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HEART FAILURE AND CARDIOMYOPATHIES

CLINICAL CASE SERIES

# Baroreflex Activation Therapy in HFrEF Patients

## Anti-Inflammatory Effects and Autonomic Restoration

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**ABSTRACT**

**BACKGROUND** Baroreflex activation therapy (BAT) may ameliorate autonomic imbalance in patients after heart failure with reduced ejection fraction (HFrEF); however, its effects on systemic inflammation and autonomic indices remain unknown.

**CASE SUMMARY** Seven patients with advanced HFrEF underwent BAT implantation. Three cases are presented in detail, illustrating distinct response patterns: clinical improvement, robust parasympathetic restoration, and anti-inflammatory response.

**DISCUSSION** After BAT, patients demonstrated improvements in quality of life, heart rate variability (HRV), and inflammatory biomarkers (tumor necrosis factor-α, interferon-γ). These preliminary findings suggest that BAT may exert therapeutic benefits through both autonomic restoration and anti-inflammatory modulation.

**TAKE-HOME MESSAGES** An aggregate analysis of 7 patients with HFrEF who received BAT demonstrated favorable responses in inflammatory biomarkers, HRV, and clinical outcomes. BAT led to decrease in tumor necrosis factor-α and interferon-γ and autonomic balance restoration as measured by HRV. These findings support further investigation into the mechanisms of action of BAT. (JACC Case Rep. 2026;31:108309) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Heart failure with reduced ejection fraction (HFrEF) is a syndrome associated with substantial morbidity, frequent hospitalizations, and high mortality.[1] While guideline-directed medical therapy (GDMT) improves outcomes in most patients, there is a large population who remain symptomatic despite medical optimization.[2] Recent studies have implicated imbalance between sympathetic and parasympathetic function, as well as immune dysfunction, in the pathophysiology of HFrEF.[3] The condition is associated with cardiac and systemic immune dysfunction, for which there is strong mechanistic and clinical evidence.[4] Autonomic imbalance may itself be implicated in the

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## ABBREVIATIONS AND ACRONYMS

**6MWT** = 6-minute walk test

**BAT** = baroreflex activation therapy

**GDMT** = guideline-directed medical therapy

**HFrEF** = heart failure with reduced ejection fraction

**HRV** = heart rate variability

**ICD** = implantable cardioverter-defibrillator

**IFN-γ** = interferon-gamma

**LVEF** = left ventricular ejection fraction

**NT-proBNP** = N-terminal pro-B-type natriuretic peptide

**TNF-α** = tumor necrosis factor-alpha

pathogenesis of inflammation, as sensory vagal and spinal afferents are activated by inflammatory cytokines, and vagal and sympathetic efferents regulate the systemic inflammatory response through the splenic neuroimmune pathway.[5] Chronic systemic inflammation due to release of damage-associated molecular patterns may exacerbate HFrEF and contribute to cardiac hypertrophy and fibrosis.[1]

