Current Heart Failure Reports (2019) 16:38–46
https://doi.org/10.1007/s11897-019-0422-3

DEVICES (C VELTMANN, SECTION EDITOR)

Cardiac Contractility Modulation and Baroreflex Activation Therapy in Heart Failure Patients

James A. Mann[1] · William T. Abraham[1]

Published online: 14 February 2019

Abstract

Purpose of Review Despite advances in medical therapy, heart failure with reduced ejection fraction (HFrEF) is still a leading cause of mortality, hospitalizations, and healthcare costs. In this review, we describe two novel, implantable devices for the treatment of patients with HFrEF, cardiac contractility modulation (CCM), and baroreflex activation therapy (BAT), and summarize literature regarding these devices from the last 5 years.

Recent Findings CCM improves quality of life and functional capacity as assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) score, 6-min hall walk test (6MHWT) distance, New York Heart Association (NYHA) functional class, peak oxygen consumption (pVO_2), heart failure (HF) hospitalizations, and mortality. BAT improves MLHFQ, 6-min walk test distance, NYHA functional class, and HF hospitalizations. Both devices have been shown to be safe.

Summary CCM and BAT have been shown to be safe and effective treatment modalities for HFrEF. CCM has been approved for use in Europe and has been implanted in thousands of patients. BAT has also been approved in Europe and continues to show promise in treating patients with HFrEF who fail optimal medical therapy (OMT). At present, both therapies are considered investigational in the USA.

Keywords Cardiac contractility modulation · Baroreflex activation therapy · Device therapy for heart failure with reduced ejection fraction

Introduction

In the USA, HF is a major contributor to morbidity, mortality, poor quality of life, hospitalizations, and healthcare costs with HFrEF being responsible for about half of all HF cases. Despite advancements in medicine and device therapies, the incidence of HF has remained largely stable with greater than 650,000 new cases diagnosed annually. The lifetime risk of developing HF is 20% for Americans 40 and older and the incidence increases with age. The prevalence of HF continues to rise over time. Between 2011 and 2014, 6.5 million Americans 20 years of age or older had HF compared to 5.7 million between 2009 and 2012. Survival rates have improved but the mortality rate 5 years after diagnosis remains approximately 50%. The all cause rehospitalization rate for patients with HF is 25% within 1 month and the USA spends more than $30 billion annually on HF care [1, 2, 3•].

Among HFrEF patients who fail optimal medical therapy, a large treatment gap exists between those who qualify for cardiac resynchronization therapy (CRT) and those who qualify for left ventricular assist devices (LVAD) or heart transplantation. CRT is currently indicated for HFrEF in patients with New York Heart Association (NYHA) class II - ambulatory class IV symptoms despite ≥ 3 months of guideline-directed medical therapy (GDMT), have an EF ≤ 35%, QRS duration ≥ 150 ms, LBBB pattern, and sinus rhythm (level of evidence A for class III/IV; level of evidence B for class II) [4]. Although somewhat weaker, indications for CRT also exist for those meeting the above criteria with QRS duration ≥ 120 ms and < 150 ms and LBBB and for those in atrial fibrillation and those who are dependent on ventricular pacing [4].

This article is part of the Topical Collection on *Devices*

✉ James A. Mann
james.mann@osumc.edu

[1] Division of Cardiovascular Medicine, Wexner Medical Center at The Ohio State University, 473 W. 12th Avenue Suite 200, Columbus, OH 43210, USA

Patients that do not meet these criteria and are not symptomatic enough for an LVAD are the patients with greatest need and the greatest possibility of benefit from novel device-based treatment interventions. Although many patients in this group still qualify for implantable cardioverter defibrillator (ICD) therapy to prevent sudden cardiac death, they still have no device-based treatment option to improve the symptoms associated with HF. As will be presented in this review, CCM and BAT have been shown to be potentially important new options for these patients.

Cardiac Contractility Modulation

The Device

The CCM device (Impulse Dynamics, Stuttgart, Germany) has gone through several generations since its inception. The Optimizer System for the delivery of CCM appears similar to a pacemaker in that it consists of a pulse generator and intracardiac leads. In previous versions of the device, an atrial lead was used for sensing and was placed intravascularly similar to standard pacemakers. The newest generation, the Optimizer Smart (Fig. 1), has only two ventricular leads used for both sensing and pacing that are screwed into the right ventricular septum. A small prospective blinded randomized trial in 2017 showed that the efficacy and safety of CCM were similar when the impulse signal was delivered through either one or two ventricular leads supporting investigation into the use of a single ventricular lead in future models [5••]. The pulse generator is most often placed in the right pectoral region. The generator has a rechargeable battery and the system comes with a battery charger that patients can use at home.

