Safety and efficacy of baroreflex activation therapy for heart failure with reduced ejection fraction: a rapid systematic review

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Abstract

To retrieve and assess the available data in the literature about the safety and efficacy of baroreflex activation therapy (BAT) in heart failure with reduced ejection fraction (HFrEF) patients, through a rapid systematic review of clinical studies. Rapid systematic review of literature. Searched electronic databases included PubMed, EMBASE, CENTRAL, Scopus, and Web of Science using Mesh and free terms for heart failure and BAT. No language restriction was used for the searches. We included full peer reviewed publications of clinical studies (randomized or not), including patients with HFrEF undergoing BAT, with or without control group, assessing safety and efficacy outcomes. One reviewer conducted the analysis of the selected abstracts and the full-text articles, performed data extraction, and evaluated the methodological quality of the selected articles. The methodological quality was assessed according to the Cochrane Collaboration instruments. A descriptive summary of the results is provided. Of the 441 citations screened, 10 publications were included (three were only conference abstracts), reporting data from three studies. Only one study was a randomized clinical trial. Two studies reported a 6 month following, and the other study analysed outcomes up to 41 months. The procedure seems to be safe when performed by a well-trained multi-professional team. An 86% rate of system and procedure-related complication-free was reported, with no cranial nerve injuries. Improvements in New York Heart Association class of heart failure, quality of life, 6 min walk test, and hospitalization rates, as well as in muscle sympathetic nerve activity. No meta-analysis was conducted because of the lack of homogeneity across studies; the results from each study are reported individually. BAT procedure seems to be safe if appropriate training is provided. Improvements in clinical outcomes were described in all included studies. However, several limitations do not allow us to make conclusive statements on the efficacy of BAT for HFrEF. New well-designed trials are still needed.

Keywords Baroreflex activation therapy; Heart failure; Rapid review

Introduction

Mortality, morbidity, and healthcare costs related to heart failure with reduced ejection fraction (HFrEF) remain unacceptable high although the advances in the medical field.¹,² The symptoms and the progression of the disease are promoted by sympathovagal imbalance, including an excessive activation of the sympathetic and inhibition of the parasympathetic nerves system.³,⁴ In this context, baroreflex activation therapy (BAT), which is a treatment based on the stimulation of the baroreceptors located at the carotid sinus⁵ and supposedly restores sympathovagal balance, has been reported in the literature.⁶,⁷ Large animal studies demonstrated a survival benefit when compared with untreated controls, as well as improvements in cardiac function, susceptibility to ventricular arrhythmias.⁸-¹⁰ The first-in-human study,⁶ which was a single-centre, open-label trial including 11 patients, was published in 2014. The study included patients with New York Heart Association (NYHA) Class III, ejection fraction lower than 40%.
optimized medical therapy, and ineligible for cardiac resynchronization. The results showed that BAT was safe and provided chronic improvements in muscle sympathetic nerve activity (MSNA), quality of life, and functional capacity.\textsuperscript{6}

In 2015, the first randomized clinical trial (RCT) was published in the literature including 76 patients underwent to BAT and 70 controls. Similarly, the study showed that BAT is safe and improves functional capacity, quality of life, exercise capacity, N-terminal pro-brain natriuretic peptide, and possibly the burden of heart failure (HF) hospitalizations.\textsuperscript{7}

Although the promising result, it is still unclear in the literature the effect of BAT in patients with HF. Thus, the aim of this study was to retrieve and assess the available data in the literature about the safety and efficacy of BAT in HFrEF patients, through a rapid systematic review of clinical studies.

**Methods**

**Protocol and registration**

This rapid review was designed using as guidance the Preferred Reporting Items for Systematic Reviews and Meta-analyses \textsuperscript{11} and is registered in the PROSPERO (International Prospective Register of Systematic Reviews) database,\textsuperscript{12} under the code [CRD42018114741].

**Eligibility criteria**

We included full peer reviewed publications of clinical studies (randomized or not), including patients with HFrEF undergoing BAT, with or without control group, assessing safety and efficacy outcomes. Abstracts from conferences were included if they provided enough information to judge eligibility and evaluate the outcomes. We excluded case reports and literature reviews.

**Information sources and literature search**

We searched the following electronic databases: PubMed, EMBASE, CENTRAL, Scopus, and Web of Science. In addition, we searched the references of the included articles manually, as well as performed a citation analysis of the included studies using Google Scholar. The initial search comprised the Mesh term ‘Heart Failure’ followed by its related entry terms and other free terms and free terms related to ‘baroreflex activation therapy’. We did not use limits for language or date when conducting the searches.

**Study selection**

Titles and abstract of the retrieved articles were independently evaluated by one reviewer. Abstracts that do not provide enough information regarding the eligibility criteria will be kept for full-text evaluation. One reviewer evaluated full-text articles and determined study eligibility.

**Data abstraction**

One reviewer conducted data extraction and included study title, author, journal and year of publication, study design, population, inclusion and exclusion criteria, study arms and sample size, intervention description, outcomes definitions, measurement and results (as presented in the included studies), and follow-up period.

**Risk of bias assessment**

To assess the risk of bias of the RCT, we used the Cochrane Risk of Bias tool that considers bias related to selection, performance, detection, attrition, reporting, and other possible.\textsuperscript{13} For the non-randomized studies, we used the ROBINS-I tool (Risk Of Bias In Non-randomized Studies—of Interventions), also from Cochrane Collaboration.\textsuperscript{14} The following types of bias were considered: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measuring of outcomes, bias in selection of the reported result, and overall bias. The evaluation was conducted independently by one reviewer.

