 10%. All patients were on diuretic medications as well as anti-hypertensive medications (80% on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 60% on mineralocorticoid receptor antagonists, 20% on calcium channel blockers, and 10% on other vasodilators). All patients were on stable baseline medications for a least 30 days prior to enrolment.

Table 1 Baseline demographic characteristics ($n = 10$)

Age (years), mean ± SD	70 ± 10
Female sex	50%
Body mass index (kg/m^2), median [IQR]	31 [29, 35]
Comorbidities	
History of atrial fibrillation	90%
Hypertension	80%
Diabetes	60%
Coronary artery disease	60%
Previous myocardial infarction	40%
Left ventricular ejection fraction (%), mean ± SD	58 ± 10
NYHA class I/II/III/IV (%)	0/0/100/0
Arterial blood pressure, systolic/diastolic (mmHg), mean ± SD	130/81 ± 15/14 80 ± 14
Resting heart rate (bpm), mean ± SD	
NT-proBNP (pg/mL), median [IQR]	1572 [542, 2501]
Creatinine (mg/dL), median [IQR]	1.01 [0.93, 1.26]
eGFR (mL/min/1.73 m^2), median [IQR]	63 [56, 75]
HF or HTN medication	
Loop diuretic	100%
ACEi or ARB	80%
Beta-blocker	80%
MRA	60%
Digoxin	30%
CCB	20%
Other vasodilators	10%

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

Procedure and safety endpoints

In all cases GSN ablation coincided with an expected, transient reduction in systolic arterial blood pressure of approximately 10–20 mmHg.[25] This transient reduction in systolic blood pressure resolved within approximately 1 h. Histopathology confirmed presence of GSN in the excised tissue (*Figure 2*); in one case where the nerve was transected, excision was not feasible. Several expected, but serious adverse events related to the surgical procedure itself were observed: one instance of surgical site infection, one instance of haematoma due to inadvertent puncture of an intercostal artery

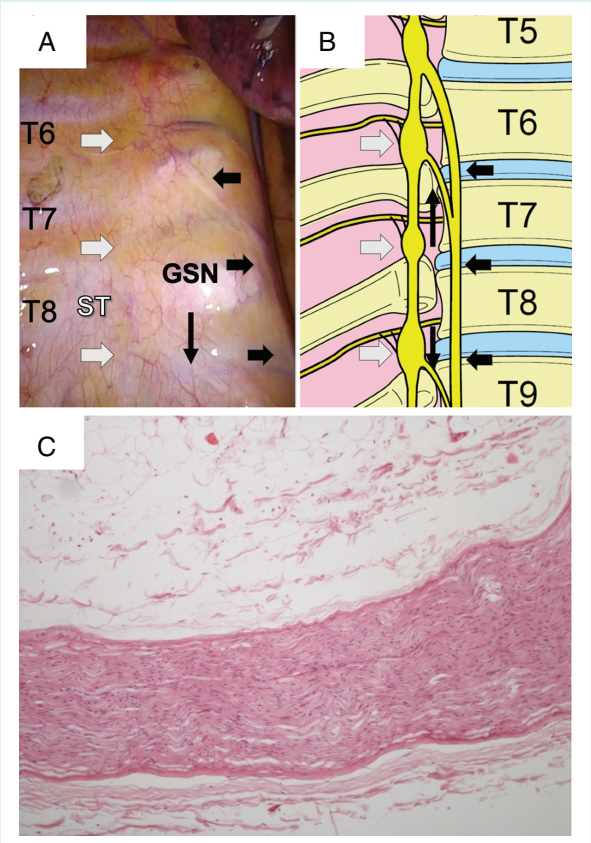


Figure 2 Surgical procedure, target nerve and confirmatory histology. (*A*) Identification of the sympathetic trunk (ST, white arrows), the right greater splanchnic nerve (GSN) trunk (thick black arrows) and GSN roots (thin black arrows) using a thoracoscopic camera in study subject 001–001 (right hemithorax, cephalad to the right). (*B*) Illustration of anatomy shown in panel *A*. (*C*) Microscopic examination of resected nerve tissue from patient 001–001 showing presence of nerve cells consistent with the GSN (haematoxylin and eosin stain, magnification ×100).