The fact that the newest version, Optimizer Smart, no longer requires an atrial lead for atrial sensing means that CCM can now be offered to patients with atrial fibrillation. The previous version, the Optimizer IVs, required sinus rhythm to function properly because the algorithm requires intracardiac P wave sensing to correctly time the ventricular impulse. However, one study presented five patients with atrial fibrillation who were able to achieve 96–100% CCM ventricular stimulation with the Optimizer IVs. All patients had a concomitant CRT device. They achieved intentional atrial undersensing by the CRT device by programming atrial sensitivity to 4 mV which caused 100% atrial stimulation. This atrial stimulation was sensed by the CCM device and allowed appropriately timed CCM impulse delivery to the ventricles [6].

The ventricular leads deliver a biphasic impulse to the right ventricular septum. The mechanism of action is multifactorial and involves improved uptake of calcium into the sarcoplasmic reticulum which improves extracellular calcium intake during depolarization and calcium-induced calcium release

Fig. 1 The Optimizer Smart—the newest cardiac contractility modulation device

from the sarcoplasmic reticulum thereby increasing contractility [7]. CCM has been shown to reverse some of the pathological remodeling and gene expression associated with HFrEF. Two patients with HFpEF were implanted with CCM and were followed longitudinally. They showed improvement in symptoms (MLHFQ), functional status (NYHA, 6MHWT), and histology on endomyocardial biopsy. Histologically and biochemically, there was an increase in titin, troponin, myosin light chain, kinases, calcium handling, and an improvement in collagen composition. There was also an early improvement in diastolic function and EF reserve [8].

The impulses delivered by CCM are said to be "non-excitatory" in that they are delivered during the absolute refractory period and do not cause a new depolarization or contraction. Instead, these carefully timed stimuli increase the strength of ventricular contraction in a way that is different than CRT therapy [9]. In fact, these effects have been shown to be additive in patients with CRT and a prolonged QRS [10].

The total duration of impulse delivery per day varied between trials and is currently based on patient and physician preferences. A small single-center pilot study consisting of 19 patients suggested there was no difference between CCM

Fig. 2 The Barostim Neo—the newest baroreflex activation therapy device

delivery for 3, 5, or 7 h per day in regard to MLHFQ, pVO_2, NYHA classification, and 6-min walk test [11].

Target Patient Population

Current evidence suggests that CCM is best suited for HFrEF patients with a normal or mildly prolonged QRS duration < 130 ms (i.e., patients that generally are not candidates for CRT), with mild to moderate reduction in LVEF ranging from 25 to 45%. The EchoCRT trial showed that CRT did not reduce the rate of death or hospitalization for heart failure and even may increase the rate of mortality in patients with HFrEF and a QRS < 130 ms [12]. In addition, the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure state that CRT is contra-indicated in patients with a QRS duration < 130 ms [13]. Therefore, CCM has the potential to fill a significant gap in device-based therapy (Fig. 2). The FIX-HF-5C or "confirmatory" trial was a prospective randomized controlled comparison of OMT alone versus OMT plus CCM in this group of patients [14, 15]. It was designed to confirm observations from a prospective subgroup analysis of the FIX-HF-5 trial [16, 17]. FIX-HF-5 did not meet its primary efficacy endpoint of ventilatory anaerobic threshold (VAT) but did show improvement in pVO_2 and MLHFQ. FIX-HF-5C enrolled a specific group of patients defined by the subgroup analysis from the FIX-HF-5 trial: those with NYHA functional class III and ambulatory IV HF despite OMT, EF of 25–45% by echocardiography and normal sinus rhythm with QRS duration < 130 ms. All patients with EF ≤ 35% were required to have an ICD. Investigators showed that in this specific group of patients, CCM was shown to be safe, improve exercise tolerance, quality of life, and the composite of cardiovascular death and HF hospitalizations [15].

In a study by Zhang et al., there were similar decreases in left ventricular end systolic volume (LVESV) between patients with a QRS duration < 120 ms who received CCM compared to patients with a QRS duration of 120–150 ms who received CRT and no CCM [18]. This was an observational study with a 3-month follow-up period.

To summarize the effects of CCM in the targeted HF population (Table 1)

A. *Quality of life and exercise/functional capacity:* Evidence for CCM's benefit is strongest for improvements in quality of life (QoL), exercise capacity, and functional capacity. The primary endpoint of FIX-HF-5C was improvement in the average difference in pVO_2 [15]. At 24 weeks, the average difference between treatment and control was 0.836 mL O_2/kg/min which was significant based on the Bayesian credible interval. The secondary endpoint for FIX-HF-5C was the change in QoL measured by the MLHFQ score and NYHA functional class. The mean

Table 1 Major beneficial effects of CCM and BAT in recent literature

CCM	BAT
Improved MLHFQ Score	Improved MLHFQ Score
Increased 6MHWT Distance	Increased 6MHWT Distance
Improved NYHA Functional Class Ranking	Improved NYHA Functional Class Ranking
Shown to be safe	Shown to be safe
Increased pVO_2	Decreased MSNA
Decreased mortality and HF hospitalizations	Decreased HF hospitalizations