**Synthesis**

Descriptive analyses of studies will be performed including study characteristics and main results.

**Results**

**Study selection**

Our search strategies yielded 441 citations from the five electronic databases. After excluding duplicates and screening titles and abstracts for eligibility, 20 publications were kept for full-text evaluation. Finally, 10 publications were included in our rapid review, representing data from three studies. Figure 1 demonstrates the study selection process.
Study characteristics

First study (reported in three publications and one conference abstract)
Study from Gronda et al.\(^6\) was the first-in-human study evaluating BAT for HFrEF published in the literature. The study included a series of 11 patients and reported a 6 month follow-up. A year later, another publication\(^15\) reported the long-term follow-up of this study, including results at 12 and 21 ± 5 months after intervention. In 2016, another article\(^16\) reporting data from the same study was published. However, this publication added data from nine controls, who were treated congestive HFrEF patients to assess the effects of chronic baroreceptor activation on arterial stiffness. In 2017, the authors published an abstract in a conference\(^17\) reporting the 42 month follow-up of those 11 patients. The main characteristics of these publications are described in Table 1.

Second study (reported in four publications and one conference abstract)
Study from Abraham et al.\(^7\), named HOPE4HF, was the first and only RCT found in the literature assessing BAT for HFrEF patients. The study included 140 patients, mostly men, with a mean ejection fraction of 24 ± 7%. Still in 2015, a sub-analysis of this RCT, study from Zile et al.\(^18\) was published comparing patients with or without cardiac resynchronization therapy. In 2016, Weaver et al.\(^19\) published the intraoperative experience and the 12 month safety and efficacy results of the HOPE4HF trial. A year after, Wachter et al.\(^20\) presented an abstract in a conference reporting another sub-analysis of the HOPE4HF trial comparing patients with systolic blood pressure equal or lower to 16 mmHg with >16 mmHg. Last, Halbach et al.\(^21\) published one more sub-analysis of the same trial in the literature, separating patients with or without coronary artery disease. The main characteristics of these publications are described in Table 1.

Third study (reported in one conference abstract)
Mueller-Ehmsen et al.\(^22\) published an abstract in a conference reporting the European experience with BAT in HFrEF. The abstract included the results of 57 patients from centres in Germany, Italy, and France. We could not find a full text of this study; thus, we understand it was not published yet. The main characteristics of this study are described in Table 1.

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**Figure 1** Study selection process.

| TOTAL OF 441 RECORDS |
|----------------------|
| PubMed: 68 records  |
| Embase: 141 records |
| Scopus: 146 records |
| CENTRAL: 29 records |
| Web of Science: 57 records |

| Identification |
|----------------|
| 47 Duplicates removed |

| Screening |
|-----------|
| 394 Records after duplicates removed |
| 374 Records excluded based on review of title and/or abstract |

| Eligibility |
|------------|
| 20 Full-text articles for eligibility assessment |
| 1 Review of literature |
| 5 Abstracts which the corresponding full-text were already published and included in our review |
| 1 Did not report any outcomes of interest |
| 4 Duplicate data |

