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# Device Therapy for Heart Failure: New Approaches Under Investigation

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Despite optimal medical therapy (OMT) in patients with chronic heart failure (CHF), disease progression persists and is associated with morbidity and mortality. Novel devices are being designed to capitalize on newer understandings of the pathophysiology of CHF, such as the role of autonomic dysfunction. Devices for baroreceptor activation therapy (BAT), vagal nerve stimulation (VNS), cardiac contractility modulation (CCM), and sleep apnea were reviewed in this session.

The benefits of neuromodulation with BAT were suggested by 2 studies reviewed by Edoardo Gronda, MD, IRCCS MultiMedica, Milan, Italy. BAT, comprising electrical stimulation of the carotid baroreceptors, reduced excessive sympathetic tone that persists despite OMT and contributes to adverse outcomes. Previous work supports targeting baroreceptors in CHF [Floras JS. *J Am Coll Cardiol*. 2009].

In a single-center, open-label, proof-of-concept study, the Barostim Neo device, similar in size to a cardiac pacemaker, was implanted in 10 patients with NYHA class III HF and a LVEF <40% who were on OMT and were not eligible for cardiac resynchronization therapy (CRT) [Gronda E et al. *Eur J Heart Fail*. 2014]. At 6 months, muscle sympathetic nerve activity (MSNA) was improved, with significant reductions in the bursts/minute (from 45.1 to 31.3) and bursts/100 heartbeats (67.6 to 45.1; $P<.01$ for both). Baroreflex sensitivity was significantly improved ($P<.001$ vs baseline), and HF hospitalization (HFH) was reduced. Follow-up to 21 months showed these improvements were sustained, with a consistent decrease in MSNA coupled with an increase in baroreceptor reactivity and reduced HFH.

The first multinational, randomized, clinical trial of BAT with the Barostim Neo device added to OMT showed it was safe and effective at 6 months in 140 patients with HF and reduced EF (HFrEF) [Abraham WT et al. *JACC Heart Fail*. 2015]. The baseline level of NT-pro BNP was higher in the BAT group vs OMT group (1422 vs 1172 pg/mL; $P<.05$), and the level was significantly reduced with BAT ($P=.02$). Systolic blood pressure and pulse pressure were improved with BAT.

Notably, the benefits were greater in the patients ineligible for CRT (n=95) vs those who were eligible for this therapy (n=45) [Zile MR et al. *Eur J Heart Fail*. 2015]. The 6-minute walk distance (6MWD) was improved with BAT by 85.5 vs 16.4 meters in the no-CRT and CRT groups, respectively. The significant improvement in left ventricular ejection fraction (LVEF) with BAT in the no-CRT group (4.3% vs –0.1 with OMT alone; $P<.03$) was comparable with the improvement in LVEF achieved with CRT vs medical therapy in the CARE-HF study, noted Prof Gronda. An impressive reduction was seen in NT-pro BNP with BAT in the no-CRT group (–97 pg/mL vs +79.8 pg/mL in CRT group). Also, HFH days were improved with BAT, and this reduction was greater in the no-CRT group (–8.9 days vs –1.0 in CRT group).

## VAGAL NERVE STIMULATION FOR CHRONIC HEART FAILURE

The results of the Cardio-Fit pilot study, which showed benefit with the VNS device, along with mixed results from the NECTAR-HF and ANTHEM studies, favor the continued development of VNS, according to Martin Borggrefe, MD, University Hospital Heidelberg, Heidelberg, Germany. However, results of ongoing, randomized studies are needed to provide outcomes data to support this approach.

VNS for CHF is an old concept first introduced by Braunwald in 1967 that is being applied with new technology. In CHF, increased sympathetic activity and reduced vagal activity are associated with increased mortality. Among the beneficial effects of parasympathetic VNS are improved baroreflex sensitivity, increased heart rate variability (HRV), changes in expression of nitric oxide and cytokines, and antiarrhythmic effects [Olshansky B et al. *Circulation*. 2008].

A feasibility study of VNS with the CardioFit device in 32 patients with NYHA II to III CHF and an LVEF ≤35% showed it was safe, with successful device implantation in all patients with note of 2 serious adverse events (1 acute pulmonary edema and 1 loose-set screw) and anticipated side effects (cough, dysphonia, and mandibular pain) [De Ferrari GM et al. *Eur Heart J*. 2011]. A clear improvement was seen in NYHA class at 1 year, and heart rate at rest significantly decreased from 81.9 bpm at baseline to 76.0 bpm at 6 months ($P=.038$). At 6 months, vs baseline, there were significant improvements in the Minnesota Living with Heart Failure (MLWHF) score (32 vs 49; $P=.0001$) and 6MWD (471 vs 411 meters; $P=.0012$). Parameters of LV function were also improved at 6 months vs baseline; LV end-diastolic volume (LVEDV) index was 125 vs 132 mL/m$^2$ (no $P$ value reported), LV end-systolic volume (LVESV) index was 89 vs 103 mL/m$^2$ ($P=.02$), and LVEF was 29 vs 22% ($P=.0003$). The improvements with CardioFit were durable at 12 and 24 months, with levels similar to those at 6 months and statistically significant compared with baseline.

CardioFit plus OMT vs OMT alone is being compared in the large-scale, randomized INOVATE-HF trial

[NCT01303718] in approximately 650 patients in the United States and Europe. The primary safety outcome is 90-day system-related complications, and the primary efficacy outcome is unplanned HFH and mortality. Three smaller trials are examining the impact of other neuromodulation devices on LV parameters in patients with HFrEF.