requiring 2 units of blood transfusion, one prolonged hospitalization following surgery. Procedures lasted 60–180 min. After the procedure, all patients complained of noticeable pain and soreness associated with surgical access sites. No patient had peri-procedural or major adverse cardiac events including death or myocardial infarction during planned initial 3-month follow-up. During the entire 12-month follow-up period, one patient died due to complications related to pneumonia. The deceased patient was hospitalized for pneumonia with inflammatory changes present predominantly in the left lung close to a year after the initial procedure. The patient died subsequently of pneumonia and was not able to complete study follow-up. Therefore, this patient was excluded from 12-month invasive haemodynamic data analysis.

There were no instances of adverse events from the absence of the right GSN that would be expected based on the reported side effects of the equivalent procedure for the management of pain related to severe pancreatitis or abdominal cancer.[26] This includes no instances of acute or chronic hypotension or orthostasis, no instances of abdominal colic, no instances of nausea or vomiting.

Haemodynamics

There was a trend to reduced resting CVP at each follow-up compared to baseline that reached significance at 12 months (*Table 2*). Resting systolic pulmonary artery pressure decreased from baseline [38.5 (33, 43) mmHg] to 1 month [33.5 (25, 39); $P = 0.004$] but was unchanged from baseline at subsequent follow-ups. At baseline the average PCWP was elevated at rest [16.5 (13, 20) mmHg] and increased markedly with leg raise [22.0 (18, 23) mmHg] and mild (20 W) and peak exercise [26.0 (23, 29) mmHg, 26.0 (24, 27), respectively] (*Table 2*). Patients showed a trend towards reduction in resting PCWP compared to baseline at 1 month [median: −4 mmHg (95% CI −7 to 1); $P = 0.020$], 3 months [median: −2.5 mmHg (95% CI −9 to 2); $P = 0.10$] and 12 months [median: −5 mmHg (95% CI −8 to −1); $P = 0.10$] (*Figure 3*).

At 3 months post-GSN ablation, patients showed a reduction in 20 W exercise PCWP when compared to baseline [−4.5 mmHg (95% CI −14 to −2); $P = 0.006$] (*Table 2*, *Figure 4*) which carried over to peak exercise [−5 mmHg (95% CI −11 to 0); $P = 0.016$] (*Table 2*, *Figure 4*).

At 12 months post-GSN ablation, patients showed a reduction in exercise PCWP at 20 W of −4 mmHg (95% CI −13 to −3; $P = 0.004$) when compared to baseline. As compared to baseline the PCWP at peak exercise was −4 mmHg (95% CI −23 to −1; $P = 0.043$).

Exercise capacity

Patients exhibited improvement in the duration of the CPET at 1, 3, 6 and 12 months of 73.5 s (95% CI −13 to 191; $P = 0.084$), 173 s (95% CI −11 to 228; $P = 0.039$), 123 s (95% CI 2 to 368; $P = 0.027$) and 134 s (95% CI 12 to 261; $P = 0.008$), respectively, and an improvement of peak oxygen consumption at 6 and 12 months after surgery of +2.3 mL/kg/min (95% CI −0.2 to 4.5; $P = 0.039$) and +1.6 mL/kg/min (95% CI −0.3 to 5.7; $P = 0.050$). Patients exhibited an improvement (decrease) of the minute ventilation/carbon dioxide output relationship by 6 and 12 months after surgery of −8.5 (95% CI −24.9 to −1.4; $P = 0.027$) and −4.6 (95% CI −22.8 to 3.0; $P = 0.16$).

Clinical effects

At 1 month post-procedure 70% of patients reported improvement by one NYHA functional class, whereas 30% remained unchanged. All patients experienced a reduction by at least one NYHA functional class by the 3-month follow-up, with two patients dropping two classes to NYHA functional class I by the 12-month follow-up (*Table 3*, *Figure 5A*). Overall, there was no change in arterial blood pressure, resting heart rate, patients' weight, N-terminal pro B-type natriuretic peptide level, and serum creatinine following GSN ablation (*Table 3*).