CCM cardiac contractility modulation, *BAT* baroreflex activation therapy, *MLHFQ* Minnesota Living with Heart Failure Questionnaire, *6MHWT* 6-minute hall walk test, *NYHA* New York Heart Association, *pVO_2* peak oxygen uptake, *MSNA* muscle sympathetic nerve activity, *HF* heart failure

difference in MLHFQ score at 24 weeks between CCM and control was −11.7 points where a negative value indicates improvement. The odds of improving by at least 1 NYHA functional class with CCM was 5.97 times the odds of improving among control patients.

Consistent with these findings, Kuschyk et al. showed in a retrospective single-center trial consisting of 81 patients that mean NYHA class significantly improved from 3.0 ± 0.5 to 2.3 ± 0.9. pVO_2 also increased in the CCM group but not significantly [19].

A meta-analysis including three randomized trials (FIX-HF-4, FIX-HF-5 pilot study and FIX-HF-5) and 641 patients showed that CCM significantly improved pVO_2, 6MHWT distance, and MLHFQ score. The mean difference in pVO_2 was 0.71 mL O_2/kg/min, in 6MHWT distance was 13.92 m and the MLHFQ score was −7.17 [20].

B. *Mortality:* Several studies have suggested improvement in survival in CCM patients; however, most trials are relatively small. In the study by Kuschyk et al., mortality rates were lower in NYHA II-III HF patients treated with CCM than rates predicted by the MAGGIC integer score [19]. The mean follow-up was 34 months. Mortality rates were significantly lower at 1 year for CCM patients (5.2%) than that predicted by the MAGGIC score for the same patients (18.4%). The difference at 3 years was not statistically significant but the log-rank analysis for all events up to 3 years showed that CCM patients had significantly lower mortality rates.

Kloppe et al. showed that mortality rates in heart failure patients with NYHA class II-III and QRS ≤ 130 ms were significantly lower when patients were treated with CCM than survival predicted by the Seattle Heart Failure Model at 1- (0% vs. 6.1%), 2- (3.5 vs. 11.8%), and 5- (14.2% vs. 27.7%) year follow-up. However, the cohort contained only 68 patients from two German cities [21].

A case-control study by Liu et al. showed a significant difference in mortality in the entire cohort of 41 patients compared to 41 controls after a mean follow up of 75 ± 19 months and 69 ± 17 months, respectively. Mortality in the CCM group was 39% versus 71% in matched controls but when stratified by baseline EF, CCM patients with EF < 25% had no mortality benefit while patients with EF ≥ 25–40% had significant mortality benefit [22].

There was no difference in overall survival in the FIX-HF-5C trial but the treatment group did show improvement in the composite of cardiovascular death and HF hospitalizations [15]. Taking into account the totality of mortality data, it is fair to conclude that CCM is safe (i.e., unlikely to have an adverse effect on survival) and demonstrates the potential to improve clinical outcome.

C. *Hospitalizations:* HF hospitalizations were lower in CCM patients with EF ≥ 25–40% compared to matched controls in the case-control study by Liu et al. However, there was no significant difference in HF hospitalization in the cohort as a whole [22].

There was no significant difference in survival free of hospitalization in FIX-HF-5C trial, although there were fewer HF hospitalizations in the CCM group [15].

D. *Safety:* CCM has been shown to be safe in recent trials. FIX-HF-5C met the primary safety endpoint of an 89.7% complication-free rate. The criterion for satisfying the safety analysis was that the proportion of complication-free subjects was significantly larger than 70% (one-sided significance level of 0.025) [15].

However, one study showed a higher number of adverse events in a 143 patient cohort. Müller et al. showed an aggregate of 34 device and/or procedure-related serious adverse events reported in 25 patients during a 2-year study period, most commonly due to lead migration [23].

E. *Other outcomes:* In the small retrospective trial by Kuschyk et al., left ventricular mean EF significantly increased from 23.1 ± 7.9 to 29.4 ± 8.6% and mean end diastolic and systolic diameters significantly decreased from 66.5 ± 7.7 and 57.9 ± 7.8 mm to 64.6 ± 8.9 and 54.8 ± 9.2 mm, respectively. Mean NT-proBNP, a strong correlate of HF outcomes, also decreased [19].

Seventy patients treated with CCM had no change in mean QRS duration after 2.8 year mean follow-up in a study published in 2014 by Röger et al. [24]. Investigators noted that CCM prevented the chronic ventricular depolarization delay that often occurs in heart failure patients and is known to be a negative prognostic indicator. They speculated that CCM's preservation of QRS duration was indicative of positive prognostic effects of the device.