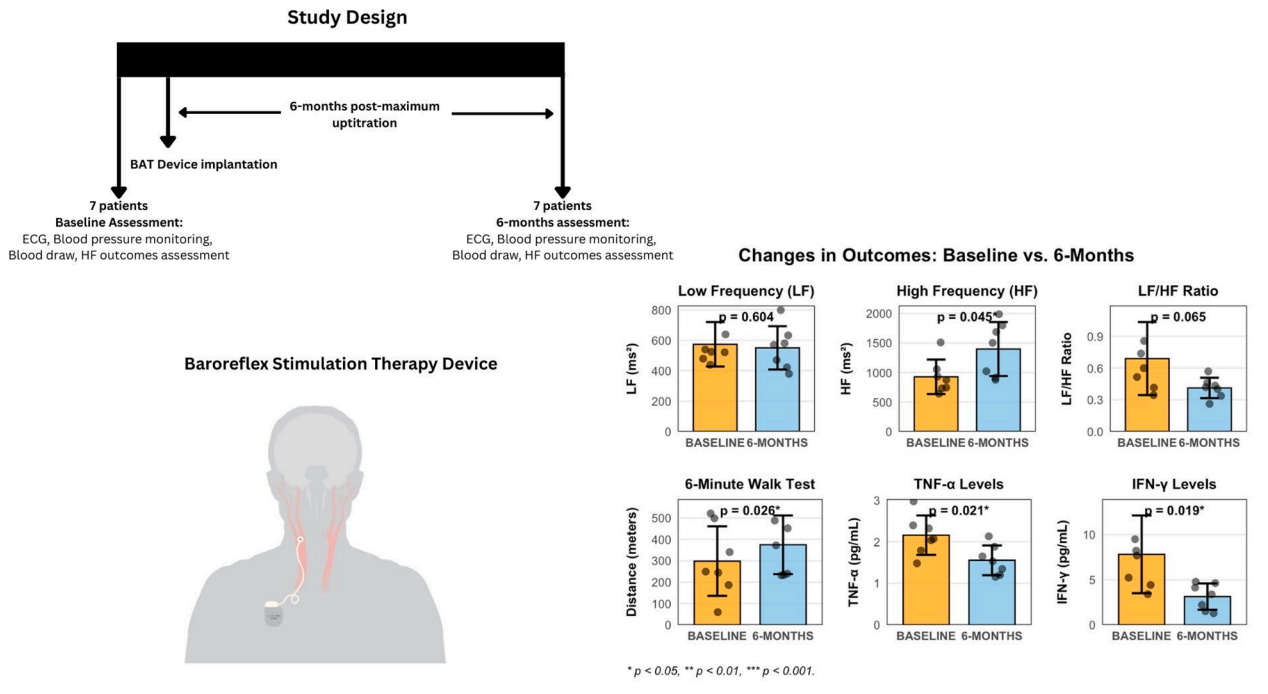
Baroreflex activation therapy (BAT) has emerged as a promising treatment modulating cardiac afferent signaling to the brain via the carotid sinus nerve.[6,7] Preclinical and clinical studies have shown that BAT reduces sympathetic tone and enhances parasympathetic tone to the heart, increasing heart rate variability (HRV), a commonly used index of autonomic balance that is affected in HFrEF.[7,8] This raises the intriguing possibility that BAT may exert part of its beneficial effects in HFrEF by modulating the systemic inflammatory state. However, the effects of BAT on inflammatory markers of patients with HFrEF are unknown.

### TAKE-HOME MESSAGES

- An aggregate analysis of 7 patients with HFrEF who received BAT demonstrated favorable responses in inflammatory biomarkers, heart rate variability, and clinical outcomes.
- BAT led to decreases in TNF-α and IFN-γ and autonomic balance restoration as measured by heart rate variability.
- The study findings support further investigation into the mechanisms of action of BAT therapy.

Given the dual challenge of sympathovagal imbalance and inflammatory mechanisms in HFrEF, this study aimed to determine the immunologic profile and HRV of patients before and after BAT treatment, in addition to assessing clinical variables. By investigating these parameters, we sought to better understand the mechanisms by which BAT

**VISUAL SUMMARY** **Baroreflex Activation Therapy in Patients With HFrEF: Dual Mechanisms of Autonomic Restoration and Anti-Inflammatory Modulation**




Baroreflex activation therapy (BAT) stimulates the carotid sinus, leading to improved parasympathetic tone and reduced systemic inflammation, resulting in clinical improvement in patients with HFrEF. ECG = electrocardiogram; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; IFN = interferon; TNF = tumor necrosis factor.

may ameliorate the burden of HFrEF and potentially offer a substantial improvement in clinical outcomes.

Herein, we present an aggregate analysis of 7 patients with advanced HFrEF treated with BAT, with assessments of inflammatory biomarkers (tumor necrosis factor-alpha [TNF-α], interferon-gamma [IFN-γ]) and autonomic function (HRV characteristics)—parameters not previously reported in the BAT literature—as well as clinical outcomes (6-minute walk test [6MWT], number of heart failure hospitalizations, and Minnesota Living with Heart Failure Questionnaire [MLHFQ] scores). We also highlight 3 of these cases suggesting potential mechanisms of action that may partially explain the sustained clinical benefits observed with this therapy.