| Included |
|---------|
| 10 publications included (Data from 3 studies) |

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**Table 1**

| Study Characteristics | Description |
|-----------------------|-------------|
| First study           | Study from Gronda et al.\(^6\) was the first-in-human study evaluating BAT for HFrEF published in the literature. The study included a series of 11 patients and reported a 6 month follow-up. A year later, another publication\(^15\) reported the long-term follow-up of this study, including results at 12 and 21 ± 5 months after intervention. In 2016, another article\(^16\) reporting data from the same study was published. However, this publication added data from nine controls, who were treated congestive HFrEF patients to assess the effects of chronic baroreceptor activation on arterial stiffness. In 2017, the authors published an abstract in a conference\(^17\) reporting the 42 month follow-up of those 11 patients. The main characteristics of these publications are described in Table 1. |
| Second study          | Study from Abraham et al.\(^7\), named HOPE4HF, was the first and only RCT found in the literature assessing BAT for HFrEF patients. The study included 140 patients, mostly men, with a mean ejection fraction of 24 ± 7%. Still in 2015, a sub-analysis of this RCT, study from Zile et al.\(^18\) was published comparing patients with or without cardiac resynchronization therapy. In 2016, Weaver et al.\(^19\) published the intraoperative experience and the 12 month safety and efficacy results of the HOPE4HF trial. A year after, Wachter et al.\(^20\) presented an abstract in a conference reporting another sub-analysis of the HOPE4HF trial comparing patients with systolic blood pressure equal or lower to 16 mmHg with >16 mmHg. Last, Halbach et al.\(^21\) published one more sub-analysis of the same trial in the literature, separating patients with or without coronary artery disease. The main characteristics of these publications are described in Table 1. |
| Third study           | Mueller-Ehmsen et al.\(^22\) published an abstract in a conference reporting the European experience with BAT in HFrEF. The abstract included the results of 57 patients from centres in Germany, Italy, and France. We could not find a full text of this study; thus, we understand it was not published yet. The main characteristics of this study are described in Table 1. |
| Study, Year | Study design | Population | Study arms, if applicable | Number of patients | Age (Mean ± SD) | Female N (%) | Hypertension N (%) | LVEF Mean ± SD (%) | Outcomes | Follow-up (months) |
|-------------|--------------|-------------|---------------------------|--------------------|----------------|--------------|-------------------|-------------------|----------|------------------|
| Gronda et al., 6 | Single-centre, open-label study | HF patients NYHA Class III, EF < 40%, optimized medical therapy, and ineligible for CRT | Single arm | 11 | 67 ± 9 | 3 (27.3) | NA | 31 ± 7 | MSNA, changes in NYHA functional class and quality-of-life score | 1, 3, and 6 |
| —Long-term follow-up of Gronda et al., 6 | Single-centre, open-label study | HF patients NYHA Class III, EF < 40%, optimized medical therapy, and ineligible for CRT | Single arm | 11 (nine alive at the end of the follow-up) | 67 ± 9 | 3 (27.3) | NA | 31 ± 7 | MSNA, baroreflex sensitivity data and hospitalization rate, changes in NYHA functional class and quality-of-life score | 6 and 21.5 ± 4.2 |
| Gronda et al., 16 | Single-centre, open-label study | NYHA Class III HFrEF patients | BAT | 9 | 66 ± 8 | 1 (11.1) | NA | 32.4 ± 8 | Arterial stiffness—pulse wave velocity | 3 |
| —Partially duplicated population with Gronda et al., 6 | | | Control | 9 | 68 ± 1 | 1 (11.1) | NA | 35.6 ± 6 | | |
| Gronda et al., 17 | Single-centre, open-label study | HF patients NYHA Class III, EF < 40%, optimized medical therapy, and ineligible for CRT | Single arm | 11 (seven alive at the end of the follow-up) | NA | NA | NA | NA | MSNA, quality-of-life score, 6 min hall walk distance, LVEF, hospitalization | 21.5 ± 4.7 and 41.5 ± 3.5 |
| —Long-term follow-up of Gronda et al., 6 | | | | | | | | | System-related and procedure-related major adverse neurological and cardiovascular events, changes in NYHA functional class, quality-of-life score, and 6 min hall walk distance | 3 and 6 |
| Abraham et al., 7 | HOPE4HF study | RCT Chronic HF with LVEF of 35% or less | BAT—Barostim neo system | 71 | 64 ± 7 | 9 (12.7) | 19 (57.6) | 24 ± 7 | | |
| Zile et al., 18 | | RCT Chronic HF with LVEF of 35% or less | Control—standard medical therapy CRT (divided in BAT and control) | 69 | 66 ± 1 | 11 (15.9) | 21 (56.8) | 25 ± 7 | Changes in NYHA functional class, quality-of-life score, and 6 min hall walk distance | 6 |
| —Sub-analyses of HOPE4HF study | | | 45 (24 BAT and 21 control) | 68 ± 9 | 9 (8.9) | 8 (36.4) | 24 ± 6 | | |
| Weaver et al., 19 | RCT Chronic HF with LVEF of 35% or less | No-CRT (divided in BAT and control) | | 95 (47 BAT and 48 control) | 63 ± 1 | 16 (16.8) | 32 (66.7) | 25 ± 7 | System-related and procedure-related | 12 |
| —Long-term | | BAT—Barostim neo system | | 71 | 64 ± 7 | 9 (12.7) | 19 (57.6) | 24 ± 7 | | |

(Continues)
| Study, Year | Study design | Population | Study arms, if applicable | Number of patients | Age (Mean ± SD) | Female N (%) | Hypertension N (%) | LVEF Mean ± SD | Outcomes | Follow-up (months) |
|-------------|-------------|------------|---------------------------|--------------------|----------------|--------------|-------------------|----------------|----------|-------------------|
| (continued) | | | | | | | | | | related major adverse neurological and cardiovascular events, changes in NYHA functional class, quality-of-life score, and 6 min hall walk distance | |
| | | | Control—standard medical therapy | 69 | 66 ± 1 | 11 (15.9) | 21 (56.8) | 25 ± 7 | | 6 | |
| Wachter et al. | RCT | Chronic HF with LVEF of 35% or less | SBP ≤ 116 mmHg (divided in BAT and control) | 71 (42 BAT and 29 control) | NA | NA | NA | NA | Changes in NYHA functional class, quality-of-life score, and 6 min hall walk distance | |
| | | | SBP > 116 mmHg (divided in BAT and control) | 69 (29 BAT and 40 control) | NA | NA | NA | NA | | 6 | |
| Halbach et al. | RCT | Chronic HF with LVEF of 35% or less | CAD (divided in BAT and control) | 101 (52 BAT and 49 control) | NA | NA | NA | NA | Changes in NYHA functional class, quality-of-life score, and 6 min hall walk distance | |
| | | | No-CAD (divided in BAT and control) | 39 (19 BAT and 20 control) | NA | NA | NA | NA | | 6 | |
| Mueller-Ehmsen et al. | Multicentre, open-label study | HF patients NYHA Class III, EF ≤ 40% | Single arm | 57 | | | | | Changes in NYHA functional class, quality-of-life score, HF medications and renal function | |

BAT, baroreflex activation therapy; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MSNA, muscle sympathetic nerve activity; NYHA, New York Heart Association; RCT, randomized controlled trial; SBP, systolic blood pressure.
Risk of bias

Risk of bias was assessed in Gronda et al.\textsuperscript{6,15–17} and HOPE4HF\textsuperscript{3,7,18–20} studies. We did not assessed risk of bias of the Mueller-Ehmsen et al.\textsuperscript{22} because the abstract did not provide enough information to allow it. The study from Gronda et al. was considered of low risk of bias due to confounding, selection of participants, missing data, and selection of the reported result; and of moderate risk of bias due to classification of intervention, deviations from intended interventions, and measuring of outcomes. HOPE4HF trial was considered of low risk of bias related to selection, performance, detection, attrition, and reporting.