FIX-HF-5 and FIX-HF-5C investigators noticed a particularly strong effect of CCM on subjects with EF ≥ 35% when compared to subjects with EF < 35%. Compared to control, treatment effects in the ≥ 35% subgroup were statistically significant and were increased pVO_2 by 1.76 mL/kg/min, improved MLHFQ by 15 points, improvement in NYHA functional class by ≥ 1 in 71% of treatment patients compared with only 57% in the control group, and increase in 6MHWT distance by 43 ± 80.7 m in the treatment group compared to 9.3 ± 87.4 m in the control group [15, 17].

Baroreflex Activation Therapy

The Device

Autonomic nervous system imbalance, specifically, increased sympathetic tone and decreased parasympathetic tone, is known to contribute to HFrEF etiology and progression [25]. Baroreflex activation therapy works by activating the parasympathetic system and inhibiting the sympathetic system at the level of the baroreceptors in the carotid sinus with an electrical impulse from an implanted pulse generator similar to that of a pacemaker or neurostimulation device. The fact that BAT both stimulates vagal outflow and inhibits sympathetic outflow makes it distinctly different from vagal stimulation alone. The direct effect is favorable change in vascular resistance. Because of this effect, BAT has been shown in several studies to be effective in treating resistant hypertension [26, 27].

The Barostim neo device (CVRx, Inc., Minneapolis, MN) (Fig. 2) is the newest generation device for the delivery of BAT. It consists of a pulse generator similar to a pacemaker and a carotid sinus lead that terminates into a small circular electrode. The device uses a wireless programmer that uses a laptop, custom software, and a transceiver [28•].

The implantation procedure has been extensively explained previously by Weaver et al. [28•] and is briefly summarized here. The right carotid artery is preferentially chosen for its increased sensitivity to BAT [29]. After exposure of the artery, mapping for sensory endings of the carotid sinus nerve, or baroreceptors, is initiated. Stimulation is activated to test the baroreflex response which is represented by decreased heart rate and systolic blood pressure. After the location of maximum response is identified, the electrode is sutured onto the carotid artery. Finally, an infraclavicular subcutaneous chest wall pocket is created for the pulse generator and the lead is routed around the sternocleidomastoid and into the pulse generator [28•].

The results of the ongoing Barostim Neo-Baroreflex Activation Therapy for Heart Failure (BeAT-HF) pivotal trial are eagerly anticipated [30]. The BeAT-HF trial is a randomized controlled trial that is actively recruiting patients with NYHA functional class II HF and EF 35% despite GDMT but excluding patients actively receiving CRT. The experimental arm receives BAT and GDMT while the control group continues to receive GDMT alone. The primary outcomes are rate of cardiovascular mortality and heart failure morbidity, major adverse neurological and cardiovascular events (MANCE), NT-proBNP, 6MHWT, and MLHFQ. The estimated enrollment is 480 participants, with an adaptive trial design that allows for sample size re-estimation to a larger number of participants. The BeAT-HF trial is one of the first studies accepted into the U.S. Food and Drug Administration's novel Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions (EAP) program [31]. The study start date was April 2016 and the estimated completion date is April 2021 [30].

Target Patient Population

The target population for BAT is not as clearly defined as it is for CCM. A group of Italian investigators suggest possible characteristics that may help to identify patients that are most likely to benefit from BAT [32•]. They suggested escalating diuretic requirements, recurrent heart failure hospitalizations, and poor heart failure prognosis as determined by the North American Interagency Registry for Mechanically Assisted Circulatory Support (NAIRMACS) scale may identify potential candidates for BAT. Patients that fit into profiles 6 (exertion limited) and 7 (advanced NYHA class III symptoms) on the NAIRMACS scale are likely good candidates for BAT. Patients with profiles 1–5 and patients with end stage or unstable HF may have irreversible disease and would not be likely to benefit from BAT. Additionally, patients with several comorbidities associated with HF such as obstructive sleep apnea (OSA), diabetes, and chronic kidney disease, may be less likely to respond to BAT because the symptoms may be related to the comorbidities rather than HF, especially considering diseases such as OSA increase sympathetic activation. That said, recent clinical trial data suggests that BAT may benefit NYHA Class III patients with reduced EF, as summarized below (Table 1, Fig. 3):

A. *Quality of life and functional/exercise capacity:* Abraham et al. evaluated 146 patients in the first randomized trial comparing GDMT alone versus GDMT plus BAT. Compared to controls, patients in the BAT group experienced significant and substantial improvements in the 6MHWT distance (59.6 ± 14 m vs. 1.5 ± 13.2 m; $p = 0.004$), MLHFQ score (-17.4 ± 2.8 points vs. 2.1 ± 3.1 points; $p < 0.001$), NYHA functional class, and NT-proBNP at 6 months. A follow-up study on this patient population showed that BAT plus GDMT at 12-month follow-up had significant improvement in NYHA functional class, MLHFQ, and 6MWT distance compared to GDMT alone, demonstrating the durability of BAT effectiveness [28•]. This study also demonstrated the potential for BAT to reduce the risk of HF hospitalizations in these HF patients [33••].