VNS was not successful in the NECTAR-HF sham-controlled, randomized study of 96 patients designed to examine whether a single dose would reduce cardiac remodeling [Zannad F et al. *Eur Heart J*. 2015]. No difference was found for the primary outcome of LVESV at 6 months or all-cause mortality at 18 months. The open-label ANTHEM-HF study showed improvement in LVEF, LVESV, and LVEDV with VNS in patients with HFrEF, but it did not show there was a difference in outcomes with right-sided vs left-sided cervical VNS [Premchand RK et al. *J Cardiac Fail*. 2014].

## CARDIAC CONTRACTILITY MODULATION

CCM is being investigated to treat patients with CHF and who either have a narrow QRS (<120 ms), have LVEF >35%, or do not respond to CRT, a large population for whom treatment is lacking, stated Gerhard Hindricks, MD, University Leipzig, Leipzig, Germany. CCM, which delivers a high-voltage current in the refractory cardiac cycle, had an impressive positive effect on acute hemodynamics, and significantly improved myocardial gene expression during treatment [Butter C et al. *J Am Coll Cardiol*. 2008].

About 2000 patients have been treated with CCM, some followed for >8 years, including 167 patients in the FIX-HF-4 study and 428 patients in the FIX-HF-5 study.

The double-blind FIX-CHF-4 study randomized patients to CCM plus OMT (Group 1; n=80) or OMT alone (Group 2; n=84) for 3 months and then crossed them over to the opposite therapy for another 3 months. CCM was delivered for 7 hours daily [Borggrefe M et al. *Eur Heart J*. 2008]. At baseline, the QRS was 102 ms and LVEF was 29%. The primary outcome of $VO_2$ max increased at 3 months in both groups, but at 6 months it was decreased by 0.86 mL/kg/min in Group 1, which had been switched to sham treatment for the second 3 months, and increased by 0.16 mL/kg/min in Group 2. A similar pattern of improvement in Group 1 vs Group 2 for quality of life and exercise capacity was also seen. Prof Hindricks noted that there appeared to be a significant placebo effect because both groups had improvements during the initial study phase.

The largest clinical trial of CCM to date is the unblinded FIX-CHF-5 study, with a FDA-mandated 6-month efficacy outcome of anaerobic threshold to eliminate the possibility of a placebo effect and a 1-year safety outcome of combined all-cause mortality and all-cause hospitalization. Patients were randomized to CCM (5 h/d; n=215) plus OMT or OMT alone (n=213) and followed for 12 months. Baseline QRS was 102 ms, and LVEF was 26%. CCM was not shown to be noninferior to OMT, with a similar reduction of about –0.15 mL/kg/min in both groups. However, there was a significant difference in the change in peak $VO_2$ (by 0.65 mL/kg/min) with CCM vs OMT ($P$=.024). CCM vs OMT also provided greater improvements in the MLWHF score (–9.7 points; $P$<.001) and NYHA class ($P$=.026). The benefits achieved in FIX-HF-5 were greater in patients with LVEF >35% vs 30% to 35%.

According to Prof Hindricks, CCM provides the only electrical therapy for patients with HFrEF and a narrow QRS, and has been shown to be safe, with no concern for proarrhythmia. Although CCM improved HF-related parameters, there are no data yet to show CCM improves hard outcomes such as hospitalization, morbidity, and mortality.

## IMPLANTABLE DEVICES FOR SLEEP APNEA

Obstructive sleep apnea (OSA) is a comorbidity seen in about 38% of patients with CHF, whereas central sleep apnea (CSA), seen in about 37% of patients, is a contributor to CHF pathophysiology. Implantable devices are being investigated as an alternative to mask-based therapies because of poor adherence and, importantly, to better mimic normal breathing, stated William T. Abraham, MD, Ohio State Wexner Medical Center, Columbus, Ohio, USA.

Hypoglossal nerve stimulation with the Inspire system was shown to effectively treat OSA in the STAR study [Strollo PJ Jr et al. *N Engl J Med*. 2014]. At 12 months, the primary outcome of the median apnea–hypopnea index was reduced from 29.3 to 9.0 events/h ($P$<.001), and the oxygen desaturation index was reduced from 25.4 to 7.4/h ($P$<.001). However, this was primarily a study of OSA, as only 2% of the 126 patients had CHF.

Transvenous phrenic nerve stimulation is postulated to be more effective in CHF because it restores more physiologic breathing. In a prospective, nonrandomized, multicenter pilot study of the **rem**ed® System, which is implanted transvenously in a manner similar to a cardiac device, CSA was effectively treated [Abraham WT et al. *JACC Heart Fail*. 2015].

At 6 months, 76% of the 46 patients had mild, moderate, or marked improvement in their global assessments. The primary outcome of the apnea–hypopnea index was reduced from 49.5 to 22.4 events/h ($P$<.001). Clinically meaningful improvements were seen in heart rate variability at 6 months and in the MLWHF score at 6 and 12 months. In 24 patients who underwent echocardiography, LVEF improved from 26.4% to 29.7% ($P$=.0123), and the diastolic and systolic LV 4-chamber changed from 241.6 and 181.5, respectively, to 222.1 ($P$=.0046) and 160.0 ($P$=.008).

Despite these improvements, further study is required to understand the use of implantable devices to treat OSA and CSA in patients with and without CHF.