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CASE REPORT

Aortic thoracic neuromodulation in heart failure with preserved ejection fraction

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Abstract

The inadequacy of medical therapies for heart failure with preserved ejection fraction (HFpEF) is driving the development of device-based solutions targeting underlying pathophysiologic abnormalities. The maladaptive autonomic imbalance with a reduction in vagal parasympathetic activity and increased sympathetic signalling contributes to the deterioration of cardiac performance, patient fitness, and the increased overall morbidity and mortality. Thoracic aortic vagal afferents mediate parasympathetic signalling, and their stimulation has been postulated to restore autonomic balance. In this first-in-man experience with chronic stimulation of aortic vagal afferents (Harmony™ System, Enopace, Israel), we demonstrate improved left atrial remodelling and function parallel with improved left ventricular performance. The observed favourable structural and functional cardiac changes remained stable throughout the 1 year follow-up and were associated with improved symptoms and physical fitness. The current experience warrants further validation of the endovascular stimulation of aortic thoracic afferents as a new interventional approach for device-based treatment in HFpEF.

Keywords Aortic thoracic neuromodulation; Heart failure with preserved ejection fraction (HFpEF); Autonomic imbalance; Harmony™ system; Enopace

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Introduction

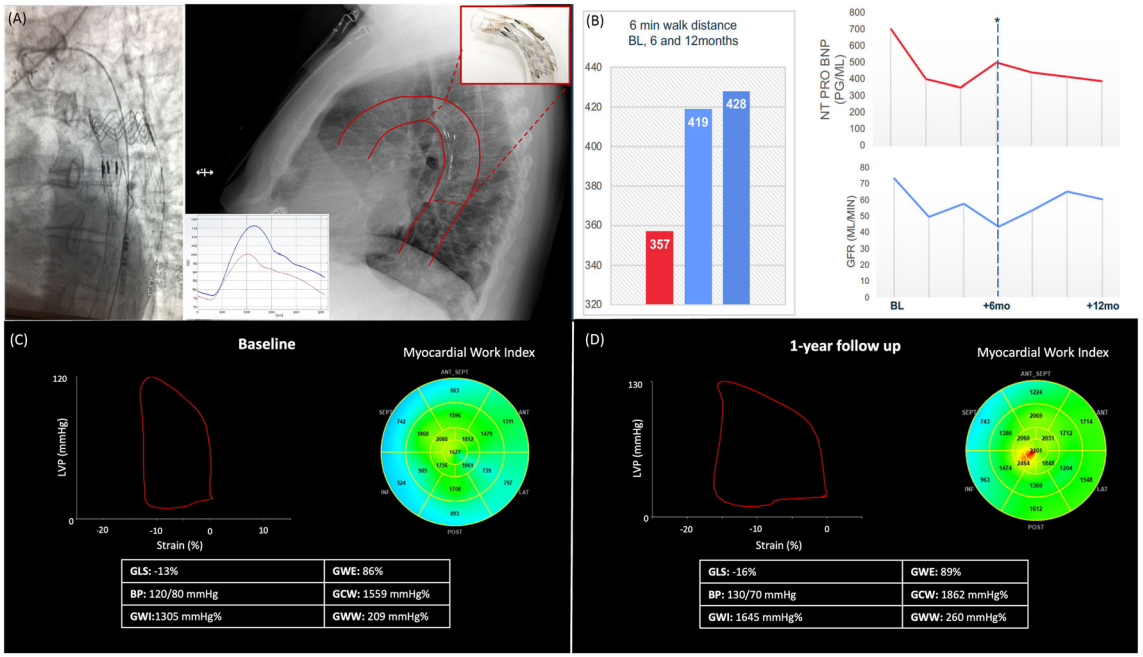
Heart failure with preserved ejection fraction (HFpEF) has become the dominant form of heart failure (HF) and is associated with significantly impaired quality of life and poor clinical outcomes.[1] Its increasing prevalence is affected by the aging population with multiple cardiac and non-cardiac comorbidities.[2,3] The combination of these traits represents a challenge in identifying adequate medical therapies. In fact, medical options and standard of care are often falling short in improving the patient's symptoms and prognosis, stimulating the search for new therapies. Autonomic imbalance with reduced vagal parasympathetic activity and increased sympathetic signalling has been demonstrated as a universal maladaptive response in HF.[4] This imbalance contributes to the deterioration of cardiac performance, patient fitness and overall morbidity and mortality risk.[5,6] Accordingly, approaches that restore autonomic balance are being investigated to improve clinical outcomes. The upper part of the thoracic aorta contains the aortic vagal afferents securing the neural parasympathetic transmission to the brain. In addition, aortic endothelial cells are involved in controlling aortic compliance and participate in overall ventricular-arterial coupling to restore autonomic balance, and ventricular-arterial mismatch.[7,8] Experimental studies indicated that vagal stimulation restores this autonomic balance by increasing parasympathetic activity.[5,6] A recent clinical evaluation of device-based chronic parasympathetic activation at the carotid location was associated with sympathetic withdrawal, reduced HF biomarkers, and improved left ventricular (LV) function.[9] Here, we report the first-in-man experience with an endovascular stent-based platform that modulates parasympathetic tone by chronic stimulation of the aortic vagal afferents.

