Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

ROZPRAWA DOKTORSKA

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„Ocena odpowiedzi hemodynamicznej na wysiłek fizyczny u chorych z niewydolnością serca z zachowaną frakcją wyrzutową lewej komory (HFpEF) – implikacje patofizjologiczne i terapeutyczne”

Hemodynamic response to exercise in patients with heart failure with preserved ejection fraction (HFpEF) - pathophysiological and therapeutic implications

Promotor: prof. dr hab. Piotr Ponikowski

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Badania przedstawione w niniejszej rozprawie doktorskiej pt. „**Ocena odpowiedzi hemodynamicznej na wysiłek fizyczny u chorych z niewydolnością serca z zachowana frakcją wyrzutową lewej komory (HFpEF) – implikacje patofizjologiczne i terapeutyczne**” zostały wykonane w Katedrze i Klinice Chorób Serca i Instytucie Chorób Serca Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu kierowanym przez Pana prof. dr hab. n. med. Piotra Ponikowskiego, Klinice Chirurgii w 4 Wojskowym Szpitalu Klinicznym we Wrocławiu oraz Centrum Chorób Serca w Szpitalu Na Homolce w Pradze.

Promotorem rozprawy doktorskiej jest Pan prof. dr hab. n. med. Piotr Ponikowski

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1. WYKAZ PUBLIKACJI STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

Lek. Piotr Gajewski

Cykl publikacji

Lp	Opis bibliograficzny	IF	Punkty
1	Malek Filip, **Gajewski Piotr**, Zymliński Robert, Janczak Dariusz, Chabowski Mariusz, Fudim Marat, Martinca Tomas, Neuzil Petr, Biegus Jan, Mates Martin, Krüger Andreas, Skalsky Ivo, Bapna Anisha, Engelman Zoar J., Ponikowski Piotr P.: Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: first-in-human clinical trial, European Journal of Heart Failure, 2021, vol. 23, nr 7, s. 1134-1143, DOI:10.1002/ejhf.2209	18,174	200
2	**Gajewski Piotr**, Fudim Marat, Kittipibul Veraprapas, Engelman Zoar J., Biegus Jan, Zymliński Robert, Ponikowski Piotr: Early hemodynamic changes following surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction, Journal of Clinical Medicine, 2022, vol. 11, nr 4, art.1063 [6 s.], DOI:10.3390/jcm11041063	4,964*	140
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2. STRESZCZENIE

Niewydolność serca (ang. *heart failure* - HF) jest jednostką chorobową charakteryzującą się występowaniem objawów przedmiotowych i podmiotowych (m.in. duszności, pogorszeniem tolerancji wysiłku fizycznego, narastaniem obrzęków obwodowych), które są wynikiem zaburzeń czynności lub struktury serca. Na niewydolność serca choruje około 2-3% populacji dorosłych, a częstość jej występowania wzrasta z wiekiem. W krajach rozwiniętych stanowi ona ciągle poważne wyzwanie medyczne i socjoekonomiczne.

Aktualne wytyczne Europejskiego Towarzystwa Kardiologicznego (ang. *European Society of Cardiology* - ESC) dzielą chorych z HF na trzy grupy, w zależności od frakcji wyrzutowej lewej komory: z zachowaną frakcją wyrzutową (HFpEF), łagodnie upośledzoną frakcją wyrzutową (HFmrEF) oraz upośledzoną frakcją wyrzutową (HFrEF).

Blisko połowa chorych z HF są to pacjenci z niewydolnością serca z zachowana frakcją wyrzutową lewej komory (HFpEF). Prezentują oni najczęściej typowe objawy HF, czemu towarzyszą cechy dysfunkcji rozkurczowej lewej komory oceniane w badaniu echokardiograficznym oraz podwyższone wartości peptydów natriuretycznych w surowicy krwi (BNP > 35 pg/ml i/lub NTproBNP > 125 pg/ml).

Cechą charakterystyczną przewlekłej niewydolności serca z zachowana frakcją wyrzutową lewej komory jest nietolerancja wysiłku fizycznego objawiająca się dusznością wysiłkową oraz zmęczeniem, co wiąże się z pogorszeniem jakości życia.

Heterogenność populacji pacjentów z HFpEF oraz niska swoistość zgłaszanych objawów przyczynia się do trudności diagnostycznych.

Mechanizmy wpływające na upośledzoną tolerancję wysiłku u pacjentów z HFpEF nie są w pełni poznane. Proponuje się podział tych mechanizmów na dwie grupy: centralne jak np. częstość akacji serca, objętość wyrzutowa lewej komory, rzut minutowy serca, ciśnienie napełniania lewej komory oraz obwodowe: zużycie tlenu przez mięśnie szkieletowe, indeks masy ciała, funkcja nerek, wartości hemoglobiny.

Jedna z hipotez zakłada, iż w HFpEF nietolerancja wysiłku fizycznego związana jest z zaburzoną reakcją hemodynamiczną, szybkim i znacznym wzrostem ciśnienia napełniania lewej komory w odpowiedzi na wysiłek fizyczny. Potencjalnym mechanizmem, który może się przyczynić do wzrostu ciśnienia napełniania lewej komory, jest redystrybucja krwi między różnymi kompartmentami naczyniowymi w organizmie człowieka.

Około 70% całkowitej objętości krwi zlokalizowana jest w układzie żylnym. Wysoka podatność naczyń żylnych umożliwia łatwiejsze dostosowanie się do zmian objętości krwi.

Narządy jamy brzusznej, w porównaniu do innych organów mają stosunkowo dużą objętość krwi względem objętości tkanki. Ze względu na niski opór naczyniowy i wysoką podatność żył, przez układ trzewny przepływa około 25% pojemności minutowej serca. Natomiast żyły trzewne są w stanie pomieścić od 20% do 50% całkowitej objętości krwi, co stanowi główny zbiornik krwi w organizmie. Systemem kontrolującym ten kompartment naczyniowy są włókna współczulne regulujące napięcie zarówno tętnic jak i żył układu trzewnego.

Aktywacja nerwów trzewnych, w odpowiedzi na bodźce tak jak między innymi wysiłek fizyczny, wzrost wartości ciśnienia tętniczego czy infekcja, powoduje skurcz naczyń krwionośnych, zmniejszenie naczyniowej pojemność trzewnej, co prowadzi do redystrybucji krwi z krążenia trzewnego do centralnego, czego konsekwencją może być wzrost ciśnienia napełniania prawej i lewej komory. Patomechanizm ten może być odpowiedzialny za nietolerancję wysiłku fizycznego u chorych z HFpEF.

Głównym celem przedstawionych badań jest poznanie patofizjologii odpowiedzi hemodynamicznej na wysiłek fizyczny oraz identyfikacja mechanizmów determinujących nietolerancję wysiłku u osób z HFpEF.

Przeprowadzone badania będą stanowiły podstawę dla przyszłych badań oraz nowych form terapii ukierunkowanych na poprawę tolerancji wysiłku fizycznego oraz jakości życia u pacjentów z HFpEF. W ramach badań opisanych w publikacji “Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: first-in-human clinical trial” udowodniono, iż modyfikacja układu współczulnego poprzez jednostronną ablację nerwu trzewnego większego jest bezpieczna, redukuje spoczynkowe oraz wysiłkowe ciśnienia wewnątrzsercowe co może potencjalnie wpływać na poprawę jakości życia.

W ramach badań przedstawionych w publikacji Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction wykazano, że zmniejszenie ciśnień panujących wewnątrz serca następuje już po 24 godzinach od zabiegu ablacji nerwu trzewnego większego. Powyższe badania podsumowane w dwóch publikacjach dostarczają nowych danych na temat mechanizmów objawów niewydolności serca oraz patofizjologicznych aspektów odpowiedzi hemodynamicznej na wysiłek fizyczny u chorych z HFpEF.

3. *SUMMARY*

Heart failure (HF) is a disease with presence signs and symptoms (e.g. dyspnoea, intolerance the exercise, increasing peripheral edema), which are the result of dysfunction or structure of the heart. About 2-3% of the adult population suffer from heart failure, and its incidence increases with age. In developed countries, it is still a serious medical and socio-economic challenge.

The current guidelines of the European Society of Cardiology (ESC) divide patients with HF into three groups depending on the ejection fraction (EF): heart failure with preserved ejection fraction (HFpEF), heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with reduced ejection fraction (HFrEF).