Table 2 Right heart catheterization at baseline and exercise at baseline and follow-up visits

Parameter	Baseline (*n* = 10)	1 month (*n* = 10)	3 months (*n* = 10)	12 months (*n* = 9)
Resting CVP (mmHg)	10.5 (5, 11)	7.0 (5, 9)	5.5 (3, 11)	6.0 (2, 7)[a]
Resting PAP-S (mmHg)	38.5 (33, 43)	33.5 (25, 39)[a]	40.5 (30, 53)	37.0 (26, 45)
Resting PCWP (mmHg)	16.5 (13, 20)	12.5 (11, 15)[a]	14.5 (10, 17)	10.0 (9, 15)
Leg-up PCWP (mmHg)	22.0 (18, 23)	16.5 (12, 18)[a]	17.0 (14, 19)	16.0 (13, 18)[a]
20 W PCWP (mmHg)	26.0 (23, 29)	18.5 (16, 22)[a]	20.0 (14, 22)[a]	19.0 (15, 21)[a]
Peak PCWP (mmHg)	26.0 (24, 27)	22.0 (15, 22)[a]	20.5 (15, 25)[a]	20.0 (19, 23)[a]
Work indexed peak PCWP (mmHg/W/kg)	84 (59, 131)	45 (37, 75)[a]	54 (32, 71)[a]	40 (38, 46)[a]
Total workload (W)	28 (24, 33)	35 (28, 40)[a]	39 (30, 44)	46 (39, 54)

Values are given as median (interquartile range).
P-values calculated using Wilcoxon signed-rank test.
CVP, central venous pressure; PAP-S, systolic pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure.
[a]$P < 0.05$ compared to baseline.

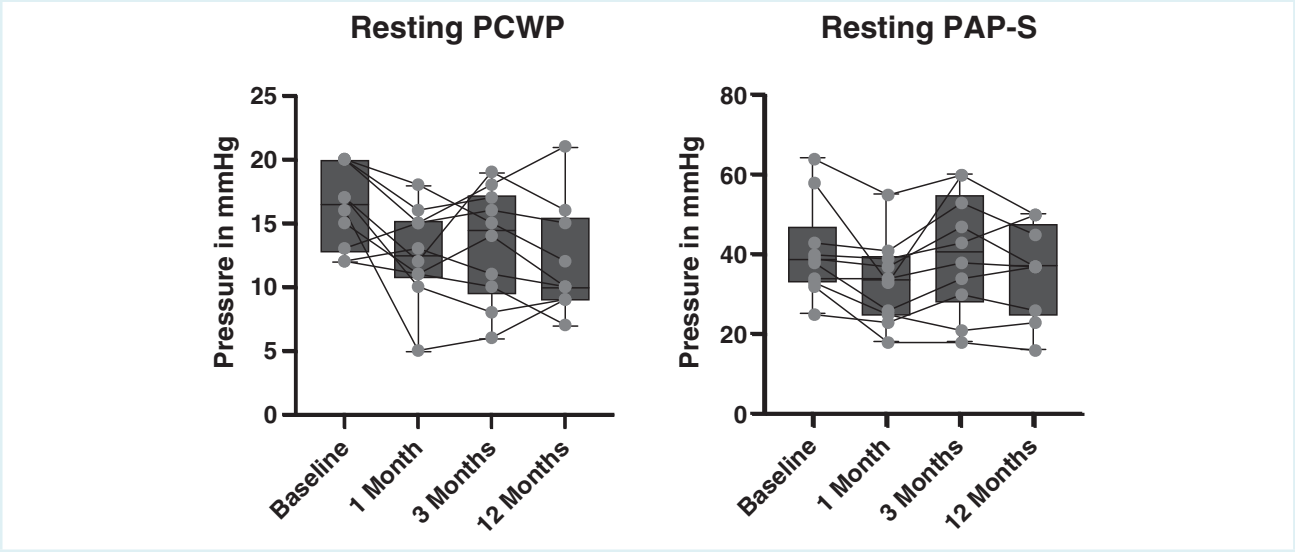


Figure 3 Resting haemodynamics. Pulmonary capillary wedge pressure (PCWP) and systolic pulmonary artery pressure (PAP-S) for all patients at 1, 3, and 12 months with median (95% confidence interval) for each time-point.