Synthesis of results

Safety

Both, study from Gronda and the HOPE4HF trial, used the same delivery system, the Barostim neo, CVRx, Inc, Minneapolis, MN, USA. The system consists of a pulse generator similar in size and shape to an implanted defibrillator coupled with a carotid sinus lead. The device is implanted subcutaneously in the right or left pectoral region with the lead tunnelled from a small (2.5–5 cm) cutaneous incision to affix over the ipsilateral carotid bifurcation. Safety related to this system has been previously reported\textsuperscript{23} and comparable with a pacemaker. Study from Mueller-Ehmsen et al.\textsuperscript{22} did not report details on the BAT system used; however, it mentions that the system safety profile is similar to a pacemaker. Thus, we believe they may have used the same system in their study. Table 2 describes the system and procedure-related events reported in the included studies.

Efficacy

Changes in New York Heart Association class

New York Heart Association HF class measurement was reported in all three studies and in nine of the 10 publications. Gronda et al.\textsuperscript{6,15} reported improvements in NYHA class of HF at 3, 6, and 21.5 ± 4.2 month follow-ups. The report of the 4 year follow-up did not show data on this outcome. Improvements in class of HF were also demonstrated in the original publication\textsuperscript{7} and all the sub-analyses\textsuperscript{3,18–20} of the HOPE4HF study, in patients undergoing BAT at 6 months when compared with baseline. Similarly, the study from Mueller-Ehmsen et al.\textsuperscript{22} also reported improvement of NYHA class of HF at 6 month follow-up. Detailed data on this outcome are shown on Table 3.

Quality of life

Quality of life was measured in the three studies and reported in all publications. Improvements in this outcome were described in all comparison, except for patients making use of cardiac resynchronization therapy undergoing BAT, when compared with controls (patients making use of cardiac resynchronization therapy not undergoing BAT) (P = 0.23). Details on quality of life measuring methods and results are described in Table 3.

Six minute walk test

Six minute walk test was applied in all studies, and results were available in all publications. Most of the reported improvements in this outcomes, except for three patients group, are as follows: patients making use of cardiac resynchronization therapy undergoing BAT, when compared with controls (patients making use of cardiac resynchronization therapy not undergoing BAT) (P = 0.38); patients with systolic blood pressure <116 mmHg undergoing BAT, when compared with controls (patients with systolic blood pressure <116 mmHg not undergoing BAT) (P = 0.08); and patients without coronary artery disease undergoing BAT, when compared with patients without coronary artery disease not undergoing BAT (P = 0.84). These results are described in details in Table 2.

Hospitalization

Hospitalization was described in two studies and seven publications. Most of the publications reported lower rates of hospitalization after BAT. There was no difference when compared patients making use of cardiac resynchronization therapy undergoing and not undergoing

Table 2 Summary of the reported system and procedure-related events reported in the included studies

| Study, Year | Number of patients submitted to BAT | BAT system | System and procedure-related events |
|-------------|-----------------------------------|------------|------------------------------------|
| Gronda et al.,\textsuperscript{6,15,16,23} | 11 | Barostim neo, CVRx, Inc, Minneapolis, MN, USA | One reported event. The patient experienced anaemia requiring a transfusion during the implant. The patient recovered with no residual effects. |
| HOPE4HF study,\textsuperscript{3,7,18–20} | 71 | Barostim neo, CVRx, Inc, Minneapolis, MN, USA | The rate of freedom from system and procedure-related complications was 86% through 12 months. There were two MANCE events (hematomas) that occurred during the six first months after BAT. In addition, the study reported three more events: urinary tract infection secondary to urinary retention, hypotension, and transection of the transverse cervical skin nerve. The complications that did occur were generally mild and short-lived. The abstract did not report any events neither data on safety. It is only mentioned that the system safety profile was similar to a pacemaker. |
| Mueller-Ehmsen et al.,\textsuperscript{22} | 57 | Details are not reported in the abstract. | |