Nearly half of the patients with HF are patients with heart failure with preserved ejection fraction (HFpEF). They often present typical symptoms of HF, accompanied by left ventricular diastolic dysfunction in echocardiography assessment and elevated serum natriuretic peptides (BNP> 35 pg / ml and / or NTproBNP> 125 pg / ml).

The heterogeneity population of patients with HFpEF and the low specificity of the symptoms contribute to diagnostic difficulties.

A hallmark of chronic heart failure with preserved ejection fraction is intolerance the exercise manifested by exertion dyspnea and fatigue, which is associated with a deterioration in the quality of life. The mechanisms of impaired exercise tolerance in patients with HFpEF are not fully understood.

It is proposed to divide these mechanisms into two groups: central, such as heart rate (HR), stroke volume (SV), cardiac output (CO), left ventricular filling pressure, and peripheral: oxygen consumption by skeletal muscles, body mass index (BMI), kidney function, values of hemoglobin.

While many mechanisms contribute to the limitations in exercise and the ability to perform activities in HFpEF, there is growing evidence of profoundly abnormal haemodynamic response to exercise characterized by rapid and marked elevation in left ventricular filling pressures. A potential mechanism that may contribute to increase left ventricular filling pressure is the redistribution of blood between different vascular compartments in the body.

About 70% of the total blood volume is in the veins. The high compliance of the venous vessels makes it easier to adapt to changes in blood volume. The abdominal organs, compared to other organs, have a relatively large blood volume in relation to the tissue mass. Due to the low vascular resistance and the high compliance of the veins, approximately 25% of the cardiac

output flows through the visceral system. In contrast, the visceral veins hold 20% to 50% of the total blood volume, which is the body's main reservoir of blood.
The main regulatory system for the splanchnic vascular capacitance ('storage space') are sympathetic fibers originating from the splanchnic nerves which control arterial and venous vascular tone. Activation of splanchnic nerves causes vasoconstriction, a decrease in splanchnic vascular capacity, which leads to redistribution of blood from the visceral to the central circulation, which may result in an increase in right and left ventricular filling pressures. This pathomechanism may be responsible for exercise intolerance in patients with HFpEF.
Aims of the presented study is to understand the pathophysiology of the hemodynamic response to exercise and to identify the mechanisms that determine exercise intolerance in patient with HFpEF.

The conducted study will form the basis for future research and new forms of therapies focused on improving exercise tolerance and quality of life in patients with HFpEF. As part of the research described in the publication "Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: first-in-human clinical trial", it has been proven that modifying the sympathetic system by unilateral ablation of the greater splanchnic nerve (GSN) is safe and reduces resting intracardiac pressure which can potentially improve quality of life. Study presented in the manuscript "Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction" showed that Permanent right GSN ablation leads to a reduction in intracardiac filling pressures during exercise, apparent as early as 24 h following the procedure. These studies, summarized in two publications, provide new data on the mechanisms of HF symptoms and the pathophysiological aspects of the hemodynamic response to exercise in patients with HFpEF.

4. WPROWADZENIE

Niewydolność serca (ang. *heart failure* - HF) jest schorzeniem o wysokim wskaźniku zapadalności i chorobowości, a także niekorzystnym odległym rokowaniu (1-3). Częste hospitalizacje (m.in. dekompensacje układu krążenia) oraz konieczne złożone strategie leczenia interwencyjnego i farmakologicznego generują bardzo duże koszty dla systemów opieki zdrowotnej na całym świecie. W związku z tym niewydolność serca stanowi jedno z wiodących wyzwań medycznych i socjoekonomicznych (2-6).

Niewydolność serca z zachowaną frakcją wyrzutową (HFpEF) stanowi około 50% wszystkich rozpoznań niewydolności serca (7-9). Jej częstość wzrasta w stosunku do niewydolności serca z obniżoną frakcją wyrzutową lewej komory (HFrEF) średnio o 1% rocznie, co jest związane ze starzeniem się populacji oraz dużym odsetkiem nadciśnienia tętniczego, cukrzycy i otyłości (10). Rokowanie w HFpEF jest równie niekorzystne co w HFrEF (10-12). Jednak w przeciwieństwie do niewydolności serca z upośledzoną frakcją wyrzutową lewej komory, gdzie w ciągu ostatnich 30 lat dokonano znacznego postępu w diagnostyce, dostępności oraz metodach leczenia (np. terapia resynchronizująca czy nowe leki takie jak antagoniści receptora dla angiotensyny II i inhibitora neprylizyny), opcje leczenia pacjentów z HFpEF są obecnie ograniczone. Główne cele terapeutyczne skupiają się na kontroli wolemii, leczeniu schorzeń towarzyszących, czy redukcji masy ciała (13,14). Dopiero wyniki badania EMPEROR-Preserved opublikowane w 2021 r. wskazują na nową opcję leczenia farmakologicznego w celu zmniejszenia ryzyka zgonu z przyczyn sercowo-naczyniowych i hospitalizacji z powodu niewydolności serca w tej grupie pacjentów (15).

Nietolerancja wysiłku fizycznego jest cechą charakterystyczną niewydolności serca z zachowaną frakcją wyrzutową (HFpEF) i wiąże się ze złą jakością życia, częstymi hospitalizacjami i zwiększoną śmiertelnością (16,17).

Mechanizm nietolerancji wysiłku fizycznego u chorych z HFpEF jest złożony i w pełni niepoznany. Istnieje jednak coraz więcej dowodów na nieprawidłową odpowiedź hemodynamiczną na wysiłek fizyczny, charakteryzującą się szybkim i wyraźnym wzrostem ciśnienia napełniania lewej komory, które zazwyczaj powraca do wartości wyjściowych po okresie odpoczynku, zwłaszcza, że część pacjentów z HFpEF prezentuje prawidłowe wartości hemodynamiczne w czasie spoczynku (18-20). Tak więc homeostaza płynów to tylko jeden z elementów odgrywających role w dekompensacji niewydolności serca. Coraz częściej akcentuje się znaczenie redystrybucji płynu w organizmie (przesunięć pomiędzy poszczególnymi kompartmentami) (21,22). Badania pokazuję, iż połowa pacjentów

zdekompensowanych miała niewielki lub brak przyrostu masy ciała poprzedzających hospitalizację z powodu ostrej niewydolności serca. Zwłaszcza pacjenci z HFpEF mają tendencję do gwałtownych wzrostów ciśnień wewnątrzsercowych, bez znaczącego przyrostu masy ciała i cech przewodnienia (23-26).

Jedną z postulowanych istotnych składowych patofizjologii HFpEF jest nadreaktywność współczulnego układu nerwowego (sympathetic nervous system - SNS), która prowadzi do przesunięć płynów między poszczególnymi kompartmentami (21,22). Gwałtowna stymulacja odpowiada za redystrybucję dużych objętości płynów z przestrzeni pozanaczyniowej (z narządów miąższowych) do przestrzeni wewnątrznaczyniowej. Prowadzi to do obciążenia objętościowego zarówno krążenia żylnego jak i tętniczego. W efekcie obserwuje się zwiększenie ośrodkowego ciśnienia żylnego, ciśnienia płucnego oraz ciśnienia w prawym i lewym sercu, co w konsekwencji powoduje zmniejszenie tolerancji wysiłku fizycznego i prowadzi do zastoju w krążeniu płucnym, dysfunkcji rozkurczowej lewej komory, narastania oporności na diuretyki (27-29).

Układ żylny zawiera około 70% całkowitej objętości krwi i jest około 30 razy bardziej podatny na zmiany objętościowe niż układ tętniczy (25). Zbiornik trzewny składający się z układu naczyniowego narządów trzewnych, w tym wątroby, śledziony, jelita cienkiego i grubego, żołądka i trzustki, może zawierać około 25% pojemności minutowej serca i od 20% do 50% całkowitej objętości krwi (22, 30-32).

Głównym systemem regulującym pojemność naczyń trzewnych są włókna współczulne pochodzące z nerwów trzewnych, które kontrolują napięcie naczyń tętniczych i żylnych.

Aktywacja nerwów trzewnych powoduje wazokonstrykcję naczyń krwionośnych, zmniejszenie pojemności trzewnej co doprowadza do przesunięcia krwi do krążenia centralnego (33, 34).