## AGGREGATE ANALYSIS

We analyzed aggregate data from 7 consecutive patients treated with BAT at our institution from 2022 to 2024 (mean follow-up: 8 months). Outcomes were assessed at baseline and at 6 months after maximum device uptitration, HRV, and inflammatory profiles. The baseline characteristics of all patients are shown in **Table 1**, and the difference in HRV and clinical parameters between baseline and 6-month follow-up are shown in **Table 2** and **Figure 1**.

## CASE PRESENTATIONS

To illustrate the diversity of response patterns and elucidate the mechanisms underlying these aggregate findings, we present 3 representative cases that exemplify distinct therapeutic phenotypes.

**CASE 1: BEST CLINICAL RESPONSE.** A 61-year-old woman with a history of nonischemic dilated cardiomyopathy presented with persistent NYHA functional class III symptoms despite GDMT, including sacubitril-valsartan 97 to 103 mg twice daily, metoprolol succinate 200 mg twice daily, and furosemide 20 mg weekly. Her medical history included diabetes mellitus, hypertension, obesity (body mass index: 36.4 kg/m$^2$), diverticulosis, and breast cancer with subsequent mastectomy/lumpectomy with chemotherapy and radiation therapy. She had experienced 5 heart failure hospitalizations in the 12 months before evaluation, representing a high-risk phenotype with frequent decompensation despite optimal medical management.

**TABLE 1 Baseline Characteristics of All Treated Patients (N = 7)**

| | |
|---|---|
| Age, y | 69.04 ± 8.74 |
| Female | 2 (28.57) |
| Race | |
| White | 3 (42.86) |
| Black | 1 (14.29) |
| Asian | 0 (0.0) |
| Hispanic | 2 (28.57) |
| Other or missing | 1 (14.29) |
| Body mass index | 30.69 ± 4.03 |
| NYHA functional status | |
| Class I | 0 (0.0) |
| Class II | 4 (57.14) |
| Class III | 3 (42.86) |
| Class IV | 0 (0.0) |
| LVEF, % | 24.55 ± 11.58 |
| Blood pressure, mm Hg | |
| Systolic | 108.44 ± 11.69 |
| Diastolic | 67.18 ± 9.61 |
| eGFR | 54.90 ± 29.25 |
| Device type | |
| Single-chamber ICD | 2 (28.57) |
| Dual-chamber ICD | 1 (14.29) |
| Biventricular ICD | 4 (57.14) |
| Comorbidities | |
| Diabetes mellitus | 2 (28.57) |
| Hypertension | 6 (85.71) |
| Liver disease | 0 (0.0) |
| Renal failure | 1 (14.29) |
| Coronary artery disease | 1 (14.29) |
| Pulmonary disease | 0 (0.0) |
| Types of prior arrhythmia | |
| AF/AFL/AT | 3 (42.85) |
| VT | 2 (28.57) |
| PVC | 2 (28.57) |
| Type of cardiomyopathy | |
| Ischemic | 1 (14.29) |
| Nonischemic | 6 (85.71) |
| Medications | |
| ACEi/ARB | 1 (14.29) |
| ARNI | 6 (85.71) |
| Beta-blocker | 7 (100.0) |
| MRA | 4 (57.14) |
| SGLT2i | 4 (57.14) |
| Diuretics | 4 (57.14) |
| AAD | 1 (14.29) |

Values are as mean ± SD or n (%).

AAD = antiarrhythmic drug; ACEi = antiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; AT = atrial tachycardia; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; PVC = premature ventricular contraction; SGLT2i = sodium glucose cotransporter-2 inhibitor; VT = ventricular tachycardia.

