Scientific letter

Baroreflex activation therapy in patients with heart failure and reduced ejection fraction

Activación barorrefleja en pacientes con insuficiencia cardiaca y fracción de eyección reducida

To the Editor,

Baroreflex activation therapy (BAT) reduces sympathetic nervous system activity and boosts the parasympathetic nervous system. BAT has been shown to improve quality of life, functional class, and natriuretic peptide levels in patients with heart failure (HF) and reduced ejection fraction (HFrEF) who are not eligible for cardiac resynchronization therapy (CRT) and remain symptomatic despite pharmacologic treatment.[1,2] Little, however, has been published on the effectiveness or safety of BAT in real-world settings.[3,4] In addition, the latest European and American HF guidelines do not establish a level of recommendation for BAT.[5,6] The aims of this study were to describe the clinical profile of the first cohort of patients to be implanted with Barostim Neo System (CVRx, USA) in Spain and to evaluate the safety and effectiveness of this device in clinical practice.

Informed consent was deemed unnecessary by the ethics committee of the coordinating center due to the observational nature of the study. We conducted a retrospective cohort study of 21 consecutive patients with HFrEF who received an implantable Barostim Neo System at a Spanish hospital between February 2017 and December 2021 and had follow-up data for 1 year. The hospitals and principal investigators are listed in the appendix. The patients' baseline characteristics are summarized in table 1 and compared with those of the patients in the intervention group in the pivotal BeAT-HF clinical trial.[2] The device was activated 17.9 ± 8.2 days after surgery. The mean amplitude achieved was 6.6 ± 1.3 mA, with a mean pulse width of 129 ± 12 μs and a mean therapy frequency of 40 pulses/s per patient. Heart rate and blood pressure decreased, but not significantly, after activation of the BAT device. The mean number of annual hospitalizations for HF after implantation of the Barostim Neo System was 1.52, which was significantly lower than the previous year (0.76, $P = .042$). A trend towards improved New York Heart Association (NYHA) functional class was also observed after 1 year of follow-up ($P = .054$). There were no differences in the annual number of outpatient intravenous diuresis visits before and after implantation (24 vs 20, $P = .450$). There were also no differences between baseline and follow-up at 1 year for mean left ventricular ejection fraction (LVEF) (30% ± 9.8% vs 31.8% ± 11.2%, $P = .689$), mean left ventricular end-diastolic diameter (58.79 ± 6.2 vs 60.6 ± 5 mm, $P = .325$), or median N-terminal pro–B-type natriuretic peptide (NT-proBNP) (1119 [interquartile range, 450-2763] vs 1149 [499-4798] pg/mL; $P = .756$) (figure 1). None of the patients developed local complications, and they had a similar

Table 1
Comparison of baseline characteristics between Spanish cohort and patients in BeAT-HF clinical trial

Baseline characteristic	Spanish cohort (n = 21)	BeAT-HF (n = 130)	*P*
Women, No.	19	20	.847
Age, y	67 ± 10	62 ± 11	.045
Body mass index	28.4 ± 5	31 ± 5	.036
Systolic blood pressure, mmHg	120 ± 14	120 ± 17	1
Diastolic blood pressure, mmHg	75 ± 9	73 ± 10	.360
Heart rate, bpm	74 ± 15	75 ± 10	.771
GFR, ml/min/m^2	50.4 ± 26.9	63.6 ± 16.8	.040
NT-proBNP, pg/mL	1119 [450-2763]	731 [475-1021]	< .001
NYHA III, %	86	93	.469
LVEF, %	30 ± 9.8	27 ± 7	.190
Atrial fibrillation, %	76	29	< .001
ACE inhibitors/ARA-II/ARNIs, %	100	88	.520
MRA, %	90	48	< .001
Beta-blockers, %	66	95	< .001
Diuretics, %	100	85	.468
[a]SGLT2 inhibitors, %	52	—	—
ICD, %	71	78	.528
[a]CRT, %	29	—	—

ACE, angiotensin-converting enzyme; ARA-II, angiotensin II receptor antagonists; ARNIs, angiotensin receptor neprilysin inhibitors; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association functional class; SGLT2, sodium-glucose cotransporter type 2.
Values are expressed as No. (%), mean ± standard deviation, or median [interquartile range].
[a] The BeAT-HF trial did not specify how many patients were on SGLT2 inhibitors or CRT.