Prawy i lewy nerw trzewny większy są bezpośrednio zaangażowane w regulację mięśni gładkich trzewnych łożysk żylnych (35,36). Kontrolowana modyfikacja funkcji SNS (sympathetic nervous system) może wyeliminować ważny z patofizjologicznego punktu widzenia mechanizm redystrybucji płynów. Ablacja nerwu trzewnego większego (GSN) prowadzi do inhibicji sympatycznego układu nerwowego, hamując tym samym przesunięcie płynu z układu trzewnego do krążenia centralnego i wtórny wzrost centralnego ciśnienia żylnego, ciśnienia płucnego oraz ciśnień wewnątrzsercowego (37-43). U pacjentów HFpEF zmiany te mogą wpłynąć korzystnie na poprawę wydolności fizycznej i poprawę jakości życia co może przełożyć się na mniejszą liczbę hospitalizacji z powodów niewydolności serca (44,45).

5. CELE I METODY BADAŃ

5.1. Cele badania

Głównym celem przedstawionych badań była analiza mechanizmów odpowiedzialnych za nietolerancję wysiłku fizycznego u chorych z niewydolnością serca z zachowaną frakcją wyrzutowa lewej komory (HFpEF).

Na podstawie wykonanych badań postanowiono zweryfikować postawione hipotezy, że inhibicja sympatycznego układu nerwowego poprzez selektywną ablację prawego nerwu trzewnego większego (grater splanchnic nerve - GSN) u pacjentów z HFpEF doprowadza do zahamowania przesunięć płynów między naczyniami krwionośnymi układu trzewnego a krążeniem centralnym co wpływa na zmniejszenie ciśnienia napełniania lewej komory w trakcie wysiłku fizycznego.

Szczegółowe cele badań opisanych w publikacji pt.: "*Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: first-in-human clinical trial"* (46)*:*

- ocena bezpieczeństwa i tolerancji ablacji nerwu trzewnego większego (GSN) określane jako okołozabiegowe i trwające do 3 miesięcy po zabiegu poważne działania niepożądane ze strony układu sercowo - naczyniowego lub przewodu pokarmowego,
- ocena skuteczności klinicznej ablacji nerwu trzewnego większego (GSN) określana jako zmniejszenie ciśnienia zaklinowania w tętnicy płucnej (pulmonary capillary wedge pressure – PCWP) w spoczynku i w trakcie wysiłku fizycznego w porównaniu do wartości początkowej oraz poprawa jakości życia (ocenianej za pomocą kwestionariusz MLWHFQ i klasy NYHA).

Szczegółowe cele badań opisanych w publikacji pt.: "*Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction"* (47)*:*

- wczesna ocean skuteczności klinicznej ablacji nerwu trzewnego większego (GSN) określana jako zmniejszenie centralnego ciśnienia żylnego (central venous pressure - CVP), ciśnienia w tętnicy płucnej (pulmonary artery pressure - PAP) oraz ciśnienia zaklinowania w tętnicy płucnej (pulmonary capillary wedge pressure – PCWP) w spoczynku i w trakcie wysiłku fizycznego 24 godziny po zabiegu.

5.2. Metody badania

Wszystkie badania przedstawione w niniejszym opracowaniu zostały wykonane w Katedrze i Klinice Chorób Serca Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu, Klinice Chirurgii w 4 Wojskowym Szpitalu Klinicznym we Wrocławiu oraz Centrum Chorób Serca w Szpitalu Na Homolce w Pradze.

Zgodę na przeprowadzenie badań wydały lokalne Komisje Bioetyczne. Wszyscy pacjenci wyrazili świadomą zgodę na udział w badaniu.

Pacjenci, którzy spełniali kryteria włączenia oraz nie spełniali kryteriów wyłączenia zostali poddani ocenie na początku badania (baseline) oraz 1, 3, 6 i 12 miesięcy po operacji. We wszystkich punktach czasowych testy obejmowały: badanie przedmiotowe, ocenę jakości życia za pomocą kwestionariusza Minnesota Living With Heart Failure Questionnaire (MLWHFQ) i New York Heart Association (NYHA), badania laboratoryjne, badanie echokardiograficzne oraz spiroergometryczną próbę wysiłkową (CPET).

Na początku badania (baseline) oraz 1, 3 i 12 miesięcy po zabiegu ablacji nerwu trzewnego większego u wszystkich włączonych pacjentów przeprowadzono cewnikowanie prawego serca z oceną ciśnień w: prawym przedsionku (RAP), tętnicy płucnej (PAP) oraz ciśnienia zaklinowania w tętnicy płucnej (PCWP) w spoczynku, podczas manewru unoszenia nóg, i w trakcie wysiłku fizycznego na cykloergometrze w pozycji leżącej.

Zabieg ablacji nerwu trzewnego większego został wykonany torakoskopowo przez torakochirurgów w znieczuleniu ogólnym.

Szczegółowy opis protokołu badania, kryteriów włączenia i wyłączenia pacjentów oraz zabiegu ablacji nerwu trzewnego większego został przedstawiony w pracy „*Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: first-in-human clinical trial”* (46).

W ramach publikacji „*Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction”* (47) retrospektywnie przeanalizowano siedmiu z dziesięciu pacjentów, którzy 24 godziny po interwencji chirurgicznej ablacji nerwu trzewnego większego zostali poddani powtórnym inwazyjnym badaniom hemodynamicznym.

6. PUBLIKACJE

6.1. Publikacja 1

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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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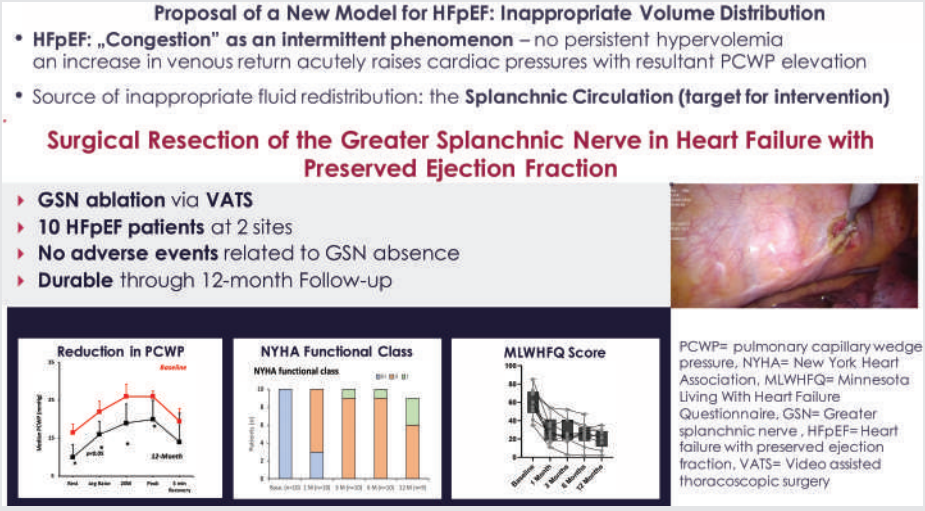
Graphical Abstract



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

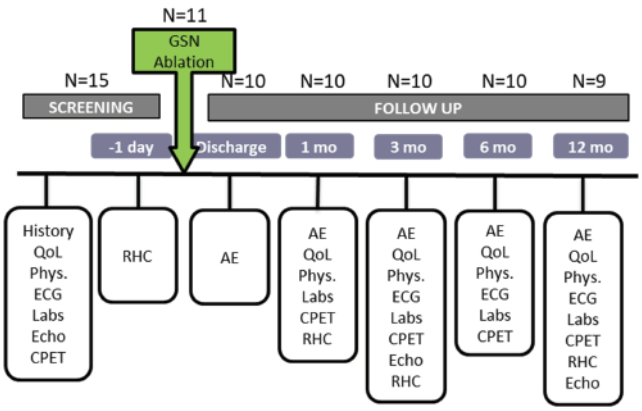


Figure 1 Study design. Study flow diagram together with the number of patients reviewed at each stage. AE, adverse event; CPET, cardiopulmonary exercise test; ECG, electrocardiogram; GSN, greater splanchnic nerve; Phys., physical; QoL, quality of life; RHC, right heart catheterization.