BAT, baroreflex activation therapy; MANCE, major adverse neurologic and cardiovascular events.
| Study, Year | Study arms, N | NYHA class | QoL | Six min hall walk distance (m) | Hospitalizations |
|-------------|--------------|------------|-----|------------------------------|-----------------|
| Gronda et al., 6 | BAT, 11 | Baseline: 11 patients at Class III 3 month variation: six patients at Class II and five patients at Class I 6 month variation: one patient at Class III, two patients at Class II, and five patients at Class I | Baseline: 33.4 ± 29.8 3 month variation: −1.7 ± 4.4 6 month variation: −10.6 ± 3.8 21.5 ± 4.2 month variation: −13.2 ± 5.4 | Baseline: 304.4 ± 49.6 3 month variation: +49.7 ± 15.7 6 month variation: +51.1 ± 25.6 | 6 months before intervention: eight of the 11 patients were hospitalized (total of 125 days) |
| | | | | | 6 months after intervention: one of the 11 patients was hospitalized (total of 6 days) |
| Gronda et al., 15 | BAT, 9 (two of the 11 patients died) | Baseline: 30.9 ± 27.8 6 month variation: −11.5 ± 4.6 21.5 ± 4.2 month variation: −13.2 ± 5.4 | Baseline: 306.4 ± 52.4 6 month variation: +69.7 ± 24.4 21.5 ± 4.2 month variation: +58.4 ± 33.4 | Baseline: 306 ± 36.2 6 month variation: +65 ± 36.2 21.5 ± 4.2 months variation: +42 ± 116 | 12 months before intervention: 1.44 ± 1.3 days/month. Total of 155 days of hospitalization (all patients together) |
| | | | | | 6 months after intervention: 0.13 ± 0.33 days/month. Total of 7 days of hospitalization (all patients together) |
| | | | | | 21.5 ± 4.2 months after intervention: 0.27 ± 0.44 days/month. Total of 45 days of hospitalization (all patients together) |
| Gronda et al., 17 [Abstract] | BAT, 7 (four of the 11 patients died) | Baseline: 31.3 ± 26.0 7.7 ± 9.2 41.5 ± 3.5 months: 1 6.9 ± 7.7 | Baseline: 306 ± 36.2 6 month variation: 21.5 ± 4.2 months: 3 21.5 ± 4.2 months variation: 41.5 ± 3.5 months: 0.87 425 ± 116 | Baseline: 17.18 21.5 ± 4.2 months: 0.93 41.5 ± 3.5 months: 0.87 | 6 months vs. baseline HF hospitalizations (days) BAT (n = 57): −0.49 ± 0.2 Control (n = 50): −0.05 ± 0.2 P < 0.05 |
| | | | | | 6 months vs. baseline HF hospitalizations (days) BAT (n = 57): −6.28 ± 2.7 Control (n = 50): 0.08 ± 1.7 P < 0.05 |
| Abraham et al., 7 HOPE4HF study | BAT, 71 Control, 69 | Baseline: 31.3 ± 26.0 7.7 ± 9.2 41.5 ± 3.5 months: 1 6.9 ± 7.7 | Baseline: 306 ± 36.2 6 month variation: 21.5 ± 4.2 months: 3 21.5 ± 4.2 months variation: 41.5 ± 3.5 months: 0.87 425 ± 116 | Baseline: 17.18 21.5 ± 4.2 months: 0.93 41.5 ± 3.5 months: 0.87 | 6 months vs. baseline HF hospitalizations (n) BAT (n = 57): −0.49 ± 0.2 Control (n = 50): −0.05 ± 0.2 P < 0.05 |
| | | | | | 6 months vs. baseline HF hospitalizations (n) BAT (n = 57): −0.49 ± 0.2 Control (n = 50): −0.05 ± 0.2 P < 0.05 |
| Zile et al., 18 Sub-analyses of HOPE4HF study | CRT | Baseline: 31.3 ± 26.0 7.7 ± 9.2 41.5 ± 3.5 months: 1 6.9 ± 7.7 | Baseline: 306 ± 36.2 6 month variation: 21.5 ± 4.2 months: 3 21.5 ± 4.2 months variation: 41.5 ± 3.5 months: 0.87 425 ± 116 | Baseline: 17.18 21.5 ± 4.2 months: 0.93 41.5 ± 3.5 months: 0.87 | 6 months vs. baseline HF hospitalizations (n) BAT (n = 57): −0.49 ± 0.2 Control (n = 50): −0.05 ± 0.2 P < 0.05 |
| | | | | | 6 months vs. baseline HF hospitalizations (days) BAT (n = 57): −6.28 ± 2.7 Control (n = 50): 0.08 ± 1.7 P < 0.05 |
| | | | | | 6 months vs. baseline HF hospitalizations (n) BAT (n = 57): −0.49 ± 0.2 Control (n = 50): −0.05 ± 0.2 P < 0.05 |

(Continues)
| Study, Year | Study arms, N | NYHA class | QoL | Six min hall walk distance (m) | Hospitalizations |
|-------------|--------------|------------|-----|-------------------------------|------------------|
| No-CRT      | Control: 47  | Control: −0.1 ± 0.2 | Control: −0.9 ± 6.0 | Control: −3.5 ± 22.9 | BAT: −0.42 ± 0.3 |
| BAT: 47     |              | P < 0.001  | P = 0.23 | P = 0.38                      | Control: −0.25 ± 0.3 |
| Control: 48 | No-CRT       | BAT: −0.4 ± 0.1 | BAT: −21.6 ± 3.6 | BAT: 85 ± 3.6           | No-CRT |
|             |              | Control: −0.2 ± 0.1 | Control: 3.5 ± 3.7 | Control: 3.6 ± 16.3     | BAT: −0.53 ± 0.2 |
|             |              | P = 0.09    | P < 0.001 | P = 0.003                     | Control: 0.05 ± 0.3 |
|             |              | Questionnaire: Minnesota Living with Heart Failure score | | | P = 0.08 |
|             |              |            |                  |                | HF hospitalizations (days) |
|             |              |            |                  |                | CRT |
|             |              |            |                  |                | BAT: −1.05 ± 1.2 |
|             |              |            |                  |                | Control: −0.13 ± 2.5 |
|             |              |            |                  |                | P = 0.78 |
|             |              |            |                  |                | No-CRT |
|             |              |            |                  |                | BAT: −8.89 ± 4.0 |
|             |              |            |                  |                | Control: 0.18 ± 2.2 |
|             |              |            |                  |                | P = 0.09 |
|             |              |            |                  |                | Not reported |

