ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 1674–1676
doi:10.1002/ejhf.2627

INVITED EDITORIAL

Baroreflex activation therapy in heart failure: targeting the right patient

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This article refers to 'Baroreflex activation therapy with the Barostim™ device in patients with heart failure with reduced ejection fraction: a patient level meta-analysis of randomized controlled trials' by A.J.S. Coats *et al.*, published in this issue on pages 1665–1673.

Despite the several therapeutic advances in the last decades, chronic heart failure (HF) still remains associated with poor exercise tolerance, reduced quality of life and life expectancy, particularly when analysing real-world data.[1] While population ageing and increased survival after acute coronary syndrome have contributed to the growing HF burden worldwide, heterogeneous efficacy of HF treatments, poor individual compliance due to adverse effects, and therapeutic inertia may hamper the prescription and/or optimal titration of guideline-directed medical therapies for HF.[1] Pre-clinical and clinical research is therefore still needed to further enrich the HF therapeutic armamentarium. In this line, it seems particularly appealing to test the safety and efficacy of novel bioelectronic medicine devices, as they may act on unchallenged pathophysiological targets,[2] decreasing at the same time the problem of multiple drug prescription and patient adherence to treatment in the long term, especially in chronic diseases.

The dysregulation of the autonomic nervous system (ANS), characterized by parasympathetic withdrawal and sympathetic predominance, is a crucial pathophysiological determinant of HF.[3] While this stress response is compensatory in the acute setting, aimed at sustaining cardiac output and vital organ perfusion, it becomes detrimental and maladaptive in chronic HF. Indeed, sympathovagal imbalance underlies adverse heart remodelling, elicits renin–angiotensin–aldosterone system (RAAS) activation, worsens clinical severity, triggers malignant arrhythmias and increases the risk of death in HF.[3] Although several evidence-based HF therapies, including beta-blockers, RAAS inhibitors, angiotensin receptor–neprilysin inhibitors (ARNI), and cardiac resynchronization therapy (CRT) positively modulate autonomic function, still residual imbalance may be documented in many HF patients.[3] Different strategies have been thus proposed to improve ANS cardiovascular control, including denervation strategies targeting cardiac, renal, or splanchnic sympathetic nerves, and vagal nerve stimulation, though definitive proof of their efficacy is still missing.[2] Therefore, acting upstream on the abnormal function of the baroreflex and chemoreflex, i.e. the main visceral reflexes modulating brain stem autonomic centres and efferent circuits, has emerged as an additional treatment option.

Consistent evidence links abnormal baroreflex control to autonomic imbalance typical of HF.[3–5] While the underlying mechanisms are not completely understood, reduced cardiac output, increased vascular stiffness, and the interaction with other reflexes (most notably the chemoreflex) may contribute to baroreflex impairment.[3] The blunted baroreflex response may sustain systemic sympathetic overdrive and decreased cardiac vagal control, increasing norepinephrine cardiac spillover and reducing heart rate variability (HRV).[3] Of note, although various treatments (e.g. beta-blockers, RAAS inhibitors, CRT) may act on baroreflex sensitivity,[6,7] residual dysfunction is observed in a significant subset of patients, more at risk of adverse events. In a recent study enrolling stable HF patients (mean age 65 ± 12 years, median left ventricular ejection fraction [LVEF] 32% [interquartile range 25–38%]) on optimal drug and device treatment (>90% on beta-blockers and RAAS inhibitors/ARNI, 35% with CRT and/or implantable-cardioverter defibrillator [ICD]), baroreflex sensitivity was reduced in 96/267 individuals (36%). Decreased baroreflex sensitivity was associated with worse functional capacity and lower HRV, and with a significantly higher risk of cardiac death, appropriate ICD shocks, and HF hospitalization at a 50-month median follow-up.[5] Restoring baroreflex function in HF patients, even on optimal HF treatment, may then improve autonomic balance, exercise tolerance, and impact on outcome.