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

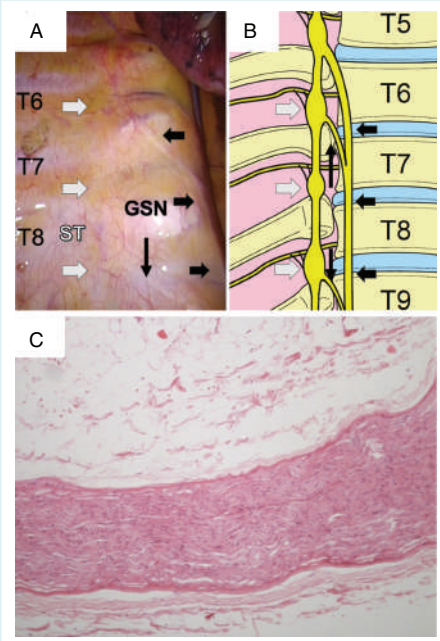


Figure 2 Surgical procedure, target nerve and confirmatory histology. (*A*) Identification of the sympathetic trunk (ST, white arrows), the right greater splanchnic nerve (GSN) trunk (thick black arrows) and GSN roots (thin black arrows) using a thoracoscopic camera in study subject 001–001 (right hemithorax, 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.

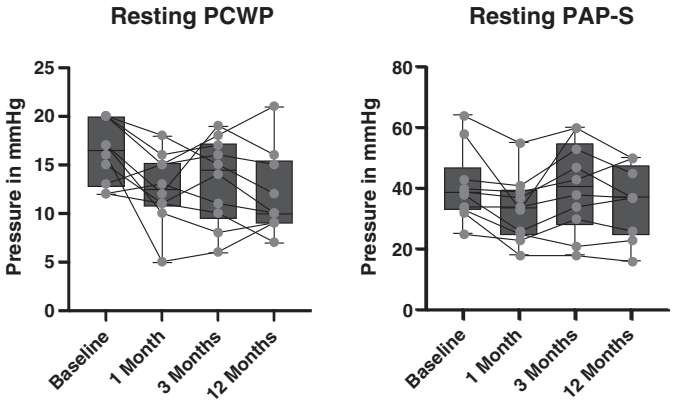


Figure 3 Resting haemodynamics. Pulmonary capillary wedge pressure (PCWP) and systolic pulmonary artery pressure (PAP-S) for all patients at 1, 3, and 12 months with median (95% confidence interval) for each time-point.

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

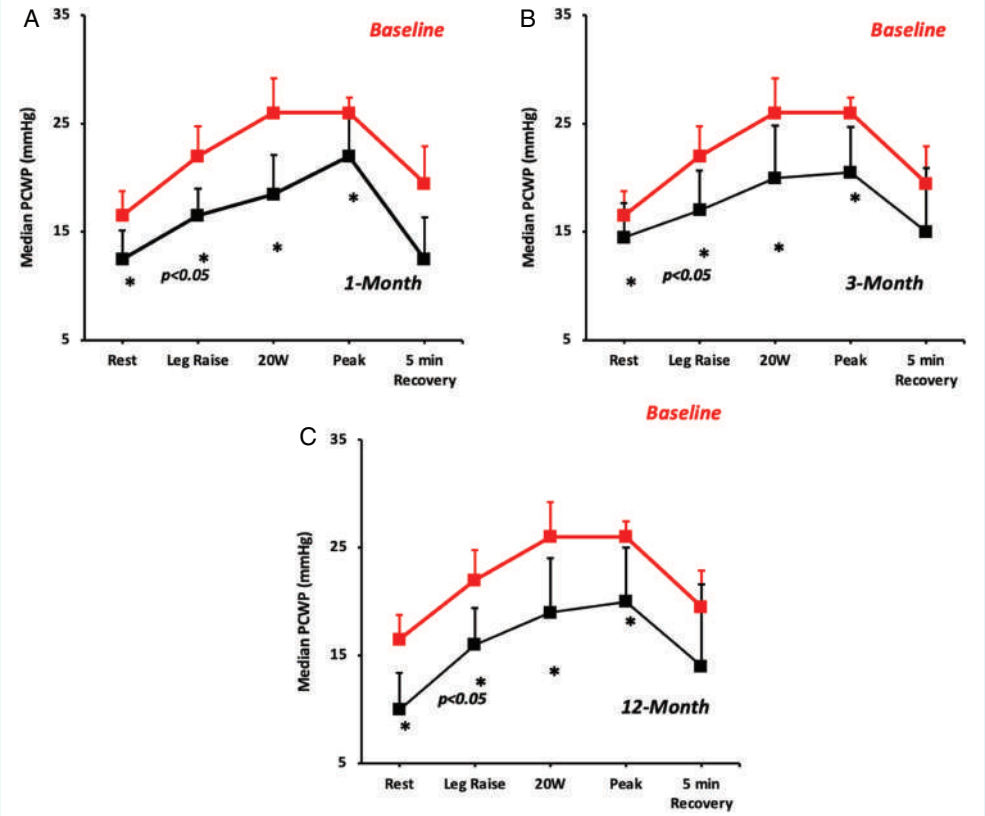


Figure 4 Resting and exercise haemodynamics. Pulmonary capillary wedge pressure (PCWP) increased to a greater extent in heart failure with preserved ejection fraction patients prior to greater splanchnic nerve ablation compared to the same patients at (*A*) 1 month, (*B*) 3 months, (*C*) 12 months after 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

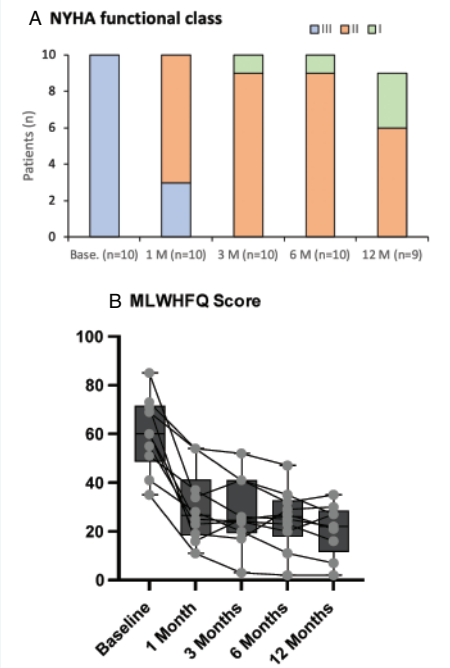


Figure 5 Functional outcomes. Changes in (*A*) New York Heart Association (NYHA) and (*B*) Minnesota Living With Heart Failure Questionnaire (MLWHFQ) during the study follow-up.

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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6.2. Publikacja 2

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Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction.
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Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction

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Abstract: Background: Permanent ablation of the right greater splanchnic nerve (GSN) has previously been demonstrated to improve quality of life and functional outcomes, as well as reduce abnormally high intracardiac filling pressures, in patients with heart failure with preserved ejection fraction (HFpEF) at 1, 3 and 12 months following the procedure. We hypothesize that hemodynamic changes that ensue from surgical right GSN ablation would be apparent as early as 24 h after the medical intervention. Methods and Results: This is a prespecified analysis of a single-arm, two-center, open-label study evaluating the effects of right GSN ablation via thoracoscopic surgery in HFpEF patients with pulmonary capillary wedge pressure (PCWP) $\geq$15 mmHg at rest or $\geq$25 mmHg with supine cycle ergometry. A total of seven patients (median age 67 years, 29% female) underwent GSN removal followed by invasive right heart catheterization within 24 h. GSN ablation resulted in a significant reduction in PCWP 24 h after the procedure compared to baseline for both 20 W exercise (baseline (28.0 $\pm$ 4.3 mmHg) to 24 h (19.6 $\pm$ 6.9 mmHg); p = 0.0124) and peak exercise (baseline (25.6 $\pm$ 2.4 mmHg) to 24 h (17.4 $\pm$ 5.9 mmHg); p = 0.0025). There were no significant changes in resting or leg-up hemodynamics. Conclusions: Permanent right GSN ablation leads to a reduction in intracardiac filling pressures during exercise, apparent as early as 24 h following the procedure.

Keywords: heart failure; HFpEF; greater splanchnic nerve ablation

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1. Background

Heart failure with preserved ejection fraction (HFpEF) comprises about 50% of today's heart failure population, and its incidence is constantly increasing [1,2]. Unlike heart failure with reduced ejection fraction (HFrEF), in HfpEF, there are no well-established drug therapies. Current clinical approaches focus on modifying risk factors and comorbidities to control symptoms in HFpEF [3,4]. The results of the EMPEROR-Preserved study published in 2021 indicate a new option for pharmacological treatment to reduce the combined risk of death from cardiovascular causes and hospitalization due to heart failure [5]. Preliminary evidence suggests that lowering exercise induces intracardiac pressures with the interatrial shunt procedure, yet the pivotal study results are pending.