   In a substudy of this investigation, BAT patients without CRT showed significant improvement in MLHFQ, NYHA functional class, NT-proBNP, EF, and rate of HF hospitalizations compared to controls. BAT patients with CRT also showed improvements in these efficacy endpoints; however, improvement was less and was not statistically significant compared to control [34•]. Thus,

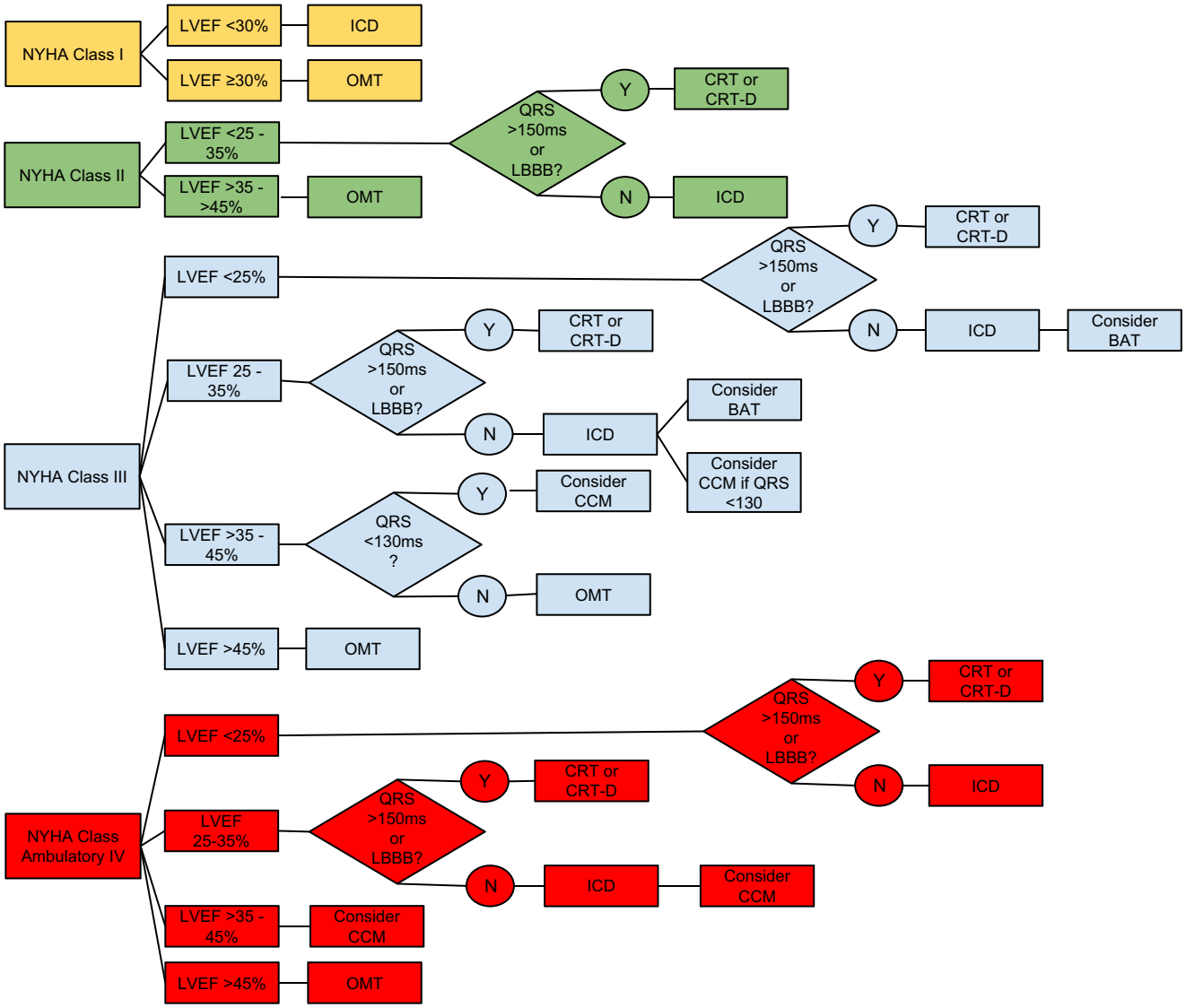

Fig. 3 Device-based flow chart for patients with heart failure and reduced ejection fraction. *NYHA*, New York Heart Association; *LVEF*, left ventricular ejection fraction; *ICD*, implantable cardioverter defibrillator; *OMT*, optimal medical therapy; *LBBB*, left bundle branch block; *CRT*, cardiac resynchronization therapy; *BAT*, baroreflex activation therapy; *CCM*, cardiac contractility modulation.
CCM and BAT are not currently FDA approved in the USA

the ongoing BeAT-HF trial excludes the enrollment of patients with or who are eligible for CRT devices.