**Table 3** (continued)

| Study, Year | Study arms, N | NYHA class | QoL | Six min hall walk distance (m) | Hospitalizations |
|-------------|--------------|------------|-----|-------------------------------|------------------|
| Weaver et al., 19 | BAT: 71 Control, 69 | 12 months vs. baseline | 12 months vs. baseline | 12 months vs. baseline | BAT: −0.42 ± 0.3 |
| —Long-term follow-up of HOPE4HF study | BAT: 71 Control, 69 | % improved | BAT: 85 ± 3.6 | BAT: 85 ± 3.6 | Control: −0.25 ± 0.3 |
| | BAT (n = 56): +45 Control (n = 42): +26 | P < 0.001 | Control (n = 39): | Control (n = 39): | No-CRT |
| | | | 13.4 ± 17.9 | 13.4 ± 17.9 | P = 0.003 |
| | | | P = 0.003 | P = 0.003 | Not reported |
| | | | | | HF hospitalizations (days) |
| | | | | | CRT |
| | | | | | BAT: −1.05 ± 1.2 |
| | | | | | Control: −0.13 ± 2.5 |
| | | | | | P = 0.78 |
| | | | | | No-CRT |
| | | | | | BAT: −8.89 ± 4.0 |
| | | | | | Control: 0.18 ± 2.2 |
| | | | | | P = 0.09 |
| | | | | | Not reported |

**Table 3** (continued)

| Study, Year | Study arms, N | NYHA class | QoL | Six min hall walk distance (m) | Hospitalizations |
|-------------|--------------|------------|-----|-------------------------------|------------------|
| Wachter et al., 20 | SBP ≤ 116 mmHg BAT: 42 Control: 29 SBP > 116 mmHg BAT: 29 Control: 40 | 6 months vs. baseline | 6 months vs. baseline | 6 months vs. baseline | BAT: −0.42 ± 0.3 |
| —Sub-analyses of HOPE4HF study [Abstract] | SBP ≤ 116 mmHg BAT (n = 37): | SBP ≤ 116 mmHg BAT (n = 37): | SBP ≤ 116 mmHg BAT (n = 37): | SBP ≤ 116 mmHg BAT (n = 37): | Control: −0.25 ± 0.3 |
| | −0.5 ± 0.1 Control (n = 22): | −0.5 ± 0.1 Control (n = 22): | −0.5 ± 0.1 Control (n = 22): | −0.5 ± 0.1 Control (n = 22): | No-CRT |
| | P = 0.008 | P = 0.008 | P = 0.008 | P = 0.008 | BAT: −0.53 ± 0.2 |
| | | | | | Control: 0.05 ± 0.3 |
| | | | | | P = 0.08 |
| | | | | | HF hospitalizations (days) |
| | | | | | CRT |
| | | | | | BAT: −1.05 ± 1.2 |
| | | | | | Control: −0.13 ± 2.5 |
| | | | | | P = 0.78 |
| | | | | | No-CRT |
| | | | | | BAT: −8.89 ± 4.0 |
| | | | | | Control: 0.18 ± 2.2 |
| | | | | | P = 0.09 |
| | | | | | Not reported |

**Table 3** (continued)

| Study, Year | Study arms, N | NYHA class | QoL | Six min hall walk distance (m) | Hospitalizations |
|-------------|--------------|------------|-----|-------------------------------|------------------|
| Halbach et al., 21 | CAD BAT: 52 Control: 49 No-CAD BAT: 19 Control: 20 | 6 months vs. baseline | 6 months vs. baseline | 6 months vs. baseline | BAT: −0.42 ± 0.3 |
| —Sub-analyses of HOPE4HF study | CAD BAT (n = 47): | CAD BAT (n = 47): | CAD BAT (n = 47): | CAD BAT (n = 47): | Control: −0.25 ± 0.3 |
| | −0.6 ± 0.1 Control (n = 36): | −0.6 ± 0.1 Control (n = 36): | −0.6 ± 0.1 Control (n = 36): | −0.6 ± 0.1 Control (n = 36): | No-CAD |
| | P = 0.003 | P = 0.003 | P = 0.003 | P = 0.003 | BAT: −0.53 ± 0.2 |
| | No-CAD BAT (n = 17): | No-CAD BAT (n = 17): | No-CAD BAT (n = 17): | No-CAD BAT (n = 17): | Control: 0.05 ± 0.3 |
| | −0.4 ± 0.2 Control (n = 18): | −0.4 ± 0.2 Control (n = 18): | −0.4 ± 0.2 Control (n = 18): | −0.4 ± 0.2 Control (n = 18): | P = 0.08 |
| | −0.1 ± 0.2 | −0.1 ± 0.2 | −0.1 ± 0.2 | −0.1 ± 0.2 | HF hospitalizations (days) |
| | | | | | CRT |
| | | | | | BAT: −1.05 ± 1.2 |
| | | | | | Control: −0.13 ± 2.5 |
| | | | | | P = 0.78 |
| | | | | | No-CRT |
| | | | | | BAT: −8.89 ± 4.0 |
| | | | | | Control: 0.18 ± 2.2 |
| | | | | | P = 0.09 |
| | | | | | Not reported |

(Continues)
Table 3 (continued)

| Study, Year | Study arms, N | NYHA class | QoL | Six min hall walk distance (m) | Hospitalizations |
|-------------|---------------|------------|-----|-----------------------------|------------------|
|             |               |            |     |                             | Control (n = 36): 0.95 ± 2.23 |
|             |               |            |     |                             | No-CAD BAT (n = 16): −3.63 ± 2.80 |
|             |               |            |     |                             | Control (n = 14): −2.14 ± 1.73 |
|             |               |            |     |                             | *P* = 0.677 |
| Mueller-Ehmsen et al., 22 [Abstract] BAT, 57 | Baseline: 3.0 ± 0.0 | Baseline: 44.1 ± 22.1 | Baseline: 301.2 ± 81.2 | Questionnaire: Living with Heart Failure score |
| 6 month variation: | −0.9 ± 0.1 | −14.4 ± 3.1 | 85.2 ± 15.2 | 0.9 ± 0.1 |
| *N* available: 50 | *P* < 0.001 | *P* < 0.001 | < *P* < 0.001 |

BAT, baroreflex activation therapy; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; NYHA, New York Heart Association; SBP, systolic blood pressure.