Baroreflex activation therapy (BAT) consists of an implantable device, composed of a subcutaneous pulse generator and an extravascular carotid sinus lead, aimed to stimulate the afferent arm of carotid baroreceptors. Following the encouraging results of

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Heart Failure* or of the European Society of Cardiology. doi: 10.1002/ejhf.2573

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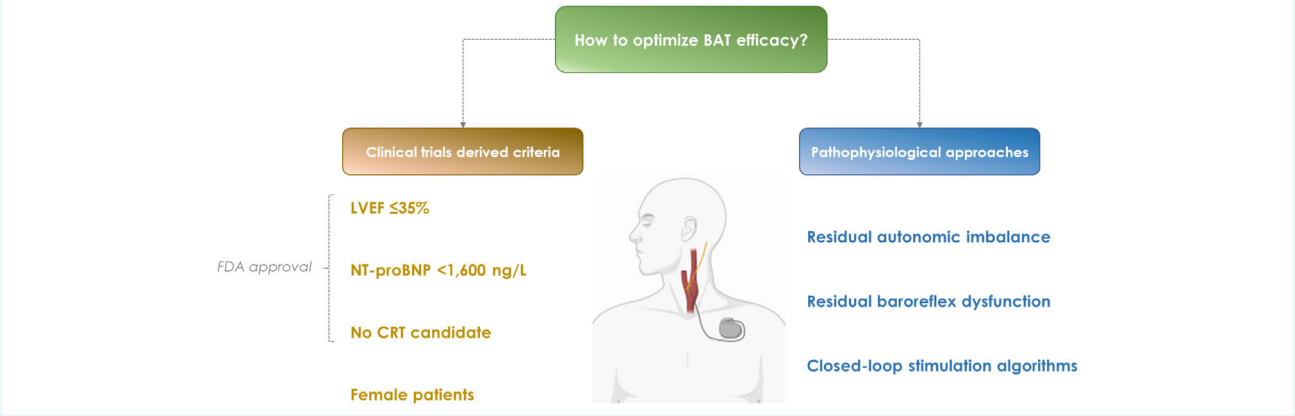

Figure 1 Different strategies to optimize the use of baroreflex activation therapy (BAT). As for other bioelectronic medicine devices, various strategies may be adopted to optimize the use of BAT. A first possibility is to test the device in a large cohort of patients, establishing *a priori* the inclusion and the exclusion criteria. *Post hoc* analyses may help to identify the patients which may benefit more from the device, while meta-analyses allow to perform subgroup analyses in larger populations. On the other hand, a tailored pathophysiological approach, e.g. identifying patients with residual baroreflex dysfunction as well as shifting from open- to closed-loop systems, is expected to maximize the efficacy of BAT, limiting the residual risk in patients which would not need reflex modulation. However, the greater technological complexity may hamper this process. CRT, cardiac resynchronization therapy; FDA, Food and Drug Administration; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

pre-clinical and proof-of-concept studies, the safety and efficacy of BAT have been tested in two randomized, open-label, controlled trials, namely the HOPE4HF and BeAT-HF.[8,9] Both trials enrolled HF patients with an LVEF ≤35%, still symptomatic for dyspnoea (i.e. New York Heart Association [NYHA] class II–III) despite stable guideline-directed medical treatment. In the HOPE4HF trial, the patients randomized to BAT (76/146) showed a significant improvement in the walked distance, quality of life scores, NYHA class, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, with an optimal safety profile.[8] Similarly, in the BeAT-HF trial, BAT improved quality of life, exercise tolerance, and NT-proBNP level, without any significant safety concern.[9]

The positive findings of these trials are further confirmed by the individual-patient meta-analysis published in this issue of the Journal by Coats *et al.*[10] Putting together the populations of the HOPE4HF and BeAT-HF (for a total of 554 randomized patients), the authors confirmed that BAT provided significant improvement in exercise capacity, quality of life, NYHA class, and plasma NT-proBNP concentration. Interestingly, the larger number of patients included in this meta-analysis allowed subgroup analyses, showing greater beneficial effects of BAT in patients with NT-proBNP level <1600 ng/L and without a clear indication for CRT, as well as in female sex, with no influence of age or presence of atrial fibrillation.[10] The authors should be commended for their work, which provides further elements about the safety and efficacy of BAT in HF patients, identifying some clinical phenotypes which may benefit more from its use.