The hallmark of HFpEF is exercise intolerance, which is manifested by exertional dyspnea or fatigue. Growing evidence shows that an uncontrolled hemodynamic response to exercise, as manifested by a rapid increase in intracardiac filling pressures (which usually return to baseline in the rest) can be responsible for this condition [6]. Volume redistribution,

in addition to total body fluid retention, is increasingly being recognized as an important contributor of elevated intracardiac pressures and clinical congestion in heart failure [7]. The splanchnic venous reservoir plays a critical role in controlling the distribution of blood between stressed and unstressed compartments in the body [8]. In heart failure, there is a decreased capacity of the splanchnic vascular reservoir to buffer volume shifts in the body, leading to an abnormal rise in central pressures during exertion, even in the setting of normal hemodynamics at rest as commonly seen in patients with HFpEF [9]. Various interventions aimed at selectively affecting the splanchnic system to improve outcomes in patients with HF have been investigated, with specific focus on targeted modulation of the greater splanchnic nerve (GSN) [10]. The potential benefits of splanchnic nerve modulation in HF are believed to be related to sympathetically mediated improvement in vascular compliance and a decrease in inappropriately high intracardiac filling pressures at rest and especially with exertion [11].

Recently, the feasibility and safety of permanent right GSN ablation in HFpEF were examined in a small proof-of-concept study [12]. This study demonstrated that right GSN ablation in HFpEF was safe, with no adverse events related to the absence of the GSN for at least 12 months. Mechanistically, there was a significant reduction in intracardiac filling pressures during exercise right-heart catheterization at 1, 3, and 12 months after the procedure compared to baseline. Clinically, patients demonstrated significant improvement in quality of life and functional capacity following GSN ablation through 12-month follow-ups as compared to baseline. The early hemodynamic changes following GSN ablation have not yet been described. In this study, we sought to examine the changes in invasive hemodynamic measurements within 24 h following surgical GSN ablation in patients with HFpEF.

2. Methods

The study design and the primary results have been previously published [11]. Briefly, patients were enrolled in a single-arm, two-center, open-label, prospective study aimed at the feasibility of elective blockade of sympathetic signaling to the splanchnic circulation by surgical ablation of the right GSN (clinicaltrial.gov, NCT03715543). To be considered for enrollment, patients had to be $\geq$18 years of age with guideline-defined HFpEF, New York Heart Association (NYHA) functional class III/IV, and pulmonary capillary wedge pressure (PCWP) $\geq$15 mmHg at rest or $\geq$25 mmHg during exercise. The original study enrolled a total of 10 patients (from 15 patients screened) between June 2016 and July 2017. All patients underwent surgical ablation of the right GSN using a multi-port video-assisted thoracoscopic approach. Seven of the ten patients who recovered from the surgical intervention underwent repeat hemodynamic testing approximately 24 h after the original procedure.

The early clinical effectiveness of GSN ablation was assessed by examining changes in hemodynamic measurements obtained from invasive right heart catheterization approximately 24 h after the procedure compared with baseline. Central hemodynamic profiles (i.e., central venous pressure (CVP) and systolic pulmonary artery pressure (PAP-S), PCWP) were measured at rest, during leg-up maneuver, and during supine bicycle exercise. Supine bicycle exercise protocol was implemented by commencing at 20 watts (W) with 10 W increments every 90 s until the patient achieved maximum effort as defined by symptom-limiting dyspnea or fatigue. The same central hemodynamic measurements were taken after a five-minute recovery from the end of maximal exertion. Summaries within a visit are presented as mean $\pm$ standard deviation or median (Q1, Q3), unless otherwise noted, and change from baseline is presented as median (95% confidence interval [CI]). Hemodynamic data were compared using Wilcoxon Signed Rank test (SAS v9.4 for Windows, SAS Institute Inc., Cary, NC, USA). A p value < 0.05 was considered statistically significant.

3. Results

Baseline characteristics of seven enrolled patients are summarized in Table 1. Patients had a median age of 67 years, were 29% female and had high burden of comorbidities

(86% with atrial fibrillation and 71% with arterial hypertension). All patients were on diuretics and had a high utilization of anti-hypertensive/HF medications. At 24 h after undergoing surgical right GSN ablation, there was no significant change in resting CVP (baseline (9.9 ± 5.0 mmHg) to 24 h (7.43 ± 2.99 mmHg); $p = 0.199$), resting PAP-S (baseline (37.0 ± 8.7 mmHg) to 24 h (37.1 ± 8.7 mmHg); $p = 0.898$) or resting PCWP (baseline (15.7 ± 2.7 mmHg) to 24 h (14.9 ± 3.5 mmHg); $p > 0.999$). In contrast, there was a significant reduction in PWCP with 20 W (baseline (28.0 ± 4.3 mmHg) to 24 h (20.7 ± 6.0 mmHg); $p = 0.0124$) and peak exercise (baseline (25.6 ± 2.4 mmHg) to 24 h (18.6 ± 5.4 mmHg); $p = 0.0025$) (Figure 1). There was a non-significant trend toward reduction in PCWP with leg-up (baseline (21.9 ± 3.6 mmHg) to 24 h (17.6 ± 4.2 mmHg); $p = 0.0714$).

Table 1. Baseline demographic characteristics (n = 7).

Age ± SD (years)	67 ± 11
Female (%)	2 (29)
Body Mass Index, median (Interquartile range) (kg/m^2)	30 (29–35)
Comorbidities	
History of Atrial Fibrillation (%)	6 (86)
Hypertension (%)	5 (71)
Diabetes (%)	3 (43)
Coronary Artery Disease (%)	4 (57)
Previous Myocardial Infarction (%)	3 (43)
Left Ventricular Ejection Fraction ± SD (%)	54 ± 7
NYHA Class I/II/III/IV (%)	0/0/100/0
Arterial Blood Pressure, systolic/diastolic ± SD (mmHg)	126/80 ± 15/14
Resting Heart Rate (beats/min)	80 ± 9
NT-proBNP, median (Interquartile range) (pg/mL)	1220 (51–2797)
Creatinine, median (Interquartile range) (mg/dL)	1.1 (1.0-1.5)
eGFR ± SD (mL/min/1.73 m^2)	63 ± 16
Heart failure or anti-hypertension medication	
Loop Diuretic (%)	7 (100)
ACEi or ARB (%)	6 (86)
Beta-Blocker (%)	6 (86)
MRA (%)	6 (86)
CCB (%)	2 (29)
Other vasodilators (%)	1 (14)

Abbreviations: NYHA, New York Heart Association; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; CCB, calcium channel blockers; NT-proBNP, N terminal pro-natriuretic peptide; eGFR, estimated glomerular filtration rate. Results are presented as mean ± standard deviation (SD) unless otherwise specified.

The early (24 h) hemodynamic changes after the GSN ablation correlated well with long-term post-procedure hemodynamic adaptations. There was a similar statistically significant reduction in PCWP with leg-up (16.9 ± 3.8 mmHg; $p = 0.0278$) and 20 W exercise (20.3 ± 6.4 mmHg; $p = 0.0217$) one year after GSN resection compared to baseline. Although the 24 h PCWPs were often lower than those measured after one year, there was no statistically significant differences between the groups for either rest ($p = 0.379$), leg-up ($p = 0.745$), or 20 W exercise ($p = 0.843$).

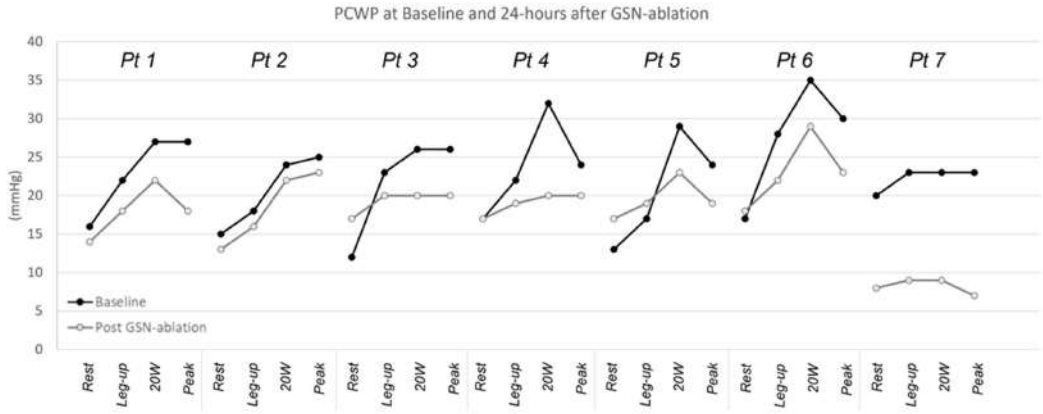

Figure 1. Resting and exercise pulmonary capillary wedge pressure. Abbreviations: GSN, greater splanchnic nerve; PCWP, pulmonary capillary wedge pressure.