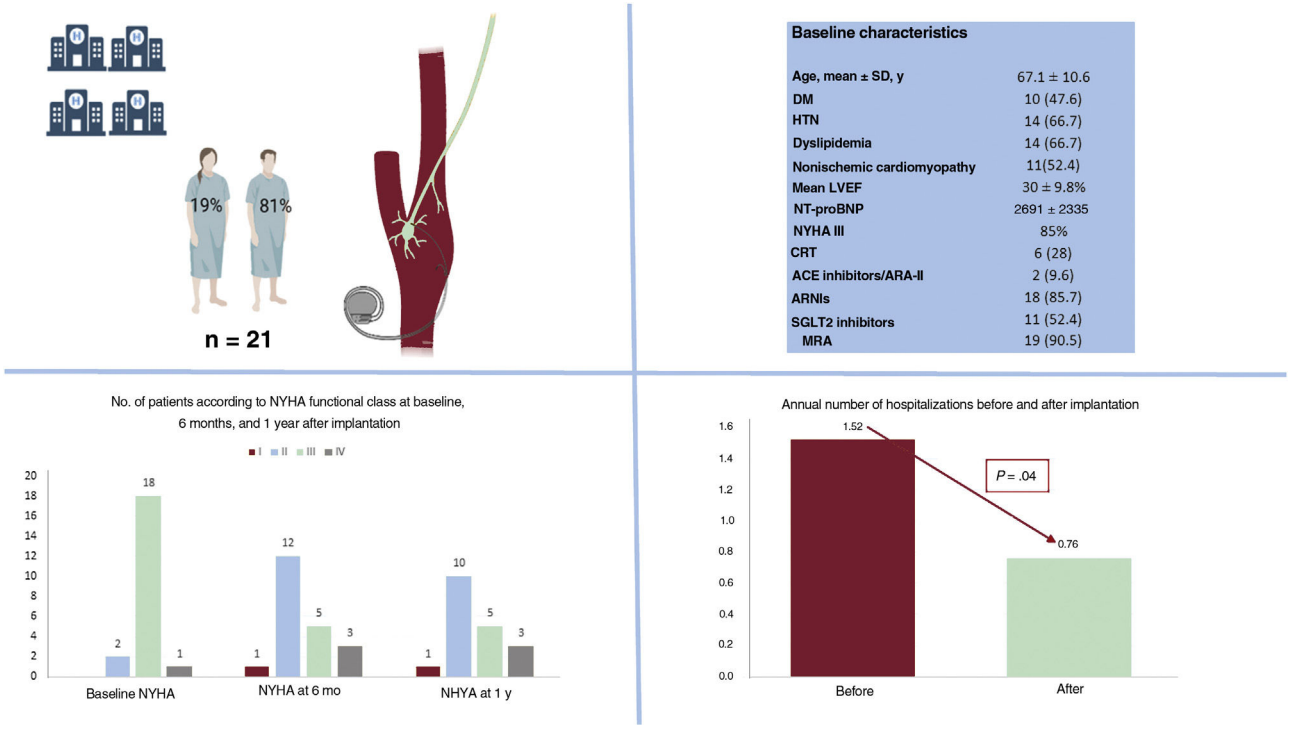

Figure 1. Comparison of annual events before and after implantation of the Barostim Neo System: mean number of hospitalizations for heart failure and mean NYHA functional class. Main baseline characteristics. ACE, angiotensin-converting enzyme; ARA-II, angiotensin II receptor antagonists; ARNIs, angiotensin receptor neprilysin inhibitors; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; HTN, hypertension; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; SD, standard deviation; SGLT2, sodium-glucose cotransporter type 2.

number of appropriate implantable cardioverter-defibrillator therapies in the year before and after implantation (0.53 vs 0.58; $P = .902$). Three patients (14.2%) developed minor BAT-related complications (hoarseness, dry cough, and neck pain) during the 12 months of follow-up. None of the complications required treatment discontinuation and all were resolved by adjusting the stimulation parameters. Three patients (14.2%) died during follow-up: 2 of refractory HF and 1 of stroke unrelated to BAT.