In this regard, the lower efficacy of BAT in patients with higher NT-proBNP level is not surprising. This subset of patients may indeed be characterized by a high-risk profile, including older age, worse renal function, mitral regurgitation, and cardiac cachexia. Furthermore, higher NT-proBNP concentration corresponds to organ congestion and increased filling pressures, which may jeopardize patients' stability independently of BAT.

On the other hand, the more pronounced efficacy of BAT in women appears less straightforward but may express gender-related differences in baseline baroreflex sensitivity both in health and disease, especially in hypertension and diabetes.[11] Whether such differences may persist also in HF patients and how they could affect the efficacy of BAT remains to be investigated. The uneven perception of symptoms and of the potential benefits related to novel therapies has also been proposed to explain the differences in NYHA class and quality of life scores between sexes.[12] The reasons behind the greater reduction in NT-proBNP in women are even less clear. Although various studies have investigated sex differences in NT-proBNP concentration, cut-offs, and effects of therapies, conclusive explanations are still missing.[13]

Nonetheless, accurate patient selection represents a critical issue when designing and testing novel bioelectronic medicine devices for clinical use. Indeed, the recognition of the pathophysiological determinants of disease and symptoms may help to tailor therapeutic strategies, maximizing their efficacy, identifying potential non-responders, and, more importantly, avoiding unnecessary risks.[14] Given that BAT aims at restoring the baroreflex control of the ANS, its efficacy may be even greater in patients with residual autonomic dysfunction.[5] The blunted improvements observed in patients with CRT, restoring *per se* baroreflex function and sympathovagal imbalance,[7] seems hence in line with this hypothesis. Unfortunately (and surprisingly), data about autonomic function and baroreflex sensitivity/resetting were not collected in the BAT trials conducted so far, even in selected subsets. HRV and baroreflex sensitivity may be easily evaluated through non-invasive and widely available instrumentation,[5] but such measures are limited to patients on sinus rhythm. Furthermore, the methods currently

used may overlook the extracardiac effects of baroreflex control either on vascular tone or other reflex systems.

Another important issue that should be mentioned is that BAT currently relies on open-loop control of the stimulation parameters. On the contrary, the baroreflex, like other visceral reflexes, constantly changes to match blood pressure oscillations in a closed-loop fashion to maintain stable organ perfusion. Although the integration of physiological mechano-sensors and real-time adapting algorithms may be technically challenging, this may maximize BAT efficacy by restoring baroreflex physiological function, reducing at the same time battery consumption due to unnecessary stimulation, and potentially decreasing adverse effects related to unphysiological long-term stimulation of the system. Therefore, future research is needed not to miss these opportunities[15] (*Figure 1*).

The lack of a sham control represents another drawback when testing implantable devices. Considering the several technical and ethical issues, the use of objective endpoints (e.g. NT-proBNP, imaging parameters) has been proposed by the Regulatory Agencies to overcome such a limit, though it may be difficult to rule out residual bias.[2] Although the overall safety of implantable devices is progressively improving parallelly to technological advances, their invasive nature, as well as the need for battery replacement, still represent major concerns for both patients and physicians, potentially hampering a wider implementation of BAT in the clinical scenario. Steering research toward device miniaturization and biocompatibility, and the design of batteryless or rechargeable systems would help to promote the use of BAT, as well as other neuromodulation devices recently proposed for HF treatment.[14]

Conflict of interest: none declared.

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