Case Report

A 71-year-old man with arterial hypertension, type 2 diabetes mellitus, hypercholesterolemia, and obesity presented with increased shortness of breath, NYHA class III, and a history of repeated HF admission. His past medical history included inferior ST-segment elevation myocardial infarction treated with percutaneous coronary intervention of the right coronary artery, chronic kidney disease, and atrial fibrillation. At cardiac catheterization performed during the latest HF hospitalization, a patent stent without progression of coronary atherosclerosis was noted. Left ventricular ejection fraction (LVEF) was normal, while right atrium (RA: 12 mmHg), pulmonary capillary wedge (PCW:25 mmHg), mean pulmonary arterial pressure (PA: 35 mmHg) and pulmonary vascular resistance (PVR:2 WU) were elevated, fulfilling hemodynamic criteria for HFpEF. Specific HFpEF aetiologies were excluded. Considering the persistent dyspnoea in NYHA Class III, despite optimal medical therapy including diuretics, mineral-corticoid antagonist, and SGLT2 inhibitor, the patient was consented and included in the Endo-HF study (**E**ndovascular **N**eurom**O**dulation for **H**eart **F**ailure, NCT02633644) evaluating the safety and early efficacy signals of aortic thoracic stimulation with the Harmony™ System (Enopace, Israel). The Harmony™ System is an implantable neuromodulation platform consisting of an implantable unit, delivery catheter, patient wearable unit, and programming unit. The implantable unit entails a nitinol 'stent-like' implant with a flexible design containing four stimulation platinum/iridium electrodes, a receiving radiofrequency antenna coil consisting of gold covered with Ethylene/PTFE, and a titanium sealed electrical circuit unit as a micro-stimulator. A wearable patient unit can be programmed by a physician to set the therapeutic intensity and duty cycle. Data are then collected and constantly transmitted to the medical reference team, who can control and optimize the therapy per patient response.

At index intervention, the implantable unit was deployed in the target aortic area, identified by detecting blood pressure reduction in response to electrical stimulation in the upper part of descending aorta, just distally of the left subclavian artery using conventional two-dimensional angiography projections (*Figure 1*). The procedure and implant delivery were uneventful. Clopidogrel for 6 months and aspirin for 1 month were initiated, whereas other medication regimens remained unchanged. Twenty-one days after the procedure, neuromodulation therapy was initiated and up-titrated to

Figure 1 (A) Nitinol stent-like device bearing four stimulation platinum/iridium electrodes, a receiving RF antenna coil (gold covered with Ethylene/PTFE), a titanium sealed electrical circuit unit implanted in the target aortic area after checking an adequate response in mean aortic pressure drop. (B) Baseline versus 6 month and 1 year improvements in functional capacity with increase in 6 min walking test (from 357 m at baseline to 419 m) and decrease of NT proBNP (from 703 to 502 pg/mL) without any change in renal function (GFR > 60 mL/min), allowing to reduce bumetanide and spironolactone. (C, D) Baseline versus 1 year improvement of GLS, GWI, and GWE. BL, baseline; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; GFR, glomerular filtration rate; BP, blood pressure; GLS, left ventricular global longitudinal strain; GWI, left ventricular non-invasive global work index; GWE, left ventricular non-invasive global work efficacy; GCW, left ventricular non-invasive global constructive work; GWW, left ventricular non-invasive global wasted work.