**TABLE 2 Characteristics at Baseline and After 6 Months of Baroreflex Activation Therapy**

| | Baseline | 6-Month Follow-Up | *P* Value |
|---|---|---|---|
| Clinical outcomes | | | |
| 6MWT distance (m) | 298.3 ± 162.2 | 374.5 ± 137.1 | 0.02 |
| Heart failure hospitalizations[a] | 3 (0-4) | 0 (0-0) | 0.007 |
| Heart rate variability | | | |
| LF (nu) | 573.1 ± 146.2 | 549.7 ± 142.4 | 0.6 |
| HF (nu) | 927 ± 291.8 | 1,397 ± 457 | 0.04 |
| LF/HF ratio | 0.68 ± 0.34 | 0.41 ± 0.09 | 0.06 |
| SDNN (ms) | 92 (89-105) | 101 (91-109) | 0.03 |
| RMSSD (ms) | 40.57 ± 9.07 | 41.71 ± 9.12 | 0.38 |
| Inflammatory biomarkers | | | |
| TNF-α | 2.15 ± 0.47 | 1.55 ± 0.35 | 0.02 |
| IFN-γ | 7.82 ± 4.3 | 3.14 ± 1.45 | 0.01 |
| MLHFQ score | | | |
| Overall | 63 (57-71.5) | 21 (19.5-21.75) | 0.002 |
| Physical subscale | 22 (13-27) | 8 (0-11) | 0.04 |
| Emotional subscale | 15 (5-20) | 5 (0-5) | 0.02 |

Values are mean ± SD or median (IQR). [a]Heart failure hospitalizations were measured 12 months before and 12 months after baroreflex activation therapy device implantation.

6MWT = 6-minute walk test; HF = high-frequency; INF = interferon; LF = low-frequency; MLHFQ = Minnesota Living with Heart Failure Questionnaire; RMSSD = root mean square of the successive differences; SDNN = standard deviation of the normal-to-normal intervals; TNF = tumor necrosis factor.

Baseline assessment:

- Left ventricular ejection fraction (LVEF): 30%
- N-terminal pro-B-type natriuretic peptide (NT-proBNP): 642 pg/mL
- Device: single implantable cardioverter-defibrillator (ICD) placed in September 2023, 8 months before BAT
- 6MWT distance: 61 m
- MLHFQ score: 52
- Heart failure hospitalizations in prior 12 months: 5
- Electrocardiogram: normal sinus rhythm

Baseline laboratory studies:

- Estimated glomerular filtration rate: >60
- Inflammatory markers:
  - TNF-α: 2.08 pg/mL
  - IFN-γ: 7.7 pg/mL

Baseline HRV:

- Low-frequency power: 874
- High-frequency power: 642
- Low-frequency/high-frequency power ratio: 01.36

A Barostim device (CVRx Inc) was implanted in May 2024. The pulse generator was placed in a subcutaneous pocket on the right chest wall with the electrode positioned on the right carotid sinus. No procedural details or complications were detected. Device activation occurred 2 weeks after implantion, with gradual uptitration over 3 months to maximum tolerated settings: (8.4 mA, 125 uS, 40 pps).

The results at the 6-month follow-up after maximum uptitration were as follows.

Clinical course:

- NYHA status improved to class I
- LVEF: 35%-40% (Δ: +17%-33%)
- 6MWT distance: 243 m (Δ: +298%)
- MLHFQ score: 21 (Δ: −60%)
- Heart failure hospitalizations: 0 in subsequent 12 months
- No device-related complications
- Sacubitril-valsartan was reduced to 49 to 51 twice daily owing to hypotension with Barostim uptitration

Laboratory response:

- TNF-α: 1.19 pg/mL (−43% from baseline)
- IFN-γ: 3.37 pg/mL (−56% from baseline)
- NT-proBNP: <36 pg/mL

HRV response:

- Low-frequency power: 798 (Δ: −9%)
- High-frequency power: 1987 (Δ: +209%)
- Low-frequency/high-frequency power ratio: 0.4 (Δ: −71%)

What makes this case notable:

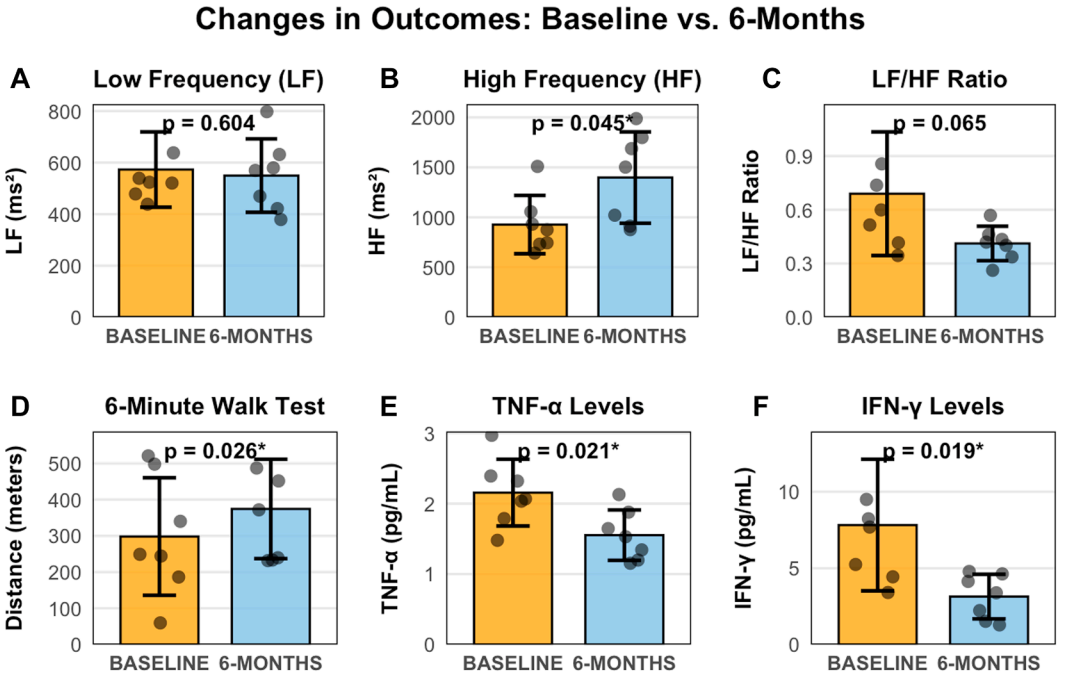
- Female patient with high baseline hospitalization rate (5 hospitalizations in 12 months and 0 hospitalizations after BAT).

**CASE 2: BEST HRV RESPONDER.** An 81-year-old man with a long-standing history of ischemic cardiomyopathy presented with persistent NYHA functional class III symptoms despite GDMT including metoprolol succinate 25 mg once daily, furosemide 20 mg once daily, and empagliflozin 10 mg once daily. His medical history included: persistent atrial fibrillation maintained on amiodarone 200 mg once daily with anticoagulation (apixaban 5 mg twice daily), anterior wall myocardial infarction with subsequent ischemic cardiomyopathy, severe mitral regurgitation, severe pulmonary hypertension, diabetes mellitus, hypertension, and obesity. He had experienced 5 heart failure hospitalizations in the 12 months before evaluation.

Baseline assessment:

- LVEF: 25%
- NT-proBNP: 1,871 pg/mL
- Device: biventricular ICD implanted in 2017, 6 years before BAT

**FIGURE 1** Changes in Autonomic Function and Clinical Parameters at Baseline and After 6 Months of Baroreflex Activation Therapy




(A to C) Heart rate variability measures and (D to F) clinical parameters were assessed at baseline and after 6 months of treatment: (A) Low-frequency power, (B) high-frequency power, (C) low-frequency/high-frequency power ratio, (D) 6-minute walk test distance, (E) tumor necrosis factor (TNF)-α, and (F) interferon (IFN)-γ. Data are presented as mean ± standard deviation. Individual data points are shown. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ by paired $t$-test.