Changes were also observed in the intracardiac pressure during the recovery phase of exercise. In all patients, there was a decrease in recovery PCWP in the first 24 h after the procedure vs. baseline (15.6 ± 4.7 vs. 20.4 ± 5.0 mmHg, $p < 0.027$). A similar trajectory was observed in the annual follow-up with mean recovery PCWP of 17.3 ± 9.1 mmHg, although this did not meet statistical significance compared to baseline ($p = 0.31$).

4. Discussion

The persistent hemodynamic and clinical benefits of permanent GSN ablation have been described previously [12]; herein, we describe for the first time in HFpEF patients undergoing permanent right GSN ablation that hemodynamic improvements occur as early as 24 h after the procedure. These results of permanent GSN ablation in HFpEF support the mechanistic insights and immediate hemodynamic benefits seen with temporary GSN modulation in both decompensated hospitalized HF (splanchnic HF-1) [13] and chronic ambulatory HF (splanchnic HF-2) [14]. As opposed to these studies, which enrolled predominantly HFrEF patients (91% HFrEF in splanchnic HF-I and 93% HFrEF in splanchnic HF-II), the current study exclusively enrolled patients with HFpEF. The consistent and favorable effects of GSN modulation on hemodynamics in the HFpEF phenotype is encouraging, as this group historically does not derive the same therapeutic benefits from HFrEF treatments.

Similar to follow-ups at 1, 3, and 12 months [12], the early hemodynamic changes following permanent GSN ablation appear to be more prominent during exercise than at rest, and they failed to reach statistical significance at 24 h follow-up. Conversely, a significant reduction in resting filling pressures was observed in splanchnic HF-I and splanchnic HF-II trials. The greater administration of supporting intravenous fluid and blood product during the surgical procedure as opposed to temporary block procedures may explain, in part, some of the observation differences in resting pressures. Despite this, patients still exhibited significant improvement in exercise hemodynamics, signifying the promising benefits of GSN ablation even in the setting of increased fluid retention. The observed difference may potentially be explained by the incremental effect of bilateral block over unilateral ablation. Nevertheless, the differential effects of GSN ablation on reducing filling pressures only during exercise highlight the important role of the splanchnic nervous system in reducing stressed blood volume that underlies exercise intolerance in HFpEF.

The consistency of hemodynamic and clinical benefits seen across these studies speaks to the importance of the splanchnic vascular reservoir in the pathophysiology of heart

failure independent of ejection fraction. These encouraging results, together with a reasonable safety profile of GSN modulation [10], pave the way for larger randomized controlled studies needed to show long-term benefits, tolerability, and safety in HF, as well as the best technical approach for GSN modulation.

5. Limitations

This study has some limitations, in addition to what was described in the original study, that need to be considered. First, not all patients underwent right heart catheterization at 24 h following surgical GSN ablation at the discretion of the treating physician. This subjects the results to possible selection bias in that only patients who recovered well enough for the catheterization and exercise could have derived greater benefits from the procedure. Second, clinical variables (e.g., weight, NT-proBNP) other than invasive hemodynamic measurements were not recorded at 24 h and were not available for comparison.

6. Conclusions

From the retrospective analysis of the single-arm, open-label, prospective study, a reduction in intracardiac filling pressures during exercise was observed as early as 24 h following permanent right GSN ablation in patients with HFpEF.

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Institutional Review Board Statement: The study was approved by the local ethic committees and was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly due to privacy restrictions.

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7. PODSUMOWANIE I WNIOSKI

W przedstawionych badaniach, opisanych w dwóch pracach oryginalnych składających się na niniejszą rozprawę doktorską (46,47) potwierdzono, że nietolerancja wysiłku fizycznego u chorych z HFpEF jest uwarunkowana licznymi często nakładającymi się procesami, z których wzrost ciśnienia napełniania lewej komory, wtórny do redystrybucji płynów odgrywa znaczącą rolę.

W ramach badań opisanych w publikacji „*Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: first-in-human clinical trial"* (46) wykazano, iż wzrost ciśnienia napełniania lewej komory występuje w wielu przypadkach przy braku przyrostu masy ciała czy towarzyszących cechach przewodnienia, co sugeruje komplementarny udział redystrybucji objętości w mechanizmie nietolerancji wysiłku fizycznego czy dekompensacji układu krążenia (48,49). Proponowana koncepcja podkreśla rolę przesunięć płynów pomiędzy poszczególnymi komparmentami, szczególnie naczyniowym łożyskiem trzewnym, który jest wysoce podatny i zawiera około 30% objętości krwi wewnątrznaczyniowej organizmu, jako możliwej przyczyny wzrostu ciśnienia napełniania lewej komory. Biorąc pod uwagę funkcję modulującą pojemność naczyń trzewnych, nerwy trzewne są integralną częścią regulującą dystrybucję objętości wewnątrznaczyniowej (22,33).
Na podstawie wykonanych badań, udowodniono, że kontrolowana inhibicja współczulnego układu nerwowego poprzez stałą ablacje prawego nerwu trzewnego większego (GSN) wpływa korzystnie na profil hemodynamiczny pacjentów z niewydolnością serca z zachowaną frakcja wyrzutową lewej komory (HFpEF). Po 3 miesiącach od ablacji GSN pacjenci wykazywali zmniejszenie ciśnienia zaklinowania w tętnicy płucnej (PCWP) w czasie wysiłku w porównaniu do wartości wyjściowych. W badanej grupie, 12 miesięcy po zabiegu odnotowano poprawę jakości życia ocenianą za pomocą kwestionariusza Minnesota Living with Heart Failure Questionnaire oraz klasy NYHA. Mając na uwadze brak istotnych zdarzeń niepożądanych ze strony układu sercowo - naczyniowego oraz przewodu pokarmowego oceniono stałą ablację prawego nerwu trzewnego większego jako bezpieczną i dobrze tolerowaną.

W ramach retrospektywnej analizy opisanej w publikacji „*Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction"* (47), wykazano, iż u pacjentów z HFpEF

zmniejszenie ciśnień napełniania lewej komory podczas wysiłku występuje już po 24 godzinach od trwałej ablacji prawego GSN.

Podsumowując, podwyższone ciśnienie napełniania lewej komory w spoczynku i podczas aktywności fizycznej jest kluczową przyczyną objawów niewydolności serca z zachowaną frakcją wyrzutową (HFpEF) i jest wskaźnikiem prognostycznym zachorowalności, dekompensacji sercowo-naczyniowej i ryzyka zgonu w tej grupie pacjentów (50-51).
Do nieprawidłowych ciśnień napełniania (zwłaszcza podczas aktywności fizycznej) przyczynia się szereg mechanizmów, w tym upośledzona relaksacja mięśnia sercowego, nieprawidłowa odpowiedź inotropowa i chronotropowa, zaburzona reakcja wazodylatacyjna oraz zwiększona sztywność naczyń krwionośnych (52). W przebiegu tych nieprawidłowości sercowo naczyniowych dochodzi do przesunięcia krwi między obwodowymi przedziałami naczyniowymi (przede wszystkim trzewnym łożyskiem naczyniowym) a centralnym przedziałem naczyniowym. Niewłaściwa kontrola dystrybucji objętości krwi w organizmie została zaproponowana jako główny mechanizm leżący u podstaw nietolerancji wysiłku w HFpEF (21,22).
Rola nerwów trzewnych w procesie redystrybucji płynów pomiędzy poszczególnymi kompartmentami jest poparta danymi przedklinicznymi i klinicznymi wskazującymi, że stymulacja nerwu trzewnego powoduje ostre zmiany hemodynamiczne, ze spadkiem podatności naczyń trzewnych i wzrostem obciążenia wstępnego serca (33,54). Tak więc celowane zmniejszenie napięcia współczulnego, poprzez ablację nerwu trzewnego większego mogłoby stanowić cel terapeutyczny dla pacjentów z niewydolnością serca z zachowaną frakcją wyrzutową lewej komory.