an output of 7.5 mA with 1 msec pulse duration, resulting in mean arterial pressure reduction by 8% as measured by the NOVA Finapress continuous blood pressure measurement unit. The patient was instructed to use the system for at least 8 hours per day. In the early days of the stimulation, he reported slight chest discomfort. A control chest X-ray confirmed the stable implant position. The impulse therapy was finetuned from 8.5 to 7 mA, enabling an effective stimulation without the discomfort sensation. He further tolerated therapy well without complaints with a median device use of 10 hours per day. The patient was followed at regular time intervals per study protocol. His symptoms and vital parameters improved over time. He remained in ambulatory care free of new HF-related events. At 6 months follow-up, favourable left atrial (LA) remodelling with reduced LA volume index from 41.3 to 31.6 and increased reservoir strain by 40% were noted in parallel with an improved diastolic filling pattern from Grade 2 to Grade 1, according to the ASE/EACVI 2016 criteria[10] as well as reduced PA pressure **(***Table 1***)**. These improvements were sustained at 12 months of follow-up. LVEF remained unchanged though LV stroke volume (SV) improved. At speckle-tracking analyses, global longitudinal strain (GLS) and non-invasive Global Work Index (GWI) and Global Work Efficacy (GWE), indices of myocardial performance adjusted for afterload, improved at 6 months and remained sustained later at 12 months (*Table 1* and *Figure 1*). Improvements in cardiac structure and function were associated with a clinically significant increase in 6 min walking distance at 6 and 12 months (*Figure 1*) and a reduction of N-terminal prohormone of brain natriuretic peptide (NT-proBNP). It is noteworthy that the NT-proBNP trend showed an upward rise at 6 months follow-up associated with a reduction in glomerular filtration. Given clinical course, bumetanide and spironolactone were reduced while sustaining the neuromod-

Table 1 Clinical and echocardiographic characteristics

	Baseline (08/01/2021)	6 months FU (04/08/2021)	1 year FU (24/01/2022)
Clinical			
BMI (kg/m^2)	34.4	33	33.7
Heart rate (b.p.m.)	57	53	53
Blood pressure (mmHg)	130/80	120/70	120/70
NYHA class	III	I	I
6 min walk test (m)	357	419	428
NT pro-BNP (pg/mL)	703	502	390
GFR (mL/min)	56	57	60
Medical therapy			
Antiplatelets	✓	✓	✓
Anti-coagulation	✓	✓	✓
Beta-blockers	✓	✓	✓
Aldosterone-blocker	✓	✓	✓
Diuretics	✓	✓	✓
RAAS-I	✓	✓	✓
SGLT2-I	✓	✓	✓
Echo parameters			
LVEDD (mm)	51	52	53
LVEDV (mm)	123	132	137
Relative wall thickness	0.27	0.31	0.32
Cardiac filling pattern			
E wave (m/s)	0.84	0.59	0.58
E/A (ratio)	1.24	0.66	0.69
E/e' average	15.3	14.7	14.5
TR V max (m/s)	3.4	3	2.5
TR gradient (mmHg)	47	35	30
LA remodelling			
LAVi (mL/m^2)	41.3	31.6	32
LA Reservoir strain (%)	15	21	20
LV performance			
LVEF (%)	50	50	50
LV SV (mL)	41	65	69
GLS (%)	−13	−15	−16
GWI (mmHg%)	1305	1,521	1,645
GWE (mmHg%)	86	89	89
GCW (mmHg%)	1,559	1868	1862
GWW (mmHg%)	209	289	260

Note: Continuous variables are presented as median (IQR); categorical ones as *n* (%).
Abbreviations: BMI, body mass index; GFR, Glomerular filtration rate; LVEDD, left ventricular end-diastolic diameter; LVEDV, two-dimensional left ventricular end-diastolic volume; 2D LVEF, two-dimensional left ventricular ejection fraction; LV SV, pulsed wave Doppler left ventricular stroke volume; TR, tricuspid regurgitation; LAVi, left atrium volume index. GLS, left ventricular global longitudinal strain; GWI, left ventricular global myocardial work index; GWE, left ventricular global myocardial work efficiency; GCW, left ventricular global myocardial constructive work; GWW, left ventricular global wasted myocardial work.

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ulation therapy. In further course, the patient remained asymptomatic, NT-proBNP further declined while renal function improved. The patient maintained his daily physical activities, including part-time work.