*Causes of death: one succumbed to septic shock that developed over pneumonia following a general decline in health 11.2 months post-activation. The second one, who was an insulin-dependent diabetic patient, died 16.2 months post-activation of electromechanical dissociation in the context of a new (first after BAT activation) episode of acute heart failure. Both patients suffered a post-ischaemic dilated cardiomyopathy.

The abstract did not report the causes of death.

Discussion

This review summarized the available evidence on the use of BAT for patients with HFrEF. The results indicate that the therapy is safe and improves clinical outcomes such as NYHA class of HF, quality of life, 6 min walk test, and hospitalization rates. BAT did not report any changes after therapy. The only RCT available reported a measure of MSNA.

**Other reported outcomes**

Besides the reported outcomes earlier, the publications from Gronda et al. reported a serial measurement of MSNA. The study from Gronda et al. also reported the effects of BAT on systolic blood pressure. Aortic stiffness was evaluated by pulse wave velocity at the third month evaluation after BAT. Interestingly, no differences were reported in the control group. No effects on aortic blood pressure were observed.

The HOPE4HF trial also reported the effects of BAT on systolic and diastolic blood pressure. It was observed an increase in systolic blood pressure as well as pulse pressure in patients who underwent BAT, 6 months after intervention. In contrast with pulse pressure, trends towards decreasing systolic blood pressure and pulse pressure were found in the control group. No effects on diastolic blood pressure were observed.

The study from Gronda et al. also reported the effects of chronic carotid baroreceptor activation on arterial stiffness in HFrEF patients. Aortic stiffness was evaluated by pulse wave velocity at the third month evaluation after BAT. Similarly, no differences were reported in the control group. The study reported a measure of 26 ± 3, which was also significantly different from baseline (*P* < 0.001).

The authors also reported the effects on diastolic blood pressure. At 6 months follow-up, the study demonstrated a reduction from 45.1 ± 7.7 to 31.3 ± 8.3 (14% decrease) and from 67.6 ± 12.7 to 51.1 ± 11.6 (33% decrease), respectively (P < 0.001). The decrease was sustained at the 2-year follow-up (215 ± 42 to 153 ± 34, 29% decrease, *P* < 0.001) and at the 4-year follow-up (247 ± 43 to 192 ± 31, 26% decrease, *P* < 0.001).

**Other reported outcomes**

Besides the reported outcomes earlier, the publications from Mueller-Ehmsen et al. reported the effects on diastolic blood pressure. At 6 months follow-up, the study demonstrated a reduction from 45.1 ± 7.7 to 31.3 ± 8.3 (14% decrease) and from 67.6 ± 12.7 to 51.1 ± 11.6 (33% decrease), respectively (P < 0.001). The decrease was sustained at the 2-year follow-up (215 ± 42 to 153 ± 34, 29% decrease, *P* < 0.001) and at the 4-year follow-up (247 ± 43 to 192 ± 31, 26% decrease, *P* < 0.001).

**Discussion**

The study from Gronda et al. also reported the effects of chronic carotid baroreceptor activation on arterial stiffness in HFrEF patients. Aortic stiffness was evaluated by pulse wave velocity at the third month evaluation after BAT. Similarly, no differences were reported in the control group. The study reported a measure of 26 ± 3, which was also significantly different from baseline (*P* < 0.001).

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**Other reported outcomes**

Besides the reported outcomes earlier, the publications from Mueller-Ehmsen et al. reported the effects on diastolic blood pressure. At 6 months follow-up, the study demonstrated a reduction from 45.1 ± 7.7 to 31.3 ± 8.3 (14% decrease) and from 67.6 ± 12.7 to 51.1 ± 11.6 (33% decrease), respectively (P < 0.001). The decrease was sustained at the 2-year follow-up (215 ± 42 to 153 ± 34, 29% decrease, *P* < 0.001) and at the 4-year follow-up (247 ± 43 to 192 ± 31, 26% decrease, *P* < 0.001).
provide additional beneficial effects on patients with HFrEF.\textsuperscript{19}

Up to now, most of the studies in human subjects evaluating BAT focused on patients with resistant hypertension. A recent meta-analysis\textsuperscript{25} published in the literature assessing safety and efficacy of BAT in patients with resistant hypertension demonstrated that systolic and diastolic blood pressure decreased in patients who underwent BAT as early as 3 months and sustained up to 24 months after therapy.\textsuperscript{25} The review included 12 studies in the qualitative analysis and five in the meta-analysis. In relation to the effects of BAT on blood pressure in patients with HFrEF, the HOPE4HF\textsuperscript{7} trial has found that BAT significantly increased blood pressure, as well as pulse pressure. In the control group, the authors reported trends towards decreasing systolic blood pressure and pulse pressure. No effects on diastolic blood pressure were identified.

Previous data have shown that the MSNA is high in both HFrEF and severe hypertension (\textsuperscript{26}), addressing similar autonomic imbalance in both conditions. In patients with advanced HFrEF, low systolic pressure is a marker of unfavourable outcomes. In relation to severe hypertensive patients, the persistency of high levels of blood pressure leads to unfavourable outcomes.