The effectiveness of BAT therapy in an open-label single-center study in an 11 patient cohort was followed over the course of three studies by one group of investigators. All patients had NYHA class III HF, EF < 40%, and OMT and were ineligible for CRT. The first study showed a significant improvement in muscle sympathetic nerve activity (MSNA) (from 45.1 ± 7.7 to 31.3 ± 8.3 bursts/min and from 67.6 ± 12.7 to 45.1 ± 11.6 bursts/100 heartbeats) at 6-month follow-up. NYHA class, MLHFQ score, 6MHWT distance, and EF compared at 1, 3, and 6 months also improved significantly [35]. During the 6 months prior to implant, 8 of the 11 patients were admitted for HF for a total of 125 days. Through the 6-month follow-up period, only one patient was admitted for HF for 6 days. Nine of the 11 patients survived the follow-up period.

The second study showed that the significant improvements seen at 6 months in MSNA, MLHFQ score, 6MHWT distance, and NYHA were maintained at 21.5 ± 4.2 month follow-up. EF remained stable and the hospitalization rate decreased significantly [36].

The third study measured these effects at a final follow-up of 43.5 ± 2.1 months. MSNA improved significantly from 46.2 ± 2.4 to 31.3 ± 3.0 e 26.6 ±

2.0 bursts/min. Hospitalization rate and EF also improved significantly. Seven of the 11 original patients survived the follow-up period [37].

B. *Hospitalizations:* As stated previously, Gronda et al. showed a significant decrease in the hospitalization rate of patients with BAT at 21.5 ± 4.2 month follow-up compared to the hospitalization rate prior to initiation of BAT. Prior to activation of BAT, the cohort spent a total of 155 days in the hospital and after BAT, they spent a total of 7 days at 6 months and 45 days at 21.5 ± 4.5 months [35, 36]. The study done at 43.5 ± 2.1 month follow-up showed a significant decrease in hospitalization rate when measured as days/years/patients from 10.3 ± 2.5 pre-implant to 1.01 ± 1.4 at 43.5 months [37•].

As noted above, the randomized pilot study of BAT demonstrated a trend toward fewer days in the hospital in BAT patients but there was no significant difference compared to controls in this study [33••].

C. *Safety:* In the study conducted by Abraham et al. [33••] BAT met the primary safety endpoint with an overall MANCE free rate of 97.2% (lower 95% confidence bound 91.4%). The system- and procedure-related complication event-free rate was 85.9% (lower 95% confidence bound 77.3%). A post hoc subgroup analysis of this study was done to investigate the efficacy and safety of BAT in patients with and without coronary artery disease (CAD). Results showed no significant differences which suggests that these results can be applied to ischemic and non-ischemic cardiomyopathy [38].

In the report from Weaver et al. [28•], there were no MANCE between 6 and 12 months (During the first 6 months there were 2 MANCE for an overall event-free rate of 97.2%.) The rate of freedom from system- and procedure-related complications was 85.9. There was no significant difference in the percentage of days without a complication related to the patient's underlying cardiovascular condition, the device, or the procedure. The mean percentage of days free from these complications was 92.1% for both the treatment and control groups.

D. *Other outcomes:* Seven patients with ICDs underwent BAT implant and at mean follow-up of 11.7 ± 6.4 months, there were no oversensing or undersensing episodes and no device-device interactions were noted. None of the seven patients received an ICD shock during the follow-up period [39]. In a case study, one patient with BAT underwent subcutaneous ICD (S-ICD) implantation. While concomitant BAT and S-ICD was determined to be safe, there was noise interaction caused by the BAT device which limited programming to maximal impulse and caused patient discomfort. However, oversensing and the inappropriate shocks did not occur [40].

One study showed a significant improvement in 3D EF at 43 months (36.7 ± 3) of BAT therapy compared to baseline (32.6 ± 6.2) [34•].

BAT surgical skill improves rapidly with increased number of procedures which can be seen by decreased total procedural time and intraprocedural mapping time. Weaver et al. [28•] showed mean implant and mapping time at first procedure performed by a center of 106 ± 37 and 41 ± 23 min, respectively, decreased to 83 ± 32 and 20 ± 14 min by the third procedure.

Conclusion

Despite major advancements in medication and device therapies, the number of patients suffering from HF symptoms and HF-related mortality has continued to rise. CCM and BAT have been shown to be safe and significantly improve quality of life, NYHA functional class, and 6MHWT. CCM also significantly improves pVO_2 and the pathologic cellular remodeling associated with HFrEF, and some evidence suggests a decrease in mortality. BAT improves MSNA and hospitalization rate, and has previously been shown in several studies to improve resistant hypertension. CCM and BAT are already approved for use in Europe, and following the results of recent and ongoing studies, these novel device therapies may soon become available in the USA.