Discussion

Treatment of HFpEF remains challenging. Besides targeting the comorbidities, the evidence-based medical treatment remains limited to diuretics, mineralocorticoid antagonists, and, more recently, empagliflozin or a dual angiotensin-neprilysin inhibitor in females, often with suboptimal impact on symptoms and prognosis.[11,12] Accordingly, new device-based strategies addressing universal pathophysiological traits in HFpEF are being explored.[13] By disrupting the adverse sympathetic trafficking in HF, neuromodulation aims to restore altered autonomic balance. Neuromodulation therapy with augmented baroreflex signalling has been tested successfully in resistant arterial hypertension.[14,15] In HFpEF baroreceptor activation therapy (BAT) of the carotid receptors resulted in clinical improvement with better quality of life and reduced re-hospitalization rates.[16] Thoracic aortic stimulation may provide a novel endovascular approach performed within the standard interventional setting. The present neuromodulation procedure with the Harmony™ System is unique as it allows immediate verification of early hemodynamic response upon acute stimulation and offers individualized finetuning and up-titration of therapy. Treatment cycles are intermittent, and non-gated on–off, enabling a sufficient washout period to avoid tachyphylaxis and thus mitigating the risk of negative feedback for prolonged vagal parasympathetic activity and attenuation of the therapeutic efficacy over time. This current first-in-man experience of chronic aortic stimulation demonstrates favourable changes in cardiac structure and function, associated with improved symptoms and physical fitness, with stable treatment intensity without a decline in responsiveness, up to a 1 year follow-up. Nevertheless, long-term data exploring potential negative feedback loops on the effectiveness of neuromodulation are required.

In-depth echocardiography speckle-tracking strain analysis provides new hypothesis-generating insights into potential mechanisms accounting for neuromodulation-related benefit in HFpEF. Non-invasive assessment of myocardial work (MW) integrates both mechanical and energetic-metabolic components, i.e. stroke work and myocardial oxygen consumption, offering additional insight into the pathophysiology by estimating LV wasted energy and efficacy of the contraction (GWE). Although the contractile performance of the myocardium is dependent on energy production by substrate oxidation, not all energy generated by oxidative metabolism is converted into effective work. In HFpEF, the impaired relaxation and lower LV compliance as well as increased aortic resistance are responsible for the higher energy production needed for the overall contraction-relaxation cycle.[17–19] Thus, as part of this energy is wasted, mechanical efficiency is undermined, as evidenced in HFpEF patients with acute heart failure.[20] In the current first-in-man experience, the restored autonomic balance has been associated with improved MW efficiency, suggesting improved mechano-energetic coupling.

Beneficial myocardial improvements were associated with mild LV dilation. The increase in LV end-diastolic volume (LVEDV) together with higher SV and unchanged LVEF is consistent with the recruitment of preload reserve in improving mechanical efficiency. Although hypothetical, this observation might be related to a nitric oxide-cyclic guanosine monophosphate (cGMP) right and downward shift in the diastolic pressure-volume relationship.[3,21] This hypothesis requires further validation by direct assessment of cGMP levels and urine output, before and after stimulation. Alternatively, afterload reduction triggered by reduced sympathetic activity and/or improved coronary microvascular function might also contribute to the observed effects.[22] Overall, these beneficial structural and functional effects resulted in a sustained improvement in exercise performance through 1 year follow-up, tracked by a reduction in NT-proBNP despite the reduction of diuretics and mineralocorticoid antagonists. If similar efficacy signals can be confirmed in a larger patient population and over long-term follow-up, this therapy may offer a viable therapeutic option in HFpEF.

In summary, endovascular thoracic aorta neuromodulation therapy appears to exert favourable effects on cardiac structure and function consistent with improved symptoms and physical fitness. This early experience warrants further validation of neuromodulation therapy as an effective therapy to improve outcomes in patients with HF.

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Conflict of interest

AD is employee of Enopace. Other authors report no conflicts of interest.

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Author contributions

P.P. and E.G wrote the first draft of the manuscript. D.T.B., C. D.C., and A.M. collated data. J.B., A.D., M.V.D., I.D., and M.P. corrected and approved the revisions and final version of the manuscript. A.D. and J.B. are responsible for the conception and design of the study. J.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the final version of the manuscript.

Statement of guarantor

J.B. is the guarantor of the research.

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