- 6MWT distance: 61 m
- MLHFQ score: 52
- Heart failure hospitalizations in prior 12 months: 0
- Electrocardiogram: normal sinus rhythm

Baseline laboratory studies:

- Estimated glomerular filtration rate: 44
- Inflammatory markers:
  - TNF-α: 2.08 pg/mL
  - IFN-γ: 7.7 pg/mL

Baseline HRV:

- Low-frequency power: 478
- High-frequency power: 931
- Low-frequency/high-frequency power ratio: 0.51

A Barostim device was implanted in 2017. The pulse generator was placed in a subcutaneous pocket on the right chest wall with the electrode positioned on the right carotid sinus. No procedural details or complications were detected. Device activation occurred 2 weeks after implantation, with gradual uptitration over 2 months to maximum tolerated settings (8.6 mA, 125 uS, 40 pps).

The results at the 6-month follow-up after maximum uptitration are as follows.

Clinical course:

- LVEF: 62% (Δ: +148%)
- NYHA status improved to class II
- 6MWT distance: 244 m (Δ: +300%)
- MLHFQ score: 21 (Δ: −60%)
- Heart failure hospitalizations: 0 in subsequent 12 months
- No device-related complications
- GDMT remained stable

Laboratory response:

- TNF-α: 1.63 pg/mL (−22% from baseline)
- IFN-γ: 4.14 pg/mL (−46% from baseline)
- NT-proBNP: 467 pg/mL

HRV response:

- Low-frequency power: 569 (Δ: +19%)
- High-frequency power: 1,687 (Δ: +81.2%)
- Low-frequency/high-frequency power ratio: 0.33 (Δ: −35.3%)

What makes this case notable:

- Largest parasympathetic restoration demonstrating robust vagal activation.

**CASE 3: MARKED INFLAMMATORY RESPONSE.** A 54-year-old man with a 2-year history of nonischemic cardiomyopathy presented with persistent NYHA functional class III symptoms despite GDMT including sacubitril-valsartan 97 to 103 mg twice daily, metoprolol succinate 100 mg twice daily, spironolactone 25 mg once daily, and empagliflozin 10 mg daily. His medical history included hypertension, cardiac sarcoidosis, left bundle branch block, and accessory pathway ablation with inducible ventricular tachycardia and subsequent implantation of biventricular ICD.

Baseline assessment:

- LVEF: 30%
- NT-proBNP: 197 pg/mL
- Device: biventricular ICD implanted in 2022, 1 year before BAT
- 6MWT distance: 243.8 m
- MLHFQ score: 62
- Heart failure hospitalizations in prior 12 months: 0
- Electrocardiogram: normal sinus rhythm

Baseline laboratory studies:

- Estimated glomerular filtration rate: 95
- Inflammatory markers:
  - TNF-α: 2.97 pg/mL
  - IFN-γ: 9.5 pg/mL

Baseline HRV:

- Low-frequency power: 521
- High-frequency power: 1,509
- Low-frequency/high-frequency power ratio: 0.35

Intervention: The Barostim device was implanted in June 2023. The pulse generator was placed in a subcutaneous pocket on the right chest wall with the electrode positioned on the right carotid sinus. No procedural details or complications were detected. Device activation occurred 2 weeks post implant with gradual uptitration over 4 months to maximum tolerated settings: (8.2 mA, 65 uS, 40 pps).

The results at the 6-month follow-up after maximum uptitration were as follows.

Clinical course:

- NYHA status improved to class I
- LVEF: 53% (Δ: +76.7%)
- 6MWT distance: 243 m (Δ: 0%)
- MLHFQ score: 0 (Δ: −100%)
- Heart failure hospitalizations: 0 in subsequent 12 months
- No device-related complications
- GDMT remained stable

Laboratory response:

- TNF-α: 1.63 pg/mL (−45% from baseline)
- IFN-γ: 4.14 pg/mL (−56% from baseline)
- NT-proBNP: 145 pg/mL

HRV response:

- Low-frequency power: 470 (Δ: −9.8%)
- High-frequency power: 1798 (Δ: −19%)
- Low-frequency/high-frequency power ratio: 0.26 (Δ: −26%)

What makes this case notable:

- Patient with cardiac sarcoidosis and high baseline inflammation.
- First case demonstrating BAT in immune-mediated cardiac disease.