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47. Gajewski P, Fudim M, Kittipibul V, Engelman ZJ, Biegus J, Zymliński R, Ponikowski P. Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction. J Clin Med. 2022 Feb 18;11(4):1063. doi: 10.3390/jcm11041063. PMID: 35207336; PMCID: PMC8878100.

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9. ZAŁĄCZNIKI

9.1. DOROBEK NAUKOWY DOKTORANTA

Wykaz publikacji

Lek. Piotr Gajewski

1. Publikacje w czasopismach naukowych

1.1 Publikacje w czasopiśmie z IF

Lp	Opis bibliograficzny	IF	Punkty
1	Biegus Jan, Zymliński Robert, Sokolski Mateusz, Siwołowski Paweł, **Gajewski Piotr**, Nawrocka-Millward Sylwia, Poniewierka Elżbieta, Jankowska Ewa A., Banasiak Waldemar, Ponikowski Piotr: Impaired hepato-renal function defined by the MELD XI score as prognosticator in acute heart failure, European Journal of Heart Failure, 2016, vol. 18, nr 12, s. 1518-1521, DOI:10.1002/ejhf.644	6,968	40
2	Biegus Jan, Zymliński Robert, Sokolski Mateusz, **Gajewski Piotr**, Banasiak Waldemar, Ponikowski Piotr: Clinical, respiratory, haemodynamic, and metabolic determinants of lactate in heart failure, Kardiologia Polska, 2019, vol. 77, nr 1, s. 47-52, DOI:10.5603/KP.a2018.0240	1,874	100
3	Biegus Jan, Zymliński Robert, **Gajewski Piotr**, Sokolski Mateusz, Siwołowski Paweł, Sokolska Justyna, Swoboda Katarzyna, Banasiak Maciej, Banasiak Waldemar, Ponikowski Piotr: Persistent hyperlactataemia is related to high rates of in-hospital adverse events and poor outcome in acute heart failure, Kardiologia Polska, 2019, vol. 77, nr 3, s. 355-362, DOI:10.5603/KP.a2019.0030	1,874	100
4	Zymliński Robert, Sierpiński Radosław, Metra Marco, Cotter Gad, Sokolski Mateusz, Siwołowski Paweł, Garus Mateusz, **Gajewski Piotr**, Tryba Joanna, Samorek Maria, Jankowska Ewa A., Biegus Jan, Ponikowski Piotr: Elevated plasma endothelin-1 is related to low natriuresis, clinical signs of congestion, and poor outcome in acute heart failure, ESC heart failure, 2020, vol. 7, nr 6, s. 3536-3544, DOI:10.1002/ehf2.13064	4,411	40
5	Sokolska Justyna Maria, Sokolski Mateusz, Zymliński Robert, Biegus Jan, Siwołowski Paweł, Nawrocka-Millward Sylwia, Swoboda Katarzyna, **Gajewski Piotr**, Jankowska Ewa Anita, Banasiak Waldemar, Ponikowski Piotr: Distinct clinical phenotypes of congestion in acute heart failure: characteristics, treatment response, and outcomes, ESC heart failure, 2020, vol. 7, nr 6, s. 3830-3840, DOI:10.1002/ehf2.12973	4,411	40
6	Sokolski Mateusz, **Gajewski Piotr**, Zymliński Robert, Biegus Jan, Ten Berg Jurrien , Bor Wilbert, Braunschweig Frieder, Caldeira Daniel, Cuculi Florim, D'Elia Emilia, Edes Istvan Ferenc, Garus Mateusz, Greenwood John P., Halfwerk Frank R., Hindricks Gerhard, Knuuti Juhani, Kristensen Steen Dalby, Landmesser Ulf, Lund Lars H., Lyon Alexander, Mebazaa Alexandre, Merkely Bela, Nawrocka-Millward Sylwia, Pinto Fausto J., Ruschitzka Frank, Semedo Edimir, Senni Michele, Sepehri Shamloo Alireza , Sorensen Jacob, Stengaard Carsten, Thiele Holger, Toggweiler Stefan, Tukiendorf Andrzej, Verhorst Patrick M., Wright David Jay, Zamorano Pepe, Zuber Michel, Narula Jagat, Bax Jeroen J., Ponikowski Piotr: Impact of coronavirus disease 2019 (COVID-19) outbreak on acute admissions at the emergency and cardiology departments across Europe, American Journal of Medicine, 2021, vol. 134, nr 4, s. 482-489, DOI:10.1016/j.amjmed.2020.08.043	5,928	140

7	Malek Filip, **Gajewski Piotr**, Zymliński Robert, Janczak Dariusz, Chabowski Mariusz, Fudim Marat, Martinca Tomas, Neuzil Petr, Biegus Jan, Mates Martin, Krüger Andreas, Skalsky Ivo, Bapna Anisha, Engelman Zoar J., Ponikowski Piotr P.: Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: first-in-human clinical trial, European Journal of Heart Failure, 2021, vol. 23, nr 7, s. 1134-1143, DOI:10.1002/ejhf.2209	18,174	200
8	Urban Szymon, Błaziak Mikołaj, Jura Maksym, Iwanek Gracjan, Zdanowicz Agata, Guzik Mateusz, Borkowski Artur, **Gajewski Piotr**, Biegus Jan, Siennicka Agnieszka, Pondel Maciej, Berka Petr, Ponikowski Piotr, Zymliński Robert: Novel phenotyping for acute heart failure - unsupervised machine learning-based approach, Biomedicines, 2022, vol. 10, nr 7, art.1514 [20 s.], DOI:10.3390/biomedicines10071514	4,757*	100
9	**Gajewski Piotr**, Fudim Marat, Kittipibul Veraprapas, Engelman Zoar J., Biegus Jan, Zymliński Robert, Ponikowski Piotr: Early hemodynamic changes following surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction, Journal of Clinical Medicine, 2022, vol. 11, nr 4, art.1063 [6 s.], DOI:10.3390/jcm11041063	4,964*	140
10	Urban Szymon, Fułek Michał, Błaziak Mikołaj, Iwanek Gracjan, Jura Maksym, Fułek Katarzyna, Guzik Mateusz, Garus Mateusz, **Gajewski Piotr**, Lewandowski Łukasz , Biegus Jan, Ponikowski Piotr, Trzeciak Przemysław, Tycińska Agnieszka, Zymliński Robert: COVID-19 related myocarditis in adults: a systematic review of case reports, Journal of Clinical Medicine, 2022, vol. 11, nr 19, art.5519 [27 s.], DOI:10.3390/jcm11195519	4,964*	140
	Podsumowanie	58,325	1040,00