This is the first study to present real-world data on BAT for HFrEF in Spain. Use of the Barostim Neo System in a population with symptomatic HF despite optimal medical management was associated with a reduction in hospitalizations for HF and a trend towards improved NYHA functional class at 1 year, with no significant complications. Our findings corroborate previous reports showing that BAT is a safe option for patients with HFrEF[1,2] and highlight the prognostic benefits of this treatment (in our case, fewer admissions for HF). No improvements were observed for natriuretic peptide levels, NYHA functional class, or LVEF at 1 year, but this is probably due to the small sample size and short follow-up period. In this first cohort of patients to receive BAT in Spain, the reduction in hospitalizations for HF is significant, as, compared with patients in the BeAT-HF trial,[2] they were considerably older and had worse kidney function, a higher prevalence of atrial fibrillation, and higher NT-proBNP levels, generally indicating more advanced HF despite optimal pharmacologic and device therapy. (Although BAT is indicated for patients who are not considered eligible for CRT, almost one-third of the patients in our cohort were receiving CRT.) We also consider that BAT could be an attractive alternative for patients intolerant to beta-blockers (34% of the present cohort). In such cases, the device settings were adjusted to achieve a stimulation energy similar to that observed in patients who tolerate these drugs (6.8 vs 6.9 mA, $P = 0.449$). This potential benefit, however, needs to be confirmed in studies designed to specifically test this hypothesis. BAT might also be useful in patients with chronic renal failure and diuretic resistance, as we observed a trend towards a reduced need for loop diuretics and lower doses of these drugs at 1 year. There was also some stabilization of glomerular filtration at this point. From a mechanistic perspective, the immediate inhibition of the sympathetic nervous system achieved by BAT could lead to greater blockade of the renin-angiotensin-aldosterone system, ultimately, resulting in cardiorenal protective effects. Again, this theory needs to be tested.

In conclusion, the 1-year results of this real-world Spanish study of BAT in patients with HFrEF who remain symptomatic despite optimal medical management are positive, as the patients required significantly fewer hospitalizations for HF, showed a trend towards improved NHYA functional class, and experienced no major complications. Long-term data from ongoing clinical trials and new findings from clinical practice will help position this promising technique in the treatment algorithm for patients with HFrEF.

FUNDING

The authors declare that they did not receive any funding for this study.

ETHICAL CONSIDERATIONS

This study was approved by the ethics committee of the coordinating center. Informed consent was not deemed necessary due to the observational, retrospective nature of the study. As a limitation, the SAGER (Sex and Gender Equity in Research) guidelines were not applied.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used in this study.

AUTHORS' CONTRIBUTIONS

D. Cordero Pereda and C. de Rueda Panadero contributed equally to this work as first authors and prepared the initial draft of the manuscript. D. Cordero Pereda and J. Álvarez-García conceived and designed the study and analyzed the data. C. de Rueda Panadero, J. de Juan Bagudá, M. Gómez Bueno, and A. Robles-Mezcua collected and interpreted the data and participated in the critical review and discussion. All authors approved the final version of the manuscript for publication.

CONFLICTS OF INTEREST

The authors do not have conflicts of interest in relation to this article.

APPENDIX. PRINCIPAL INVESTIGATORS AND PARTICIPATING CENTERS

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Baseline resting heart rate and responsiveness to a home-based inspiratory muscle training program in long COVID

Frecuencia cardiaca basal en reposo y respuesta a un programa domiciliario de entrenamiento de la musculatura inspiratoria en COVID persistente

To the Editor,

Individuals with long COVID may exhibit alterations in heart rate (HR), including an elevated resting HR (rest-HR) or diminished HR variability, among other abnormalities. These perturbations in HR dynamics are believed to be linked to underlying autonomic dysfunction and are associated with higher self-reported symptoms.[1,2]

Under normal physiological conditions, the diaphragm plays a pivotal role in modulating HR variability and regulating sympathetic tone.[3] Previous evidence has suggested that improved muscle function may have a beneficial effect on cardiovascular function and the re-establishment of sympathovagal balance facilitated by ergoreflex modulation.[4] Given these considerations, we hypothesized that, in long COVID individuals with higher baseline sympathetic tone surrogates, improved respiratory muscle function through inspiratory muscle training (IMT) may further enhance tolerance to physical activity by regulating sympathetic activation and cardiovascular stress. In this post