The median dose of orally administered furosemide (or equivalent) at baseline was 40 (20, 40) mg per day and remained unchanged at 1, 3 and 12-month follow-up visits. By 12 months, three patients had an increase in median diuretic dose from baseline [+46 (10, 80) mg], one patient had 20 mg reduction in diuretic dose compared to baseline and the remaining six patients had no change in diuretic dose.

Quality of life assessment

Quality of life measured using the MLWHFQ was improved (decrease) at 1 month [−28 (95% CI −52 to −14); $P = 0.002$], 3 months [−32 (95% CI −44 to −26); $P = 0.002$], 6 months [−34 (95% CI −44 to −26); $P = 0.002$] and 12 months [−34 (95% CI −50 to −29); $P = 0.004$] post-surgery compared to baseline (*Table 3*, *Figure 5B*).

Echocardiogram

Following GSN ablation there were no changes in left ventricular ejection fraction (*Table 3*). Diastolic function, expressed by the E/e′ ratio, changed at 3 months by −4.0 (−7 to 2) ($P = 0.020$), 6 months by −4.4 (−8 to −1) ($P = 0.002$) and 12 months by −3.1 (−7 to 2) ($P = 0.15$). Left ventricular mass index went from 132 (125, 139) g/m^2 at baseline to 116 (102, 121) g/m^2 ($P = 0.008$) at 3 months, 109 (98, 125) g/m^2 ($P = 0.006$) at 6 months, and 102 (83, 110) g/m^2 ($P = 0.023$) at 12 months.

Discussion

In this single-arm, first-in-human study, we evaluated the safety and efficacy of GSN ablation as a new therapeutic approach to the treatment of patients with chronic HFpEF (*Graphical abstract*). The