Compliance with Ethical Standards

Conflict of Interest James Mann declares he has no conflict of interest.

William Abraham has received consulting fees and speaking honoraria from CVRx and are members of the CVRx Heart Failure Executive Steering Committee and he has received consulting fees from Impulse Dynamics.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147–239.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Card Fail. 2017;23(8):628–51.
3. • Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart Disease and Stroke Statistics-2018 Update: a report from the American Heart Association. Circulation. 2018;137(12):e67–e492 **This report from the American Heart Association has the most up-to-date statistics related to heart disease, stroke, and other cardiovascular and metabolic diseases.**
4. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2013;127(3):e283–352.
5. Röger S, Said S, Kloppe A, Lawo T, Emig U, Rousso B, et al. Cardiac contractility modulation in heart failure patients: randomized comparison of signal delivery through one vs. two ventricular leads. J Cardiol. 2017;69(1):326–32.
6. Röger S, Schneider R, Rudic B, Liebe V, Stach K, Schimpf R, et al. Cardiac contractility modulation: first experience in heart failure patients with reduced ejection fraction and permanent atrial fibrillation. Europace. 2014;16(8):1205–9.
7. Lyon AR, Samara MA, Feldman DS. Cardiac contractility modulation therapy in advanced systolic heart failure. Nat Rev Cardiol. 2013;10(10):584–98.
8. Tschöpe C, Van Linthout S, Spillmann F, Klein O, Biewener S, Remppis A, et al. Cardiac contractility modulation signals improve exercise intolerance and maladaptive regulation of cardiac key proteins for systolic and diastolic function in HFpEF. Int J Cardiol. 2016;203:1061–6.
9. Borggrefe MM, Lawo T, Butter C, Schmidinger H, Lunati M, Pieske B, et al. Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. Eur Heart J. 2008;29(8):1019–28.
10. Pappone C, Rosanio S, Burkhoff D, Mika Y, Vicedomini G, Augello G, et al. Cardiac contractility modulation by electric currents applied during the refractory period in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 2002;90(12):1307–13.
11. Kloppe A, Mijic D, Schiedat F, Bogossian H, Mügge A, Rousso B, et al. A randomized comparison of 5 versus 12 hours per day of cardiac contractility modulation treatment for heart failure patients: a preliminary report. Cardiol J. 2016;23(1):114–9.
12. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med. 2013;369(15):1395–405.
13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891–975.
14. Abraham WT, Lindenfeld J, Reddy VY, Hasenfuss G, Kuck KH, Boscardin J, et al. FIX-HF-5C Investigators and Coordinators. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation in patients with moderately reduced left ventricular ejection fraction and a narrow QRS duration: study rationale and design. J Card Fail. 2015;21(1):16–23.
15. •• Abraham WT, Kuck K, Goldsmith RL, Lindenfeld J, Reddy VY, Carson PE, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. JACC: Heart Failure. 2018;6(10):874–83 **This randomized controlled trial is central to confirming the place for CCM in patients with HFrEF and is the most recent**.
16. Kadish A, Nademanee K, Volosin K, Krueger S, Neelagaru S, Raval N, et al. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. Am Heart J. 2011;161(2):329–37 e1–2.
17. Abraham WT, Nademanee K, Volosin K, Krueger S, Neelagaru S, Raval N, et al. FIX-HF-5 Investigators and Coordinators. Subgroup analysis of a randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. J Card Fail. 2011;17(9):710–7.
18. Zhang Q, Chan YS, Liang YJ, Fang F, Lam YY, Chan CP, et al. Comparison of left ventricular reverse remodeling induced by cardiac contractility modulation and cardiac resynchronization therapy in heart failure patients with different QRS durations. Int J Cardiol. 2013 Aug 10;167(3):889–93.
19. Kuschyk J, Roeger S, Schneider R, Streitner F, Stach K, Rudic B, et al. Efficacy and survival in patients with cardiac contractility modulation: long-term single center experience in 81 patients. Int J Cardiol. 2015;183:76–81.
20. Giallauria F, Vigorito C, Piepoli MF, Stewart Coats AJ. Effects of cardiac contractility modulation by non-excitatory electrical stimulation on exercise capacity and quality of life: an individual patient's data meta-analysis of randomized controlled trials. Int J Cardiol. 2014;175(2):352–7.
21. Kloppe A, Lawo T, Mijic D, Schiedat F, Muegge A, Lemke B. Long-term survival with cardiac contractility modulation in patients with NYHA II or III symptoms and normal QRS duration. Int J Cardiol. 2016;209:291–5.
22. Liu M, Fang F, Luo XX, Shlomo BH, Burkhoff D, Chan JY, et al. Improvement of long-term survival by cardiac contractility modulation in heart failure patients: a case-control study. Int J Cardiol. 2016;206:122–6.
23. Müller D, Remppis A, Schauerte P, Schmidt-Schweda S, Burkhoff D, Rousso B, et al. Clinical effects of long-term cardiac contractility modulation (CCM) in subjects with heart failure caused by left ventricular systolic dysfunction. Clin Res Cardiol. 2017;106(11):893–904.
24. Röger S, Michels J, Heggemann F, Stach K, Rousso B, Borggrefe M, et al. Long term impact of cardiac contractility modulation on QRS duration. J Electrocardiol. 2014;47(6):936–40.
25. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. J Am Coll Cardiol. 2009;54(5):375–85.
26. Bakris GL, Nadim MK, Haller H, Lovett EG, Schafer JE, Bisognano JD. Baroreflex activation therapy provides durable benefit in patients with resistant hypertension: results of long-term follow-up in the Rheos Pivotal Trial. J Am Soc Hypertens. 2012;6(2):152–8.