As said earlier, the systematic review evolving resistant hypertension patients\textsuperscript{25} and the HOPE4HF trial\textsuperscript{7} demonstrated opposite effects on blood pressure. BAT was demonstrated to rebalance the autonomic system restoring the appropriate physiological response. This result is unique in the device cardiovascular therapy setting.

In the HFrEF field, although the promising results, there is much yet to learn to achieve conclusive results about the use of BAT for HFrEF patients. Since the first-generation system, surgery duration, complexity, and the safety of BAT system have improved significantly. The available data indicate that, with proper training, the procedure is safe (19). In terms of efficacy, improvements in clinical outcomes have been reported in the included studies, as mentioned earlier. However, a pivotal trial is still need to make assertive conclusions.

This study has some limitations important to mention. Only three studies are available in the literature answering our review research question, and only one of them was designed as an RCT. In addition, three of the 10 included publications were only abstracts published in conferences and not peer review publications. The small sample size and the heterogeneity across the included studies lacked the power to make conclusive statements.

Importantly, we designed our study as a rapid systematic review. We did perform all the steps of a traditional systematic review; however, they were executed by only one reviewer. This approach has been previously described in the literature, and its value has been recognized by important organizations, such as the Cochrane Collaboration. A rapid review has a shorter time of execution, making it possible to obtain results timely and with reduced costs.

Despite those limitations, to our knowledge, this is the first review using a systematic methodology that aimed to retrieve and report the available data on the safety and efficacy of BAT for patients with HFrEF. We believe that our study can provide significant information to support future clinical trials and registries in this area.

In conclusion, the results of this review suggest that BAT is safe and improves clinical outcomes in HFrEF patients. Although the promising results, there is currently insufficient evidence on the safety and efficacy of BAT for patients with HFrEF to draw meaningful conclusions. Further high-quality RCTs with long-term follow-up are still needed in order to obtain conclusive results.

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**ESC Heart Failure 2020; 7: 3–14**

DOI: 10.1002/ehf2.12543
Appendix

PubMed search—68 citations

| Search | Query                                                                 | Items found |
|--------|----------------------------------------------------------------------|-------------|
| #3     | Search (#1 AND #2)                                                   | 68          |
| #2     | Search "Heart Failure"[Mesh] OR "Cardiac Failure"[Title/Abstract] OR "Heart Decompensation"[Title/Abstract] OR "Decompensation, Heart"[Title/Abstract] OR "Heart Failure, Right-Sided"[Title/Abstract] OR "Heart Failure, Right Sided"[Title/Abstract] OR "Right-Sided Heart Failure"[Title/Abstract] OR "Right Sided Heart Failure"[Title/Abstract] OR "Myocardial Failure"[Title/Abstract] OR "Congestive Heart Failure"[Title/Abstract] OR "Heart Failure, Congestive"[Title/Abstract] OR "Heart Failure, Left-Sided"[Title/Abstract] OR "Heart Failure, Left Sided"[Title/Abstract] OR "Left-Sided Heart Failure"[Title/Abstract] OR "Left Sided Heart Failure"[Title/Abstract] | 135 480      |
| #1     | Search "baroreflex activation"[Title/Abstract] OR barostim*[Title/Abstract] OR "baroreceptor stimulation"[Title/Abstract] OR "baroreceptor activation"[Title/Abstract] OR "carotid stimulation"[Title/Abstract] OR baroreceptor-activat* in Title Abstract Keyword AND "Heart Failure" OR "Cardiac Failure" OR "Heart Decompensation" OR " Decompensation, Heart" OR "Myocardial Failure" OR "Congestive Heart Failure" in Title Abstract Keyword—(Word variations have been searched) | 954         |

CENTRAL search—29 citations

""baroreflex activation" OR barostim* OR "baroreceptor stimulation" OR "baroreceptor activation" OR "carotid stimulation" OR baroreceptor-activat* in Title Abstract Keyword AND "Heart Failure" OR "Cardiac Failure" OR "Heart Decompensation" OR " Decompensation, Heart" OR "Myocardial Failure" OR "Congestive Heart Failure" in Title Abstract Keyword—(Word variations have been searched)

Scopus search—146 citations

("baroreflex activation" OR barostim* OR "baroreceptor stimulation" OR "baroreceptor activation" OR "carotid stimulation" OR baroreceptor-activat*) AND ("Heart Failure" OR "Cardiac Failure" OR "Heart Decompensation" OR " Decompensation, Heart" OR "Myocardial Failure" OR "Congestive Heart Failure")

Web of Science search—57 citations

("baroreflex activation" OR barostim* OR "baroreceptor stimulation" OR "baroreceptor activation" OR "carotid stimulation" OR baroreceptor-activat*) AND ("Heart Failure" OR "Cardiac Failure" OR "Heart Decompensation" OR " Decompensation, Heart" OR "Myocardial Failure" OR "Congestive Heart Failure")

EMBASE search—141 citations

("baroreflex activation‘ OR barostim* OR ‘baroreceptor stimulation’ OR ‘baroreceptor activation’ OR ‘carotid stimulation’ OR ‘baroreceptor activat*‘) AND (‘heart failure‘de OR ‘cardiac failure‘de OR ‘heart decompensation‘de OR ‘decompensation, heart‘de OR ‘myocardial failure‘de OR ‘congestive heart failure‘de)