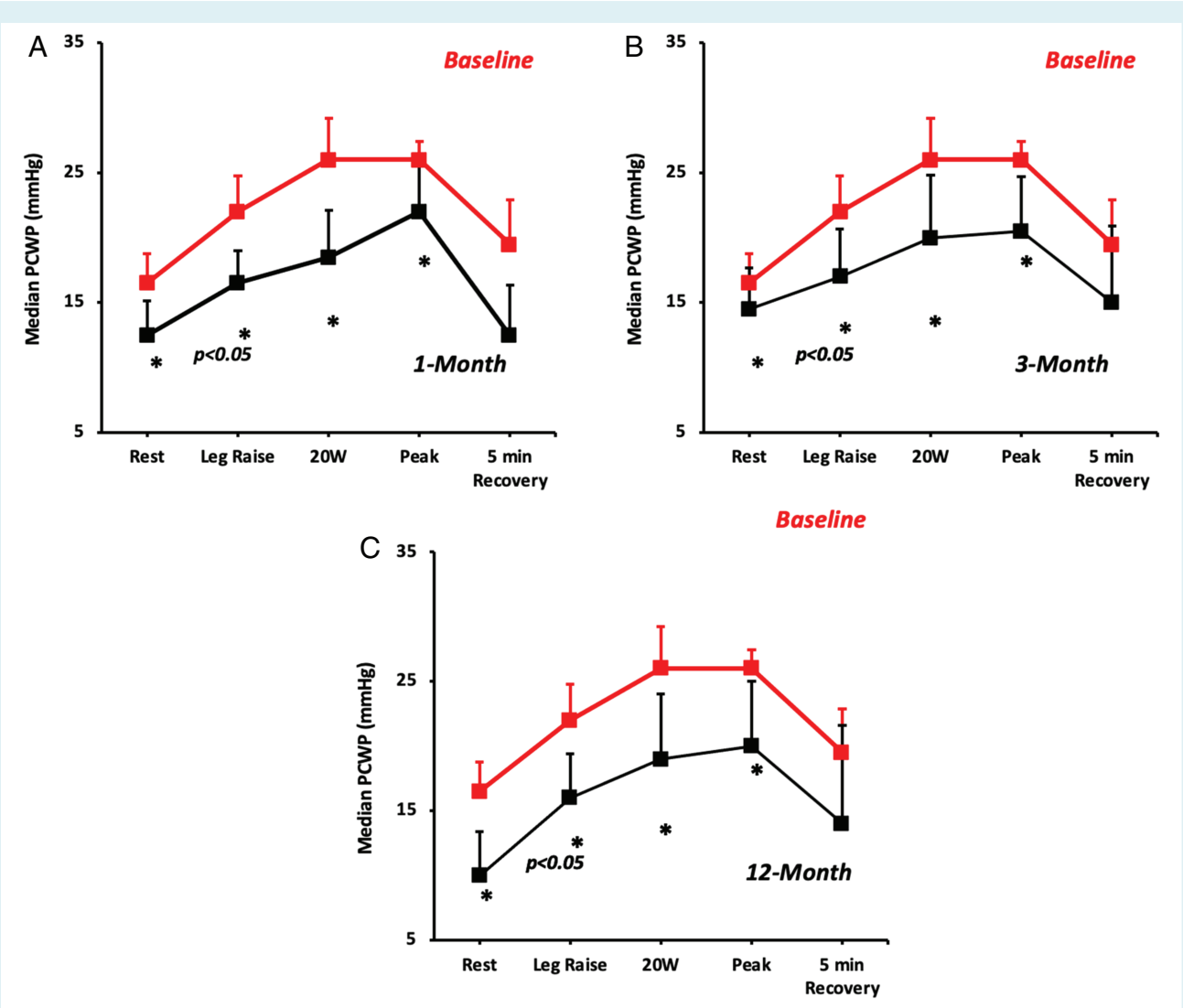


Figure 4 Resting and exercise haemodynamics. Pulmonary capillary wedge pressure (PCWP) increased to a greater extent in heart failure with preserved ejection fraction patients prior to greater splanchnic nerve ablation compared to the same patients at (*A*) 1 month, (*B*) 3 months, (*C*) 12 months after greater splanchnic nerve ablation at rest, with leg elevation and during exercise (20 W and peak). PCWP returned to pre-exercise levels soon after exercise with medians (95% confidence interval) for each time-point and statistical significance indicated.

splanchnic nerves were recently identified as potential contributors to the pathophysiology of acute and chronic HF.[10,11,19] The proposed concept emphasizes the role of volume redistribution as a possible cause of increased cardiac pressures and a trigger of cardiac decompensation. The splanchnic nerves are an integral component in the regulation of intravascular volume distribution given their modulatory function on splanchnic vascular capacitance.[11,14] We proposed that a heightened splanchnic sympathetic tone contributes to cardiac decompensation and an interruption of the right GSN would reverse the process and thus alleviate HF signs and symptoms in patients with HFpEF. Overall, our data suggest that unilateral disruption of the right GSN is well tolerated and may result in improvements of key physiological and clinical measures.

Cardiovascular or gastrointestinal side effects from the interruption of splanchnic autonomic innervation were not observed in the study cohort. GSN ablation reduced resting intra-cardiac filling pressures and paired with the improvement in exercise induced PCWP elevation resulted in a significant improvement in exercise performance. There is now strong evidence to support that high exercise PCWP is independently associated with symptoms of dyspnoea and pulmonary limitations.[27] In addition, exercise PCWP is independently associated with reduced aerobic capacity in HFpEF.[28,29] The reduction in resting and exercise PCWP could in large part explain the parallel improvement in self-reported symptoms, quality of life and an increase in peak oxygen consumption (+2.5 mL/kg/min). While this pilot trial was not powered to address hard clinical outcomes, it would be worth pointing

Table 3 Clinical parameters, quality of life, cardiac echo at baseline and follow-up visits