27. Bisognano JD, Bakris G, Nadim MK, Sanchez L, Kroon AA, Schafer J, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. J Am Coll Cardiol. 2011;58(7):765–73.
28.• Weaver FA, Abraham WT, Little WC, Butter C, Ducharme A, Halbach M, et al. Surgical experience and long-term results of baroreflex activation therapy for heart failure with reduced ejection fraction. Semin Thorac Cardiovasc Surg. 2016;28:320–8 Elsevier. **This review is a nice summary of the surgical technique required for BAT.**
29. de Leeuw PW, Alnima T, Lovett E, Sica D, Bisognano J, Haller H, et al. Bilateral or unilateral stimulation for baroreflex activation therapy. Hypertension. 2015;65(1):187–92.
30. Barostim Neo - Baroreflex Activation Therapy for Heart Failure (BeAT-HF) Trial. Available at: https://clinicaltrials.gov/ct2/show/NCT02627196?term=Barostim+Neo+-+Baroreflex+Activation+Therapy+for+Heart+Failure+%28BeAT-HF%29+Trial&rank=1. Accessed June 6, 2018.
31. U.S. Food and Drug Administration Expidited Access Pathway Program. Available at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/ucm441467.htm. Accessed June 11, 2018.
32.• Gronda E, Francis D, Zannad F, Hamm C, Brugada J, Vanoli E. Baroreflex activation therapy: a new approach to the management of advanced heart failure with reduced ejection fraction. J Cardiovasc Med (Hagerstown). 2017;18(9):641–9 **This review is a thoughtful summary of BAT including the benefits and challenges.**
33.•• Abraham WT, Zile MR, Weaver FA, Butter C, Ducharme A, Halbach M, et al. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. JACC: Heart Fail. 2015;3(6):487–96 **This paper is central to the body of evidence supporting the incorporation of BAT into common treatment for patients with HFrEF.**
34.• Zile MR, Abraham WT, Weaver FA, Butter C, Ducharme A, Halbach M, et al. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction: safety and efficacy in patients with and without cardiac resynchronization therapy. Eur J Heart Fail. 2015;17(10):1066–74 **Safety results for BAT and demonstration of better effects in patients without CRT.**
35. Gronda E, Seravalle G, Brambilla G, Costantino G, Casini A, Alsheraei A, et al. Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: a proof-of-concept study. Eur J Heart Fail. 2014;16(9):977–83.
36. Gronda E, Seravalle G, Trevano FQ, Costantino G, Casini A, Alsheraei A, et al. Long-term chronic baroreflex activation: persistent efficacy in patients with heart failure and reduced ejection fraction. J Hypertens. 2015;33(8):1704–8.
37.• Dell'Oro R, Gronda E, Seravalle G, Costantino G, Alberti L, Baronio B, et al. Restoration of normal sympathetic neural function in heart failure following baroreflex activation therapy: final 43-month study report. J Hypertens. 2017;35(12):2532–6 **The positive effects of BAT are maintained at long-term follow-up.**
38. Halbach M, Abraham WT, Butter C, Ducharme A, Klug D, Little WC, et al. Baroreflex activation therapy for the treatment of heart failure with reduced ejection fraction in patients with and without coronary artery disease. Int J Cardiol. 2018;266:187–92.
39. Madershahian N, Scherner M, Müller-Ehmsen J, Halbach M, Hickethier T, Velden R, et al. Baroreflex activation therapy in patients with pre-existing implantable cardioverter-defibrillator: compatible, complementary therapies. Europace. 2014;16(6):861–5.
40. Kuffer L, Steven D, Halbach M, Lüker J, den Bruck J, Sultan A. Combination of a subcutaneous ICD in a patient with a baroreceptor activation device: feasibility, safety and precautions: a case report. Pacing Clin Electrophysiol. 2017;40:1486–8.