* IF 2021

1.2 Publikacje w czasopiśmie bez IF -

1.3 Publikacje w czasopiśmie - prace kontrybutorskie -

2. Monografie naukowe

2.1 Książka autorska -

2.2 Książka redagowana -

2.3 Rozdziały –

3. Varia -

3.1 Komentarz -

3.2 Inne -

4. Abstrakty

Lp	Opis bibliograficzny
1	Sokolski Mateusz, Sokolska Justyna M., Zymliński Robert, Biegus Jan, Swoboda K., Siwołowski Paweł, **Gajewski Piotr**, Nawrocka-Millward S., Banasiak W., Ponikowski Piotr: The significance of plasma osmolarity for in-hospital course and long-term outcome in patients with acute heart failure, European Journal of Heart Failure, 2019, vol. 21, nr suppl.1, 106-107 poz.P454, [Heart Failure 2019 and the World Congress on Acute Heart Failure. Athens, Greece, 25-28 May 2019. Abstracts]
2	Sokolska Justyna M., Sokolski Mateusz, Zymliński Robert, Biegus Jan, Swoboda K., Siwołowski Paweł, Nawrocka-Millward S., **Gajewski Piotr**, Banasiak W., Ponikowski Piotr: Acute heart failure has many faces - clinical characteristics, response to the treatment and long-term outcome in patients with different physical presentations of cardiac decompensation, European Journal of Heart Failure, 2019, vol. 21, nr suppl.1, 539-540 poz.P2090, [Heart Failure 2019 and the World Congress on Acute Heart Failure. Athens, Greece, 25-28 May 2019. Abstracts]
3	Guzik Mateusz, Sokolski Mateusz, **Gajewski Piotr**, Garus M., Zymliński Robert, Ponikowski Piotr, Biegus Jan: Impact of admission serum osmolarity on decongestion rate and clinical outcomes in patients with acute heart failure, European Heart Journal: Acute Cardiovascular Care, 2022, vol. 11, nr suppl.1, i137 poz.20200, [ESC Acute CardioVascular Care 2022. Online, 18-19 March 2022. Abstract book], DOI:10.1093/ehjacc/zuac041.101
4	Garus M., Fudim Marat, Zymliński Robert, Niewiński Piotr, Paleczny Bartłomiej, Zdanowicz Agata, Iwanek Gracjan, **Gajewski Piotr**, Guzik Mateusz, Ponikowski Piotr, Biegus Jan: Clinical, laboratory associates and prognostic significance of hypocapnia in acute heart failure, European Journal of Heart Failure, 2022, vol. 24, nr suppl.2, s. 174-175, [The Heart Failure 2022 and the World Congress on Acute Heart Failure. Madrid, Spain, 21-24 May 2022. Abstracts]
5	**Gajewski Piotr**, Garus M., Guzik Mateusz, Zymliński Robert, Ponikowski Piotr, Biegus Jan: Relationship between renal function and subsequent readmission for heart failure, European Journal of Heart Failure, 2022, vol. 24, nr suppl.2, s. 175, [The Heart Failure 2022 and the World Congress on Acute Heart Failure. Madrid, Spain, 21-24 May 2022. Abstracts]
6	Guzik Mateusz, **Gajewski Piotr**, Garus M., Zymliński Robert, Ponikowski Piotr, Biegus Jan: Impact of vasopressin and serum osmolarity on outcome in acute heart failure, European Journal of Heart Failure, 2022, vol. 24, nr suppl.2, s. 76, [The Heart Failure 2022 and the World Congress on Acute Heart Failure. Madrid, Spain, 21-24 May 2022. Abstracts]

Impact factor: **58,325**

Punkty ministerialne: **1040,00**

	Punktacja MNiSW
do roku 2018	40,00
od roku 2019	1000,00
Razem:	**1040,00**

9.2. ZGODA KOMISJI BIOETYCZNEJ

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 209/2016

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 78/XV R/2014 z dnia 26 listopada 2014 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy | o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami) w składzie:

prof. dr hab. Maciej Bagłaj (chirurgia, pediatria)
prof. dr hab. Karol Bal (filozofia)
dr hab. Jacek Daroszewski (endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jan Kolasa (prawo)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód (duchowny)
prof. dr hab. Krystyna Orzechowska-Juzwenko (farmakologia kliniczna, choroby wewnętrzne)
prof. dr hab. Zbigniew Rudkowski (pediatria)
dr hab. Sławomir Sidorowicz (psychiatria)
Danuta Tarkowska (położnictwo)
dr hab. Andrzej Wojnar (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)

pod przewodnictwem
prof. dr hab. Jana Kornafela (ginekologia i położnictwo, onkologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.

„Chirurgiczna resekcja nerwu trzewnego większego u osób z niewydolnością serca o zachowanej frakcji wyrzutowej (HFpEF): pierwsze badanie w stadium wykonalności w populacji ludzkiej"

zgłoszonym przez **lek. med. Piotra Gajewskiego** zatrudnionego Ośrodku Chorób Serca 4 Wojskowego Szpitala Klinicznego z Polikliniką we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła wyrazić zgodę na przeprowadzenie badania w Ośrodku Chorób Serca 4 Wojskowego Szpitala Klinicznego z Polikliniką we Wrocławiu pod nadzorem prof. dr hab. Piotra Ponikowskiego.

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu

Opinia powyższa dotyczy: projektu badawczego będącego podstawą rozprawy doktorskiej

Wrocław, dnia 7 czerwca 2016 r.

Uniwersytet Medyczny we Wrocławiu
KOMISJA BIOETYCZNA
przewodniczący
prof. dr hab. Jan Kornafel

EZ

9.3. OŚWIADCZENIA O WSPÓŁAUTORSTWIE

Wrocław, 24.02.2023

Piotr Gajewski

Instytut Chorób Serca

Wrocław, Polska

Oświadczenie o współautorstwie

Niniejszym oświadczam, że w przygotowaniu publikacji pt:

1. Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: first-in-human clinical trial.
   Málek F*, **Gajewski P***, Zymliński R, Janczak D, Chabowski M, Fudim M, Martinca T, Neužil P, Biegus J, Mates M, Krüger A, Skalský I, Bapna A, Engelman ZJ, Ponikowski PP.
   Eur J Heart Fail. 2021 Jul;23(7):1134-1143. doi: 10.1002/ejhf.2209. Epub 2021 Jul 16.
   *These authors contributed equally to this manuscript

2. Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction.
   Gajewski P, Fudim M, Kittipibul V, Engelman ZJ, Biegus J, Zymliński R, Ponikowski P.J Clin Med. 2022 Feb 18;11(4):1063. doi: 10.3390/jcm11041063.

Mój udział polegał na:

Pierwsza publikacja:
- sformułowaniu problemów i hipotez badawczych
- kierowaniu projektem naukowym obejmującym badania opisane w tej pracy
- opracowaniu wyników oraz tworzeniu bazy danych
- analizie statystycznej wyników i ich interpretacji w świetle danych literaturowych
- przygotowaniu manuskrytpu
- nadzorowaniu procesu recenzji i nanoszeniu wymaganych przez recenzentów poprawek

Druga publikacja:
- sformułowaniu problemów i hipotez badawczych
- projektowaniu badania
- analizie statystycznej wyników i ich interpretacji w świetle danych literaturowych
- przygotowaniu manuskrytpu
- krytycznych poprawkach do treści manuskryptu

Gajewski Piotr
.....
podpis

Wrocław, 24.02.2023

Prof. dr hab.n.med. Piotr Ponikowski

Instytut Chorób Serca

Wrocław, Polska

Oświadczenie o współautorstwie

Niniejszym oświadczam, że w przygotowaniu publikacji pt:

1. Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: first-in-human clinical trial.
   Málek F*, **Gajewski P***, Zymliński R, Janczak D, Chabowski M, Fudim M, Martinca T, Neužil P, Biegus J, Mates M, Krüger A, Skalský I, Bapna A, Engelman ZJ, Ponikowski PP.
   Eur J Heart Fail. 2021 Jul;23(7):1134-1143. doi: 10.1002/ejhf.2209. Epub 2021 Jul 16.
   *These authors contributed equally to this manuscript

2. Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction.
   Gajewski P, Fudim M, Kittipibul V, Engelman ZJ, Biegus J, Zymliński R, Ponikowski P.J Clin Med. 2022 Feb 18;11(4):1063. doi: 10.3390/jcm11041063.

Mój udział polegał na:

Pierwsza publikacja:
- sformułowaniu problemów i hipotez badawczych
- kierowaniu projektem naukowym obejmującym badania opisane w tej pracy
- uzyskaniu finansowania badania
- nadzorze merytorycznym nad wynikami badania
- przygotowaniu manuskrytpu
- krytycznych poprawkach do treści manuskryptu

Druga publikacja:
- sformułowaniu problemów i hipotez badawczych
- projektowaniu badania
- nadzorze merytorycznym nad wynikami badania
- przygotowaniu manuskrytpu
- krytycznych poprawkach do treści manuskryptu

Uniwersytet Medyczny we Wrocławiu
Wydział Lekarski
INSTYTUT CHORÓB SERCA
dyrektor
prof. dr hab. Piotr Ponikowski

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Wrocław, 15.02.2023

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Klinika Chirurgii

Wrocław, Polska

Oświadczenia o współautorstwie

Niniejszym oświadczam, że w przygotowaniu publikacji pt:

1. 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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   *These authors contributed equally to this manuscript

Mój udział polegał na:

- sformułowaniu problemów i hipotez badawczych
- projektowaniu badania
- realizacji procedur badania
- nadzorze merytorycznym nad wynikami badania

Chabowski Mariusz
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Wydział Nauk o Zdrowiu
Katedra Pielęgniarstwa i Położnictwa
ZAKŁAD PIELĘGNIARSTWA
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Wrocław, 24.10.2022

dr hab.n.med. Jan Biegus

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- interpretation of the results
- critical comments and corrections to the manuscript content

Second publication:
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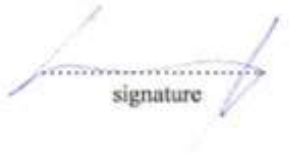

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