Parameter	Baseline ($n = 10$)	1 month ($n = 10$)	3 months ($n = 10$)	6 months ($n = 10$)	12 months ($n = 9$)
Clinical					
Weight (kg)	87 (72.5, 111)	88.5 (70, 111)	87 (73, 111)	86.5 (69, 112)	88 (74, 111)
NT-proBNP (pg/mL)	1572 (542, 2501)	2257 (396, 4363)	2129 (449, 2558)	1205 (381, 2101)	1241 (233, 2634)
Creatinine (pg/dL)	1.01 (0.93, 1.26)	1.14 (1.00, 1.45)	1.08 (0.91, 1.35)	1.24 (1.06, 1.30)	1.06 (0.95, 1.22)
eGFR (mL/min/1.73 m^2)	63 (56, 75)	61 (49,75)	64 (58, 74)	62 (39, 77)	71 (57, 76)
Resting SBP (mmHg)	130 (125, 140)	130 (120139)	135 (130, 138)	126 (120, 137)	136 (126, 137)
Resting DBP (mmHg)	86.5 (70, 90)	80 (80, 85)	80 (80, 90)	79.5 (70, 80)	80 (80, 90)
Resting HR (bpm)	79 (70, 88)	72 (64, 90)	78 (70, 85)	75 (69, 83)	76 (67, 80)
Furosemide equivalent (mg), median (IQR)	40 (20, 40)	40 (20, 40)	40 (40, 120)	40 (20, 140)	40 (20, 120)
NYHA class I/II/III (%)	0/0/100	0/70/30[a]	10/90/0[a]	10/90/0 [a]	30/60/0[a]
Quality of life					
MLWHFQ score	60 (51, 71)	26.5 (19, 37)[a]	24.5 (20, 41)[a]	26 (20, 32)[a]	22 (16, 27)[a]
Cardiac echo					
LVEF (%)	57.5 (50, 65)	N/A	55 (55, 60)	60 (55, 65)	55 (55, 60)
LVMi (g/m^2)	132 (125, 139)	N/A	116 (102, 121)[a]	109 (98, 125)[a]	102 (83, 110)[a]
E/E′	13.5 (12.2, 16.7)	N/A	8.8 (7.2, 14.3)[a]	8.7 (6.9, 10.0)[a]	9.1 (7.3, 12.8)

Values are given as median (95% confidence interval) unless otherwise specified.
DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; IQR, interquartile range; LMVi, left ventricular mass index; LVEF, left ventricular ejection fraction; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; N/A, not available; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.
[a]$P < 0.05$ compared to baseline.

out that high PCWP during exercise is associated with increased mortality.[30] Haemodynamic changes were paralleled by favourable changes in ventricular structure. These findings extend the work of temporary splanchnic nerve blockade, providing additional evidence for the mechanistic effects of GSN ablation in acute and chronic HF.[19,22]

The current guideline-recommended strategy to manage patients with HFpEF is to optimize treatment of comorbidities and to alleviate signs and symptoms of congestion with diuretics but does not address the underlying pathophysiology of the disease. This cornerstone of chronic and acute HFpEF volume management is centred around the classical model that salt and fluid retention are the causes of intravascular fluid expansion and cardiac decompensation. Notably, nearly half of all HF patients experience no or minimal change in weight in the days prior to hospitalization for acute decompensation.[31,32] In fact, intracardiac filling pressures in HF patients demonstrate that right and left-sided pressures commonly start to increase before any significant weight changes take place preceding an admission for clinical decompensation.[33,34]

Taken together, an increase in central filling pressures occurs in many cases in the absence of weight or total body volume increases, suggesting a complimentary contribution of volume redistribution to the mechanism of cardiac decompensation.[35,36] Further, patients with HFpEF are characterized by increased cardiac and vascular stiffness and are prone to activity induced elevation in pulmonary and intracardiac pressures.[37] It is now well established that abnormally high pulmonary pressures are a major limitation of exertion in HFpEF. A reduced capacity to buffer blood in the splanchnic vascular reservoir could be an additional key contributor to the reduced exercise capacity in HFpEF. To date there are no direct clinical data to confirm a reduced splanchnic vascular capacitance and the role of volume redistribution in HFpEF. However, the role of splanchnic nerves in the process of volume redistribution is supported by pre-clinical and clinical data showing that splanchnic nerve stimulation results in acute haemodynamic changes, with a decrease in splanchnic vascular compliance and an increase in cardiac preload.[12,14,38] HF is characterized by a heightened global sympathetic tone, yet untargeted pharmacological reduction in sympathetic tone can be insufficient to result in effective splanchnic vasodilatation and be detrimental due to unintended cardiovascular effects.[39] 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. Whether the ideal pathophysiology targeted by splanchnic nerve ablation differs from emerging therapies for HFpEF such as inter-atrial shunt devices or pericardiotomy remains to be investigated.[40–43] Additionally, given the considerable procedure related morbidity from a surgical GSN ablation, a catheter-based approach is being developed in order to enable larger trials and provide a less invasive method of GSN ablation.