## DISCUSSION

This case series represents to our knowledge the first report of an anti-inflammatory effect and improved autonomic markers associated with BAT in HFrEF patients. There are 3 main findings:

1. BAT was associated with an improvement in the MLHFQ score and a decrease in heart failure hospitalizations after BAT implantation.
2. BAT was associated with an improvement in the autonomic function of patients, as measured by HRV.
3. BAT was associated with a decrease in TNF-α and IFN-γ in the serum of patients.

While prior randomized trials (BeAT-HF, HOPE4HF) have demonstrated that BAT improves symptoms, quality of life, and exercise capacity, the mechanisms underlying these clinical benefits have remained incompletely understood.[1,6,7] Our findings demonstrate that BAT may potentially benefit HFrEF patients through 3 complementary, but not

necessarily independent, mechanisms: anti-inflammatory modulation, autonomic restoration, and direct clinical improvement. These findings have important implications when considered in the context of heart failure pathophysiology.

In the aggregate study of 7 patients, there was an improvement in HRV, with an increase in parasympathetic component driving the change. Autonomic abnormalities exist in HFrEF and contribute to disease progression. Sympathovagal imbalance, marked by a shift toward sympathetic predominance and diminished parasympathetic activity, has been linked to arrhythmogenesis and adverse cardiac remodeling in HFrEF patients.[6] This imbalance not only exacerbates myocardial stress but also predisposes them to malignant arrhythmic events. Increased sympathetic outflow in HFrEF along with vasoconstriction has long been thought to precipitate a positive feedback mechanism that leads to worsening of HFrEF. Activation of the carotid sinus baroreflex has been shown to reduce sympathetic outflow and augment parasympathetic vagal tone.[9] Improvement in left ventricular systolic and diastolic function has been observed as well, with the mechanism remaining unknown (**Figure 1**).

Additionally, stress and inflammatory mediators can act as direct modulators of carotid body-mediated autonomic reflex pathways. Systemic inflammation has been recognized as a common pathophysiological feature of heart failure. The role of immunologic mechanisms in HFrEF entails a complex interplay of proinflammatory cytokines, such as TNF-α and IL-6, which perpetuate cardiac remodeling and contribute to the systolic dysfunction seen in these patients.[4] Preclinical and clinical data have shown the increase of TNF-α signaling, introducing anti-TNF therapy as a promising treatment.[4] Nevertheless, high-intensity TNF blockade treatment did not improve outcomes in clinical trials; moreover, there was even a signal toward harm, with increased risk of heart failure hospitalization.[10]

Notably, individual patients exhibited differential response patterns based on their baseline characteristics, suggesting that personalized patient selection guided by inflammatory and autonomic biomarkers may benefit therapeutic outcomes. Future prospective studies with extended follow-up are essential to validate the preliminary phenotypic observations and establish causality.

**STUDY LIMITATIONS.** The findings of this study should be interpreted carefully given the small size of the cohort, its descriptive nature, and the lack of a control group. Whether reduction in inflammatory markers or autonomic restoration can partially explain the mechanism of action of BAT or whether they occur as a result of individual patients' disease improvement is unknown, and further studies are needed.

## CONCLUSIONS

This case series demonstrates that BAT in a cohort of HFrEF patients is associated with reductions in systemic inflammatory markers TNF-α and IFN-γ, alongside improvements in autonomic function as measured by HRV. These findings support a precision medicine approach to BAT patient selection and suggest a dual mechanism of action—autonomic restoration and anti-inflammatory modulation—that may explain the sustained clinical benefits observed with BAT. These observations warrant validation in larger, controlled studies with serial inflammatory assessments to establish causality and explore inflammation-guided patient selection for BAT.

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**KEY WORDS** **baroreflex activation therapy, cytokines, heart failure, heart rate variability, inflammation, neuromodulation**