Limitations

Our study has several limitations that need to be considered. First, and most importantly, considering the surgical nature of the intervention, we did not include a control with sham procedures, thus careful interpretation of subjective symptom and

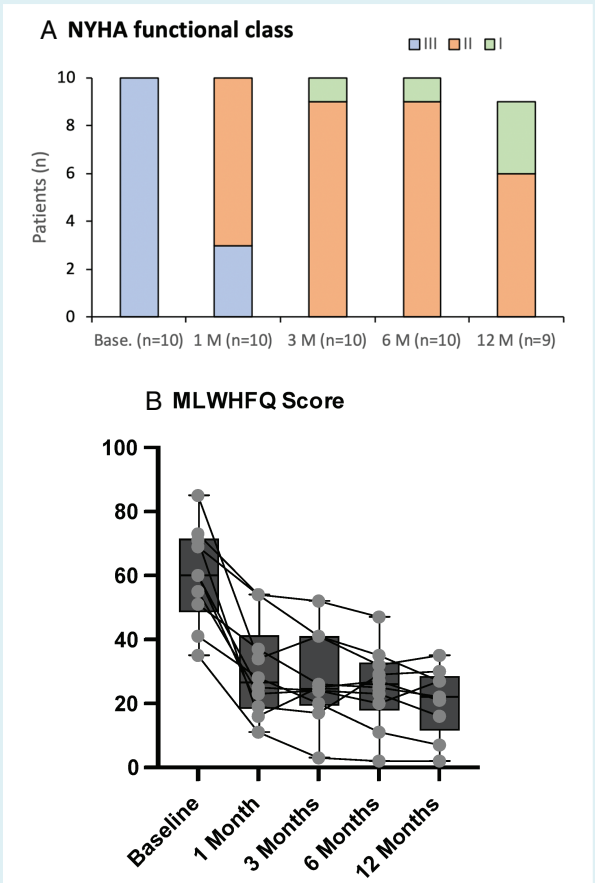


Figure 5 Functional outcomes. Changes in (*A*) New York Heart Association (NYHA) and (*B*) Minnesota Living With Heart Failure Questionnaire (MLWHFQ) during the study follow-up.

quality of life changes is required. Although the marked reduction in cardiac filling pressures and improvement in exercise capacity suggest a true therapeutic effect, unmeasured bias and regression to the mean cannot be excluded. Second, despite the exercise protocol was standardized across the two participating centres, one centre used a treadmill and one used an upright cycle ergometer. While this discrepancy prevented the pooling of peak oxygen consumption, a change in peak oxygen consumption as it was used in our study is appropriate.[44] Third, a change in splanchnic vascular capacitance could not be evaluated directly, the evaluation depended on the assessment of cardiac filling pressures as a surrogate measure. Similarly, the question of therapeutic tolerance/adaptation could not be answered conclusively but the persistence of improved filling pressures with exercise argues against tolerance to splanchnic nerve ablation. Although increases in peak oxygen consumption were seen, we did not assess cardiac output changes during invasive haemodynamic exercise testing. Fourth, given that this was a first-in-human study, our protocol did not restrict or regulate HF medication changes following GSN ablation. Although changes to the medical regimens were minimal and likely insufficient to explain the large degree of the observed changes, confounding effects on improved exercise parameters and symptoms during follow-up cannot be excluded. Finally, orthostatic hypotension may potentially complicate the GSN ablation procedure. In our study, we did not apply a systematic evaluation of supine, sitting, and standing blood pressure and heart rate, however, during the entire follow-up period no patient displayed symptoms consistent with orthostatic hypotension.

Conclusions

This is the first study to demonstrate the tolerability and potential benefits of unilateral GSN ablation in patients with HFpEF and profound exercise limitation, including reduced resting intra-cardiac filling pressures, paired with an improvement in exercise capacity and self-reported symptoms and quality of life. The study lacks a control group, but the findings justify future sufficiently powered, randomized controlled trials to confirm the value of GSN ablation for the treatment of HFpEF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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